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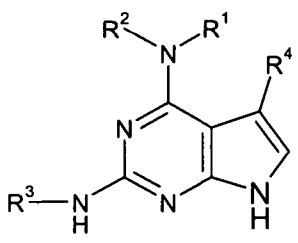
(54) Title: PYRROLOPYRIMIDINE DERIVATIVES AS SYK INHIBITORS



(I)

(57) Abstract: Pyrrolopyrimidine derivatives of formula (I) are inhibitors of Spleen Tyrosine kinase (Syk) and therefore of potential therapeutic benefit in the treatment of diseases and conditions associated with inappropriate Syk activity, in particular in the treatment of inflammatory and allergic diseases.

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PYRROLOPYRIMIDINE DERIVATIVES AS SYK INHIBITORS

Field of the Invention

The present invention relates to pyrrolopyrimidine derivatives, compositions and medicaments containing the same, as well as processes for the preparation and use of such compounds, compositions and medicaments. Such pyrrolopyrimidine derivatives are of potential therapeutic benefit in the treatment of diseases and conditions associated with inappropriate Syk activity, in particular in the treatment of inflammatory and allergic diseases.

Background to the Invention

Spleen Tyrosine Kinase (Syk) is a protein tyrosine kinase which has been described as a key mediator of immunoreceptor signalling in a host of inflammatory cells including mast cells, B-cells, macrophages and neutrophils.

These immunoreceptors, including Fc receptors and the B-cell receptor, are important for both allergic diseases and antibody-mediated autoimmune diseases and thus pharmacologically interfering with Syk could conceivably treat these disorders.

Allergic rhinitis and asthma are diseases associated with hypersensitivity reactions and inflammatory events involving a multitude of cell types including mast cells, eosinophils, T cells and dendritic cells. Following exposure to allergen, high affinity immunoglobulin receptors for IgE (FcεRI) and IgG (FcεRI) become cross-linked and activate downstream processes in mast cells and other cell types leading to the release of pro-inflammatory mediators and airway spasmogens. In the mast cell, for example, IgE receptor cross-linking by allergen leads to release of mediators including histamine from pre-formed granules, as well as the synthesis and release of newly synthesised lipid mediators including prostaglandins and leukotrienes.

Syk kinase is a non-receptor linked tyrosine kinase which is important in transducing the downstream cellular signals associated with cross-linking FcεR1 and or FcεR1 receptors, and is positioned early in the signalling cascade. In mast cells, for example, the early sequence of FcεR1 signalling following allergen cross-linking of receptor-IgE complexes involves first Lyn (a Src family tyrosine kinase) and then Syk. Inhibitors of Syk activity would therefore be expected to inhibit all downstream

signalling cascades thereby alleviating the immediate allergic response and adverse events initiated by the release of pro-inflammatory mediators and spasmogens (Wong et al 2004, Expert Opin. Investig. Drugs (2004) 13 (7) 743-762).

Recently, it has been shown that the Syk kinase inhibitor R112 (Rigel), dosed intranasally in a phase I/II study for the treatment of allergic rhinitis, gave a statistically significant decrease in PGD_2, a key immune mediator that is highly correlated with improvements in allergic rhinorrhea, as well as being safe across a range of indicators, thus providing the first evidence for the clinical safety and efficacy of a topical Syk kinase inhibitor. (Meltzer, Eli O.; Berkowitz, Robert B.; Grossbard, Elliott B, Journal of Allergy and Clinical Immunology (2005), 115(4), 791-796). In a more recent phase II clinical trial for allergic rhinitis (Clinical Trials.gov Identifier NCT0015089), R112 was shown as having a lack of efficacy versus placebo.

Rheumatoid Arthritis (RA) is an auto-immune disease affecting approximately 1% of the population. It is characterised by inflammation of articular joints leading to debilitating destruction of bone and cartilage. Recent clinical studies with Rituximab, which causes a reversible B cell depletion, (J.C.W. Edwards et al 2004, New Eng. J. Med. 350: 2572-2581) have shown that targeting B cell function is an appropriate therapeutic strategy in auto-immune diseases such as RA. Clinical benefit correlates with a reduction in auto-reactive antibodies (or Rheumatoid Factor) and these studies suggest that B cell function and indeed auto-antibody production are central to the ongoing pathology in the disease.

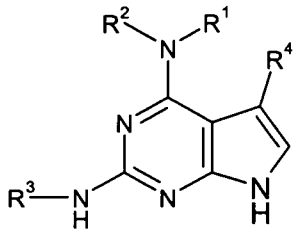
Studies using cells from mice deficient in the Spleen Tyrosine Kinase (Syk) have demonstrated a non-redundant role of this kinase in B cell function. The deficiency in Syk is characterised by a block in B cell development (M. Turner et al 1995 Nature 379: 298-302 and Cheng et al 1995, Nature 378: 303-306). These studies, along with studies on mature B cells deficient in Syk (Kurasaki et al 2000, Immunol. Rev. 176:19-29), demonstrate that Syk is required for the differentiation and activation of B cells. Hence, inhibition of Syk in RA patients, is likely block B cell function and hence to reduce Rheumatoid Factor production. In addition to the role of Syk in B cell function, of relevance to the treatment of RA, is the requirement for syk activity in Fc receptor (FcR) signalling. FcR activation by immune commplexes in RA has been suggested to contribute to the release of multiple pro-inflammatory mediators.

The contribution of Syk dependent processes to the pathology of RA has been reviewed in Wong et al (2004, Expert Opin Investig Drugs 13:743-762).

The present invention relates to novel pyrrolopyrimidine compounds, which are inhibitors of Syk kinase activity. Such pyrrolopyrimidine derivatives therefore have potential therapeutic benefit in the treatment of disorders associated with inappropriate Syk activity, in particular in the treatment and prevention of disease states mediated by Syk. Such disease states may include inflammatory, allergic and autoimmune diseases, for example, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohns disease, bronchitis, dermatitis, allergic rhinitis, psoriasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, cancer, HIV and lupus.

Brief Summary of the Invention

In one aspect of the present invention there is provided a compound of formula (I) or a salt or solvate thereof:



(I)

wherein:

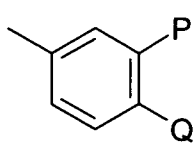
R^1 is H or C_{1-3} alkyl;

R^2 is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{1-3} alkyleneC_{3-7} cycloalkyl wherein each cycloalkyl may be substituted by one or more substituents independently selected from C_{1-3} alkyl or halogen;

R^3 is:

(a) a six membered heteroaryl group selected from 3-pyridinyl, 4-pyridinyl or 5-pyrimidinyl (each of which may be optionally substituted by one or more substituents independently selected from OH, =O, C_{1-3} alkyl, $NHCOC_{1-3}$ alkyl, C_{1-6} alkoxy, COC_{1-6} alkyl, C_{0-3} alkylene $COOC_{1-3}$ alkyl), CN;

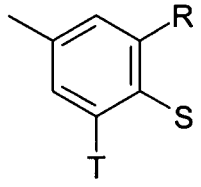
(b) a group



wherein P and Q together form a 5 - 7 membered carbocyclic, heterocyclic or heteroaryl ring, which thus formed bicyclic ring may be optionally substituted by one or more substituents independently selected from; on each carbon by up two C_{1-3}alkyl groups or halogen or by =O or by OH, C_{1-3}alkoxy, C_{1-3}haloalkyl,C_{0-3} alkyleneNR^{5}R^6, on each nitrogen by C_{1-3}alkyl, COC$_{1-3}$alkyl, C_{1-3}alkyleneC$_{3-7}$cycloalkyl, phenyl (optionally substituted by fluorine), C_{1-3}alkylOR^5, C_{0-3} alkyleneNR^{5}R^6 or SO_2R^5 or on sulphur by =O or $(=O)_2$;

R^5 and R^6 are independently H or C_{1-3} alkyl;

(c) a group



wherein one of R, S and T is H and the remaining substituents are independently selected from:

H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, OH, C_{1-6} hydroxyalkyl, CN, C_{3-7}cycloalkyl, Ophenyl, OCH_2phenyl, halogen, COOR^7, C_{1-3}alkyleneCOOR^7, XNR^{8}R^9, XCONR^{8}R^9, $XSO_2NR^8R^9$, NR^{7}COC$_{1-6}$alkyl, NR^{7}SO$_2$C$_{1-6}$alkyl, OCH$_2$CONR^{8}R^9, SO$_2$C$_{1-3}$alkyl, SO$_2$C$_{1-3}$haloalkyl, a monocyclic heteroaryl group (optionally substituted by methyl);

R^7 is H or -C_{1-3} alkyl;

X is a bond or C_{1-3}alkylene;

R^8 and R^9 are independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{3-7}cycloalkyl, C_{1-3} alkyleneC$_{3-7}$ cycloalkyl, phenyl (optionally substituted by one or more substitutents independently selected from halogen, -C_{1-3} alkyl, OC_{1-3} alkyl, CN, or SO_2CF_3), C_{1-3} alkylenephenyl, C_{1-3} alkyleneOC_{1-3} alkyl; or

R^8 and R^9 are independently heteroaryl (optionally substituted by one or more substituents independently selected from -C_{1-3} alkyl), heterocyclyl (optionally substituted by one or more substituents independently selected from -C_{1-3} alkyl, =O), C_{1-3} alkylenephenyl (substituted by one or more substitutents independently selected from halogen, -C_{1-3} alkyl or OC_{1-3} alkyl, CN, SO_2CF_3), C_{1-3} alkyleneheteroaryl (optionally substituted by one or more substituents independently selected from -C_{1-3} alkyl), C_{1-3} alkyleneheterocyclyl (optionally substituted by one or more substituents independently selected from -C_{1-3} alkyl, =O), C_{1-3} alkyleneSO$_2$C$_{1-3}$ alkyl, C_{1-3} alkyleneCONH2, C_{1-3} alkyleneCN, C_{1-3} alkyleneSO$_2$NC$_{1-3}$ alkyl, alkyleneNSO$_2$C$_{1-3}$ alkyl; or

R^8 and R^9; together with N to which they are joined form a 4-, 5- or 6 membered heterocyclic group, optionally containing a further heteroatom selected from O, S, or N and optionally substituted by on each carbon by up to two C_{1-6} alkyl or halogen, or by =O or C_{1-6} alkoxy, on any optional nitrogen by C_{1-6}alkyl, COC_{1-3}alkyl or $COOC_{1-6}$ alkyl and on any optional sulphur by =O, $(=O)_2$;
R^4 is H or -C_{1-3} alkyl.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of formula (I), or a salt or solvate, thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

In a further aspect of the present invention, there is provided a compound of formula (I), or a salt or solvate, thereof for use in therapy.

In a further aspect of the present invention, there is provided a compound of formula (I) or a salt or solvate thereof for use in the treatment of a disease or condition mediated by inappropriate Syk activity.

In a further aspect of the present invention, there is provided a method of treating a disease or condition mediated by inappropriate Syk activity in a mammal comprising administering to said mammal a compound of formula (I) or a salt or solvate thereof.

In a further aspect of the present invention there is provided the use of a compound of formula (I) or a salt or solvate thereof in the manufacture of a medicament for use in the treatment of a disease or condition mediated by inappropriate Syk activity.

Detailed Description of the Invention

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term “therapeutically effective amount” means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein the term "alkyl" refers to a straight- or branched-chain hydrocarbon radical having the specified number of carbon atoms. As used herein, the terms "C_1-C_3 alkyl" and "C_1-C_6 alkyl" refer to an alkyl group, as defined above, containing at least 1, and at most 3 or 6 carbon atoms respectively. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, and the like.

As used herein, the term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical having the specified number of carbon atoms. As used herein, the terms "C_1-C_3 alkylene" and "C_1-C_6 alkylene" refer to an alkylene group, as defined above, which contains at least 1, and at most 3 or 6, carbon atoms respectively. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, n-propylene, n-butylene, and the like.

As used herein, the term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I) and the term "halo" refers to the halogen radicals: fluoro (-F), chloro (-Cl), bromo(-Br), and iodo(-I).

As used herein, the term "haloalkyl" refers to an alkyl group as defined above, substituted with at least one halo group, halo being as defined herein. Examples of such branched or straight chained haloalkyl groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted independently with one or more halos, e.g., fluoro, chloro, bromo and iodo.

As used herein, the term "cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring containing the specified number of carbon atoms. In a like manner the term "C_3-C_7 cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring having from 3 to 7 carbon atoms. Exemplary "cycloalkyl" groups useful in the present invention include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

As used herein, thes term "carbocyclic" refers to a non-aromatic ring containing carbon and hydrogen atoms, being saturated or having one or more degrees of unsaturation.

As used herein, the term "heterocyclic" or the term "heterocyclyl" refers to a non-aromatic heterocyclic ring, being saturated or having one or more degrees of unsaturation, containing one or more heteroatom substitutions selected from S, S(O), $S(O)_2$, O, or N, and having the specified number of ring members.

As used herein, the term "alkoxy" refers to the group R_aO-, where R_a is alkyl as defined above and the terms "C_1-C_3 alkoxy" and "C_1-C_6 alkoxy" refer to an alkoxy group as defined herein wherein the alkyl moiety contains at least 1, and at most 3 or 6, carbon atoms. Exemplary "C_1-C_3 alkoxy" and "C_1-C_6 alkoxy" groups useful in the present invention include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, and t-butoxy.

As used herein, the term "haloalkoxy" refers to the group R_aO-, where R_a is haloalkyl as defined above and the term "C_1-C_6 haloalkoxy" refers to a haloalkoxy group as defined herein wherein the haloalkyl moiety contains at least 1, and at most 6, carbon atoms. Exemplary C_1-C_6 haloalkoxy groups useful in the present invention include, but are not limited to, trifluoromethoxy.

As used herein the term "hydroxy" refers to the group –OH.

The term "heteroaryl", unless otherwise specified, refers to aromatic monocyclic groups and fused bicyclic aromatic rings, having the specified number of ring members (e.g. carbon and heteratoms N, O, and/or S) and containing 1, 2, 3 or 4 heteroatoms selected from N, O and S. Examples of particular heteroaryl groups include, but are not limited to, furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, benzofuran, benzothiopene, benzazepine, benzimidazole, benzoimidazole, indole, oxindole and indazole.

As used herein, the term "hydroxyalkyl" refers to an alkyl group as defined above substituted with at least one hydroxy, hydroxy being as defined herein. Examples of branched or straight chained "C_1-C_6 hydroxyalkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted independently with one or more hydroxy groups.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

The term "Syk inhibitor", is used to mean a compound which inhibits the Syk receptor respectively.

The term "Syk mediated disease" or a "disorder or disease or condition mediated by inappropriate Syk activity" is used to mean any disease state mediated or modulated by Syk kinase mechanisms. Such disease states may include inflammatory, allergic and autoimmune diseases, for example, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDs), ulcerative colitis, Crohns disease, bronchitis, dermatitis, allergic rhinitis, psorasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, cancer, HIV and lupus, in particular, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDs), allergic rhinitis and rheumatoid arthritis.

As used herein, "a compound of the invention" means a compound of formula (I) or a salt, solvate or physiologically functional derivative thereof.

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. 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, acetone, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent is water.

The compounds of formula (I) may have the ability to crystallize in more than one form, a characteristic, which is known as polymorphism, and it is understood that such polymorphic forms ("polymorphs") are within the scope of formula (I).

Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility and melting point.

Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two enantiomers. Accordingly, the compounds of this invention include mixtures of enantiomers as well as purified enantiomers or enantiomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formula (I) above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centres are inverted.

It is also noted that the compounds of Formula (I) may form tautomers. It is understood that all tautomers and mixtures of tautomers of the compounds of the present invention are included within the scope of the compounds of the present invention.

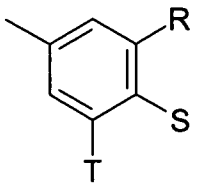
In one embodiment, R^1 represents H or methyl. In a further embodiment R^1 represents H.

In one embodiment, R^2 represents cyclobutyl, cyclopentyl, cyclohexyl, C_{1-3} alkyl, or C_{1-3} haloalkyl. In a further embodiment, R^2 represents C_{1-3} alkyl or C_{1-3} haloalkyl. In a further embodiment, R^2 is C_{1-3} haloalkyl, preferably 1-trifluoroethyl or C_{1-3} alkyl, preferably 1-methylethyl.

In one embodiment, R^1 represents H and R^2 is cyclobutyl, cyclopentyl, cyclohexyl, C_{1-3} alkyl, or C_{1-3} haloalkyl. In a further embodiment, R^1 represents H and R^2 is C_{1-3} alkyl or C_{1-3} haloalkyl. In a further embodiment, R^1 represents H and R^2 is C_{1-3} haloalkyl, preferably 1-trifluoroethyl or C_{1-3} alkyl, preferably 1-methylethyl.

In one embodiment, R^4 is H or CH_3. In a further embodiment, R^4 is H.

In one embodiment, R^3 is a group:



wherein one of R, S and T is H and the remaining substituents are independently selected from: H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, OH, C_{1-6} hydroxyalkyl, CN, C_{3-7}cycloalkyl, Ophenyl, OCH_2phenyl, halogen, $COOR^7$, C_{1-3}alkyleneCOOR^7, XNR^8R^9, $XCONR^8R^9$, $XSO_2NR^8R^9$, NR^7COC_{1-6}alkyl, $NR^7SO_2C_{1-6}$alkyl, $OCH_2CONR^8R^9$, SO_2C_{1-3}alkyl, a monocyclic heteroaryl group (optionally substituted by methyl); and

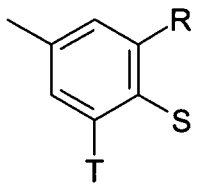
excluding compounds in which R and T is each hydrogen, S is $CONR^8R^9$, and

R^8 and R^9 are independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{3-7}cycloalkyl, C_{1-3} alkyleneC_{3-7} cycloalkyl, phenyl (optionally substituted by one or more substitutents independently selected from halogen, -C_{1-3} alkyl CN, or SO_2CF_3), C_{1-3} alkylenephenyl, C_{1-3} alkyleneOC_{1-3} alkyl; or

R^8 and R^9; together with N to which they are joined form a 4-, 5- or 6- membered heterocyclic group, optionally containing a further heteroatom selected from O, S, or N and optionally substituted on each carbon by up to two C_{1-6} alkyl or halogen, or by =0 or C_{1-6} alkoxy, on any optional nitrogen by C_{1-6}alkyl, COC_{1-3}alkyl or $COOC_{1-6}$ alkyl and on any optional sulphur by =O, or $(=O)_2$; and

R^1, R^2, R^4, R^7, R^8, R^9 and X are as otherwise hereinbefore defined.

In a further embodiment, R^3 is a group:

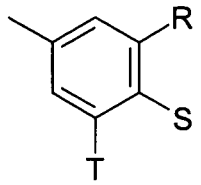


wherein R and T is each hydrogen, S is $CONR^8R^9$,

and R^8 and R^9 are independently heteroaryl (optionally substituted by one or more substituents independently selected from -C_{1-3} alkyl), heterocyclyl (optionally substituted by one or more substituents independently selected from -C_{1-3} alkyl, =O), C_{1-3} alkylenephenyl (substituted by one or more substitutents independently selected from halogen, -C_{1-3} alkyl or OC_{1-3} alkyl, CN, SO_2CF_3), C_{1-3} alkyleneheteroaryl (optionally substituted by one or more substituents independently selected from -C_{1-3} alkyl), C_{1-3} alkyleneheterocyclyl (optionally substituted by one or more substituents

independently selected from -C_{1-3} alkyl, =O), C_{1-3} alkyleneSO_2C_{1-3} alkyl, C_{1-3} alkyleneCONH2, C_{1-3} alkyleneCN, C_{1-3} alkyleneSO_2NC_{1-3} alkyl, alkyleneNSO_2C_{1-3} alkyl.

In a further embodiment, R^3 is a group:



wherein R is hydrogen, T is halogen and S is $CONR^8R^9$,
and R^8 and R^9 are as hereinbefore defined.

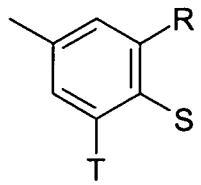
In one embodiment, R^8 and R^9 is each is hydrogen.

In one embodiment, R^8 is hydrogen and R^9 is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-7}cycloalkyl, C_{1-3} alkyleneC_{3-7} cycloalkyl, preferably n-propyl

In one embodiment, R^8 is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-7}cycloalkyl, C_{1-3}alkyleneC_{3-7} cycloalkyl and R^9 is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-7}cycloalkyl, C_{1-3}alkyleneC_{3-7} cycloalkyl.

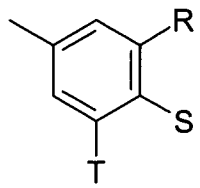
In one embodiment, R^8 and R^9, together with N to which they are joined form a 4-, 5- or 6 membered heterocyclic group, optionally containing a further heteroatom selected from O, S, or N, and optionally substituted on any optional nitrogen by C_{1-6}alkyl and on any optional sulphur by =O, or $(=O)_2$.

In a further embodiment, R^3 is a group:



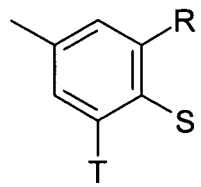
wherein R and T is H and S is NR^7COC_{1-6}alkyl, in particular $NHCOC_{1-6}$alkyl.

In a further embodiment, R^3 is a group:



wherein R and T is H and S is NR^8R^9 in which R^8 and R^9 together with the N to which they are joined form a 6 membered heterocyclic group, optionally containing a further heteroatom selected from O, S, or N and optionally substituted by on each carbon by up to two C_{1-6} alkyl or halogen, or by =O or C_{1-6} alkoxy, on any optional nitrogen by C_{1-6}alkyl, COC_{1-3}alkyl or $COOC_{1-6}$ alkyl and on any optional sulphur by =O, or $(=O)_2$; in particular morpholino.

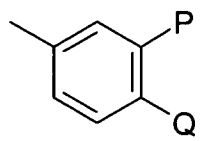
In a further embodiment, R^3 is a group:



wherein R and T is H, and S is $OCH_2CONR^8R^9$, in particular $OCH_2CONHMe$.

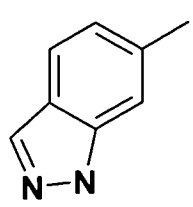
In a further embodiment, R^3 is a six membered heteroaryl group selected from 3-pyridinyl, 4-pyridinyl or 5-pyrimidinyl (each of which may be optionally substituted by one or more substituents independently selected from =O, C_{1-3} alkyl, $NHCOC_{1-3}$ alkyl, C_{1-6} alkoxy, COC_{1-6} alkyl, C_{0-3} alkylene $COOC_{1-3}$ alkyl), CN.

In a further embodiment, R^3 is a group:



wherein P and Q together form a 5 - 7 membered carbocyclic, heterocyclic or heteroaryl ring, which rings may be optionally substituted by one or more substituents independently selected from; on each carbon by up two C_{1-3}alkyl groups or halogens or by =O or by OH, C_{1-3}alkoxy, C_{1-3}haloalkyl,C_{0-3} alkyleneNR^{5}R^6, on each nitrogen by C_{1-3}alkyl, COC_{1-3}alkyl, C_{1-3}alkyleneC_{3-7}cycloalkyl, phenyl (optionally substituted by fluorine), C_{1-3}alkylOR^5, C_{0-3} alkyleneNR^{5}R^6 or SO_2R^5 or on sulphur by =O or $(=O)_2$. Representative examples of such 5 - 7 membered carbocyclic,

heterocyclic or heteroaryl ring include: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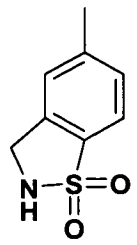
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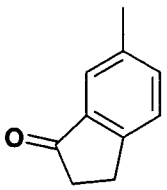
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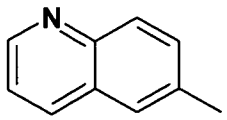
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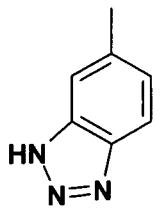
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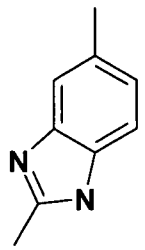
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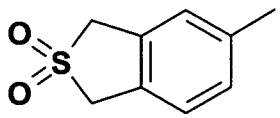
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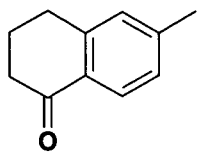
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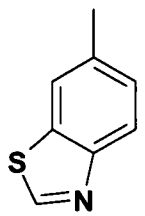
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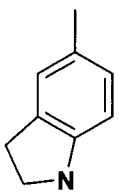
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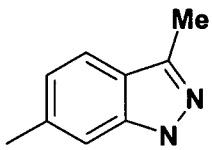
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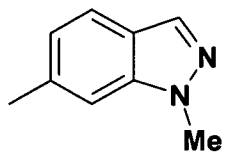
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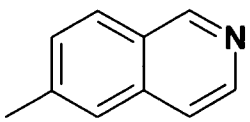
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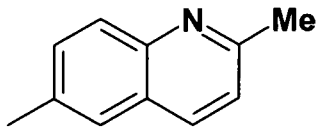
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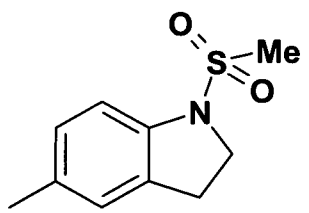
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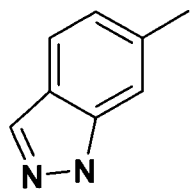
Preferred examples include the following cyclic sulphones, indazoles and quinolines: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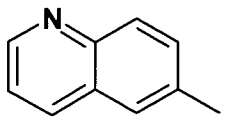
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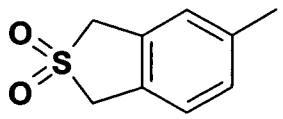
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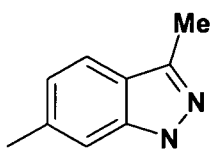
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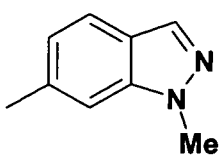
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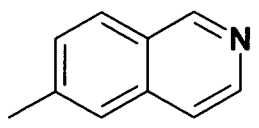
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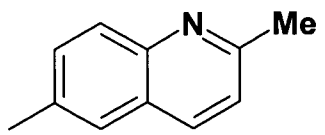


Whilst the embodiments for each variable have generally been listed above separately for each variable, this invention also includes those compounds in which several or each embodiment in formula (I) is selected from each of the embodiments listed above. Therefore, this invention is intended to include all combinations of embodiments for each variable.

Specific examples of compounds of the present invention include Examples 1 - 413 as described in the Examples section below, in particular.

N-Propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide; and

4-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide;

N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N-methyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide;

3-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzonitrile;

N^2-6-isoquinolinyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-[3-chloro-4-(methyloxy)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-(1-methyl-1*H*-indazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^4-cyclobutyl-N^2-(3-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N-(4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)-*N*-methylacetamide;

N^2-6-quinolinyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N-methyl-2-{[3-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]oxy}acetamide; and

N^2-(3-methyl-1*H*-indazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine.

or a pharmaceutically acceptable salt or solvate thereof.

The compounds of the present invention may be in the form of and/or may be administered as a pharmaceutically acceptable salt. For a review on suitable salts see Berge et al, J. Pharm. Sci. 1977, 66, 1-19.

Typically, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention.

Suitable pharmaceutically acceptable salts can include acid or base additions salts.

A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, maleic, formic, acetic, propionic, fumaric, citric, tartaric, lactic, benzoic, salicylic, glutamaic, aspartic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphthalenesulfonic such as 2-naphthalenesulfonic, or hexanoic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can comprise or be for example a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, succinate, maleate, formarate, acetate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate) or hexanoate salt.

A pharmaceutically acceptable base addition salt may, where there is a suitable acidic group, be formed by reaction of a compound of formula (I) with a suitable inorganic or organic base (e.g. triethylamine, ethanolamine, triethanolamine, choline, arginine, lysine or histidine), optionally in a suitable solvent such as an organic solvent, to give the base addition salt which is usually isolated for example by crystallisation and filtration.

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 one or more carboxylic acid moieties that may be present in the compound of formula (I).

Other non-pharmaceutically acceptable salts, e.g. oxalates or trifluoroacetates, may be used, for example in the isolation of compounds of the invention, and are included within the scope of this invention.

The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the compounds of formula (I).

The compounds of formula (I) and salts, solvates and physiologically functional derivatives thereof are believed to be inhibitors of Syk activity, and thus be potentially useful in the treatment of diseases and conditions associated with inappropriate Syk activity.

The invention thus provides compounds of formula (I) and salts, solvates and physiologically functional derivatives thereof for use in therapy, and particularly in the treatment of diseases and conditions mediated by inappropriate Syk activity.

The inappropriate Syk activity referred to herein is any Syk activity that deviates from the normal Syk activity expected in a particular mammalian subject. Inappropriate Syk activity may take the form of, for instance, an abnormal increase in activity, or an aberration in the timing and or control of Syk activity. Such inappropriate activity may result then, for example, from overexpression or mutation of the protein kinase leading to inappropriate or uncontrolled activation.

In a further embodiment, the present invention is directed to methods of regulating, modulating, or inhibiting Syk for the prevention and/or treatment of disorders related to unregulated Syk activity.

In a further embodiment, the present invention provides a method of treatment of a mammal suffering from a disorder mediated by Syk activity, which includes administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or a physiologically functional derivative thereof.

In a further embodiment, the present invention provides for the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a physiologically functional derivative thereof, in the preparation of a medicament for the treatment of a disorder mediated by Syk activity.

In a further embodiment, the disease or condition mediated by inappropriate Syk activity is rheumatoid arthritis.

In a further embodiment, the disease or condition mediated by inappropriate Syk activity is allergic rhinitis.

In a further embodiment, the disease or condition mediated by inappropriate Syk activity is chronic obstructive pulmonary disease (COPD),

In a further embodiment, the disease or condition mediated by inappropriate Syk activity is adult respiratory distress syndrome (ARDs).

While it is possible that, for use in therapy, a compound of formula (I), as well as salts, solvates and physiological functional derivatives thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provides a pharmaceutical composition, which comprises a compound of formula (I) and salts, solvates and physiological functional derivatives thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of the formula (I) and salts, solvates and physiological functional derivatives thereof, are as described above. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical composition including admixing a compound of the formula (I), or salts, solvates and physiological functional derivatives thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients.

Pharmaceutical compositions of the present invention may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 5μg to 1g, preferably 1mg to 700mg, more

preferably 5mg to 100mg of a compound of the formula (I), depending on the condition being treated, the route of administration and the age, weight and condition of the patient. Such unit doses may therefore be administered more than once a day. Preferred unit dosage compositions are those containing a daily dose or sub-dose (for administration more than once a day), as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical compositions may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical compositions of the present invention may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), inhaled, or nasalroute. Such compositions may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

In a further embodiment, the present invention provides a pharmaceutical composition adapted for administration by the oral route, for treating, for example, rheumatoid arthritis.

In a further embodiment, the present invention provides a pharmaceutical composition adapted for administration by the nasal route, for treating, for example, allergic rhinitis.

In a further embodiment, the present invention provides a pharmaceutical composition adapted for administration by the inhaled route, for treating, for example, COPD or ARDS.

Pharmaceutical compositions of the present invention which are adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by

comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging

steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit compositions for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release, for example, by coating or embedding particulate material in polymers, wax or the like.

The compounds of formula (I), and salts, solvates and physiological functional derivatives thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of formula (I) and salts, solvates and physiological functional derivatives thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Dosage forms for inhaled administration may conveniently be formulated as aerosols or dry powders.

For compositions suitable and/or adapted for inhaled administration, it is preferred that the compound or salt of formula (I) is in a particle-size-reduced form, and more preferably the size-reduced form is obtained or obtainable by micronisation. The preferable particle size of the size-reduced (e.g. micronised) compound or salt or solvate is defined by a D50 value of about 0.5 to about 10 microns (for example as measured using laser diffraction).

Aerosol formulations, *e.g.* for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide or an organic propellant such as a hydrofluorocarbon (HFC). Suitable HFC propellants include 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser. The pressurised aerosol may contain a solution or a suspension of the active compound. This may require the incorporation of additional excipients e.g. co-solvents and/or surfactants to improve the dispersion characteristics and homogeneity of suspension formulations. Solution formulations may also require the addition of co-solvents such as ethanol. Other excipient modifiers may also be incorporated to improve, for example, the stability and/or taste and/or fine particle mass characteristics (amount and/or profile) of the formulation.

For pharmaceutical compositions suitable and/or adapted for inhaled administration, it is preferred that the pharmaceutical composition is a dry powder inhalable composition. Such a composition can comprise a powder base such as lactose,

glucose, trehalose, mannitol or starch, the compound of formula (I) or salt or solvate thereof (preferably in particle-size-reduced form, e.g. in micronised form), and optionally a performance modifier such as L-leucine or another amino acid, and/or metals salts of stearic acid such as magnesium or calcium stearate. Preferably, the dry powder inhalable composition comprises a dry powder blend of lactose and the compound of formula (I) or salt thereof. The lactose is preferably lactose hydrate e.g. lactose monohydrate and/or is preferably inhalation-grade and/or fine-grade lactose. Preferably, the particle size of the lactose is defined by 90% or more (by weight or by volume) of the lactose particles being less than 1000 microns (micrometres) (e.g. 10-1000 microns e.g. 30-1000 microns) in diameter, and/or 50% or more of the lactose particles being less than 500 microns (e.g. 10-500 microns) in diameter. More preferably, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 300 microns (e.g. 10-300 microns e.g. 50-300 microns) in diameter, and/or 50% or more of the lactose particles being less than 100 microns in diameter. Optionally, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 100-200 microns in diameter, and/or 50% or more of the lactose particles being less than 40-70 microns in diameter. Most importantly, it is preferable that about 3 to about 30% (e.g. about 10%) (by weight or by volume) of the particles are less than 50 microns or less than 20 microns in diameter. For example, without limitation, a suitable inhalation-grade lactose is E9334 lactose (10% fines) (Borculo Domo Ingredients, Hanzeplein 25, 8017 JD Zwolle, Netherlands).

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical composition for inhaled administration can be incorporated into a plurality of sealed dose containers (*e.g.* containing the dry powder composition) mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose of *e.g.* the dry powder composition can be administered by inhalation via the device such as the DISKUS ^{TM} device, marketed by GlaxoSmithKline. The DISKUS ^{TM} inhalation device is for example described in GB 2242134 A, and in such a device at least one container for the pharmaceutical composition in powder form (the container or containers preferably being a plurality of sealed dose containers mounted longitudinally in a strip or ribbon) is defined between two members peelably secured to one another; the device comprises: a means of defining an opening station for the said container or containers; a means for peeling the members apart at the opening station to open the container; and an

outlet, communicating with the opened container, through which a user can inhale the pharmaceutical composition in powder form from the opened container.

Dosage forms for nasal administration may conveniently be formulated as aerosols, solutions, drops, gels or dry powders.

Pharmaceutical compositions adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurised aerosols, nebulizers or insufflators.

For pharmaceutical compositions suitable and/or adapted for intranasal administration, the compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof may be formulated as a fluid formulation for delivery from a fluid dispenser. Such fluid dispensers may have, for example, a dispensing nozzle or dispensing orifice through which a metered dose of the fluid formulation is dispensed upon the application of a user-applied force to a pump mechanism of the fluid dispenser. Such fluid dispensers are generally provided with a reservoir of multiple metered doses of the fluid formulation, the doses being dispensable upon sequential pump actuations. The dispensing nozzle or orifice may be configured for insertion into the nostrils of the user for spray dispensing of the fluid formulation into the nasal cavity. A fluid dispenser of the aforementioned type is described and illustrated in WO-A-2005/044354, the entire content of which is hereby incorporated herein by reference. The dispenser has a housing which houses a fluid discharge device having a compression pump mounted on a container for containing a fluid formulation. The housing has at least one finger-operable side lever which is movable inwardly with respect to the housing to cam the container upwardly in the housing to cause the pump to compress and pump a metered dose of the formulation out of a pump stem through a nasal nozzle of the housing. A particularly preferred fluid dispenser is of the general type illustrated in Figures 30-40 of WO-A-2005/044354.

It will be appreciated that when the compound of the present invention is administered in combination with other therapeutic agents normally administered by the inhaled, intravenous, oral or intranasal route, that the resultant pharmaceutical composition may be administered by the same routes.

It should be understood that in addition to the ingredients particularly mentioned above, the compositions may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian However, an effective amount of a compound of formula (I) for the treatment of diseases or conditions associated with inappropriate Syk activity, will generally be in the range of 5µg to 100mg/kg body weight of recipient (mammal) per day and more usually in the range of 5µg to 10mg/kg body weight per day. This amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt or solvate, thereof, may be determined as a proportion of the effective amount of the compound of formula (I) *per se*.

Compounds of the present invention, and their salts and solvates, and physiologically functional derivatives thereof, may be employed alone or in combination with other therapeutic agents for the treatment of diseases and conditions associated with inappropriate tyrosine and serine/threonine kinase activity. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a physiologically functional derivative thereof, and the use of at least one other pharmaceutically active agent. Preferably, combination therapies according to the present invention comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a physiologically functional derivative thereof, and at least one other pharmaceutically active agent. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Compounds of the present invention, and their salts and solvates, and physiologically functional derivatives thereof, may also be used in combination with other classes of therapeutic agents which are known in the art. Representative classes of agents for use in such combinations include, for treating asthma, anti-inflammatory steroids (in particular corticosteroids), topical glucocorticoid agonists, PDE4 inhibitors, IKK2 inhibitors, A2a agonists, β_2-adrenoreceptor agonists (including both slow acting and long acting β_2-adrenoreceptor agonists), alpha 4 integrin inhibitors, and anti-muscarinics, and, for treating allergies, the foregoing agents, as well as H1 and H1/H3 antagonists. Representative agents for use in combination therapy for treating severe asthma include topically acting p38 inhibitors, and IKK2 inhibitors.

Anti-inflammatory corticosteroids are well known in the art. Representative examples include fluticasone propionate (e.g. see US patent 4,335,121), beclomethasone 17-propionate ester, beclomethasone 17,21-dipropionate ester, dexamethasone or an ester thereof, mometasone or an ester thereof (e.g. mometasone furoate), ciclesonide, budesonide, and flunisolide. Further examples of anti-inflammatory corticosteroids are described in WO 02/12266 A1 (Glaxo Group Ltd), in particular, the compounds of Example 1 (6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester) and Example 41 (6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester), or a pharmaceutically acceptable salt thereof.

Examples of β_2-adrenoreceptor agonists include salmeterol (*e.g.* as racemate or a single enantiomer such as the R-enantiomer), salbutamol, formoterol, salmefamol, fenoterol or terbutaline and salts thereof, for example the xinafoate salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. Long-acting β_2-adrenoreceptor agonists are preferred, especially those having a therapeutic effect over a 24 hour period such as salmeterol or formoterol.

Examples of anti-histamines include azelastine, levocabastine, olopatidine, methapyrilene, loratadine, cetirizine, desloratadine or fexofenadine.

Examples of anticholinergic compounds include muscarinic (M) receptor antagonists, in particular M_1, M_2, M_1/M_2, or M_3 receptor antagonists, in particular a (selective) M_3 receptor antagonist. Examples of anticholinergic compounds are described in WO 03/011274 A2 and WO 02/069945 A2 / US 2002/0193393 A1 and US 2002/052312 A1. Examples of muscarinic M3 antagonists include ipratropium bromide, oxitropium bromide or tiotropium bromide.

Representative PDE4 or mixed PDE3/4 inhibitors that may be used in combination with compounds of the invention include AWD-12-281 (Elbion), PD-168787 (Pfizer), roflumilast, and cilomilast (GlaxoSmithKline). Further examples of PDE4 inhibitors are described in WO 2004/103998 (Glaxo Group Ltd).

The present invention also provides for so-called "triple combination" therapy, comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with β_2-adrenoreceptor agonist and an anti-inflammatory corticosteroid. Preferably this combination is for treatment and/or prophylaxis of asthma, COPD or allergic rhinitis. The β_2-adrenoreceptor agonist and/or the anti-inflammatory corticosteroid can be as described above and/or as described in WO 03/030939 A1. A representative example of such a "triple" combination comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, salmeterol or a pharmaceutically acceptable salt thereof (e.g. salmeterol xinafoate) and fluticasone propionate.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, for example as alkali metal or amine salts or as acid addition salts, or prodrugs, or as esters, for example lower alkyl esters, or as solvates, for example hydrates, to optimise the activity and/or stability and/or physical characteristics, such as solubility, of the therapeutic ingredient. It will be clear also that, where appropriate, the therapeutic ingredients may be used in optically pure form.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention. These combinations are of particular interest in respiratory diseases and are conveniently

adapted for inhaled or intranasal delivery.

Rheumatoid arthritis (RA) is a further inflammatory disease where combination therapy may be contemplated. Thus in a further aspect, the present invention provides a compound of formula (I) or a salt or solvate thereof in combination with a further therapeutic agent useful in the treatment of rheumatoid arthritis, said combination being useful for the treatment of rheumatoid arthritis.

The compound and pharmaceutical compositions according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from NSAIDS, corticosteroids, COX-2 inhibitors, cytokine inhibitors, anti-TNF agents, inhibitors of oncostatin M, anti-malarials, immunosuppressivess and cytostatics

Two classes of medication are contemplated for the treatment of RA, these may be classified as "fast acting" and "slow acting" or "second line" drugs (also referred to as Disease Modifying Antirheumatic Drugs or DMARDS). The first line drugs such as typical NSAIDs (e.g. aspirin, ibuprofen, naproxen, etodolac), corticosteroids (e.g. prednisone). Second line drugs include COX-2 inhibitors and anti-TNF agents. Examples of COX-2 inhibitors are celecoxib (Celebrex), etoricoxib and rofecoxib (Vioxx).

Anti-TNF agents include infliximab (Remicade), etanercept (Enbrel) and adalimumab (Humira). Other "biological" treatments include anakinra (Kineret), Rituximab, Lymphostat-B, BAFF/APRIL inhibitors and CTLA-4-Ig or mimetics thereof. Other cytokine inhibitors include leflunomide (Arava). Further second line drugs include gold preparations (Auranofin (Ridaura tablets) or Aurothiomalate (Myocrisin injection)), medicines used for malaria: (Hydroxychloroquine (Plaquenil)), medicines that suppress the immune system (Azathioprine (Imuran, Thioprine), methotrexate (Methoblastin, Ledertrexate, Emthexate), cyclosporin (Sandimmun, Neoral)), Cyclophosphamide (Cycloblastin), Cytoxan, Endoxan), D-Penicillamine (D-Penamine), Sulphasalazine (Salazopyrin), nonsteroidal anti inflammatory drugs (including aspirin and ibuprofen).

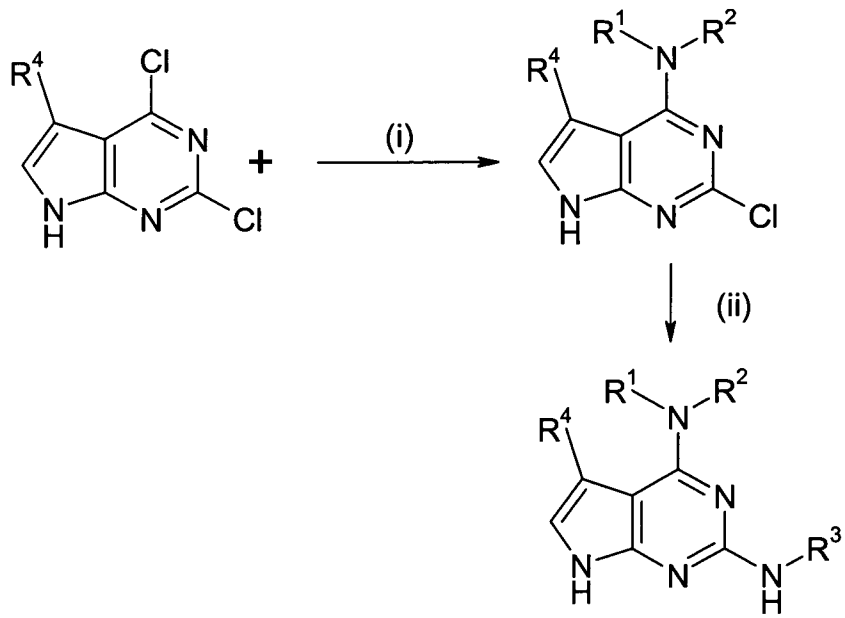
The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical

compositions. Preferably, the individual compounds will be administered simultaneously in a combined pharmaceutical composition. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the Working Examples.

Compounds of general formula (I) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthesis schemes. In all of the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (1991) Protecting Groups in Organic Synthesis, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of Formula (I). Those skilled in the art will recognize if a stereocenter exists in compounds of Formula (I). Accordingly, the present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well. When a compound is desired as a single enantiomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Organic Compounds by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

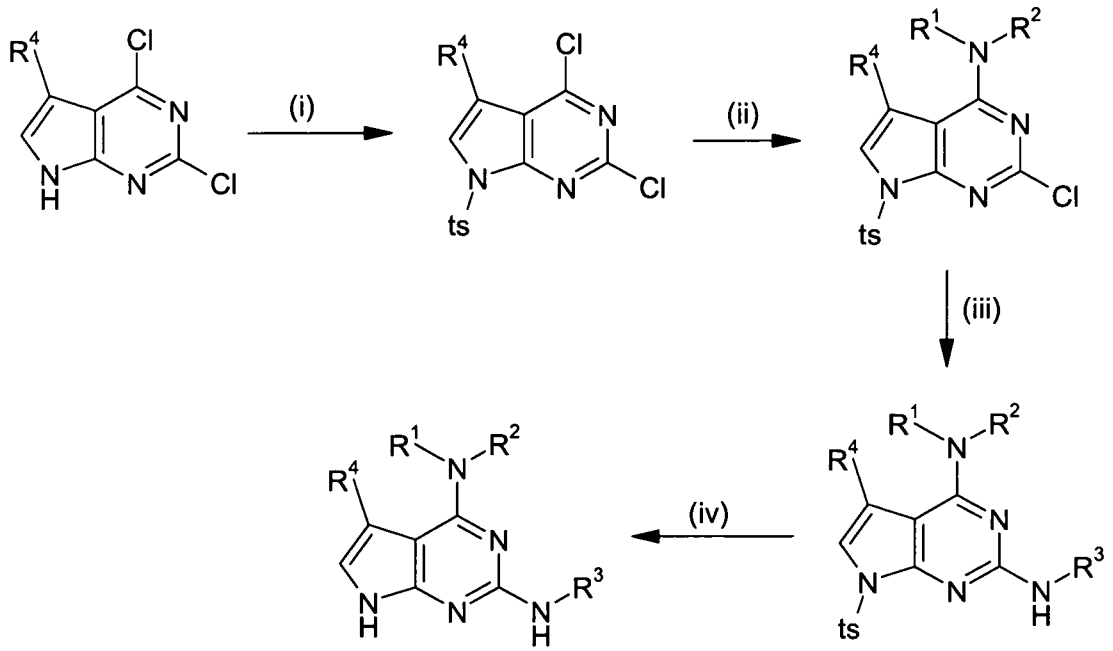
Route 1



(i) HNR^1R^2, IPA, microwave 100°C

(ii) R^3NH_2, $Pd(dba)_2$,
2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl, Cs_2CO_3, DMF, microwave 150°C

Route 2



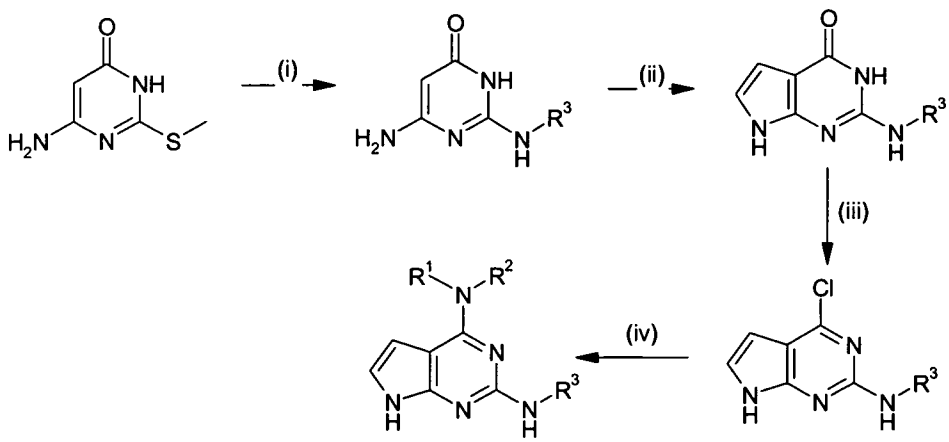
(i) NaH, TsCl, DMF

(ii) HNR^1R^2, IPA, 80°C

(iii) R^3NH_2, $Pd_2(dba)_3$, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, K_2CO_3, t-BuOH, 80°C

(iv) NaOMe, MeOH

Route 3



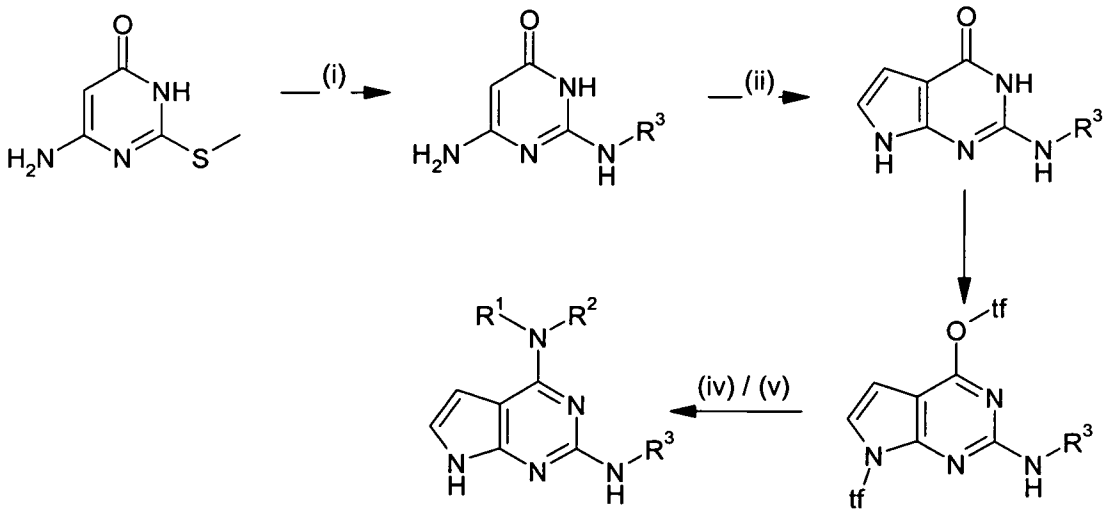
(i) R^3NH_2, 190°C

(ii) $ClCH_2CHO$, NaOAc, IPA/H_2O, 80°C

(iii) $POCl_3$, 120°C

(iv) HNR^1R^2, IPA, microwave 100°C

Route 4



(i) R^3NH_2, 190°C

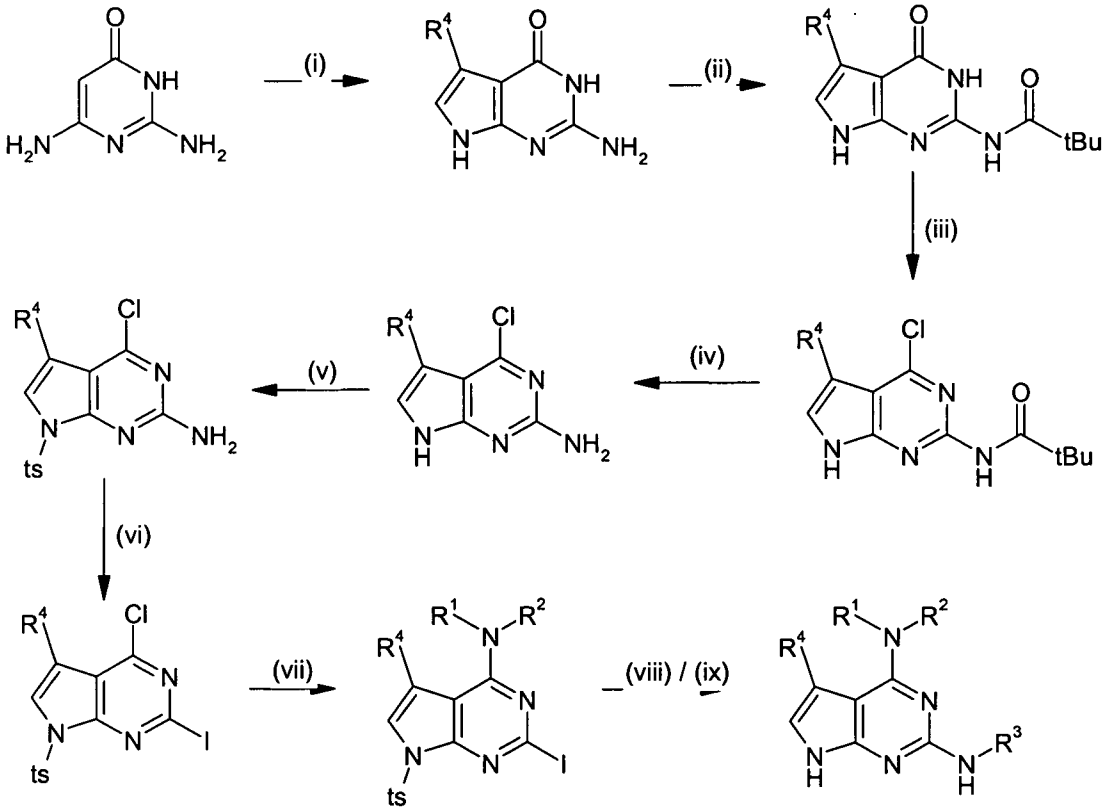
(ii) $ClCH_2CHO$, NaOAc, IPA/H_2O, 80

(iii) $(CF_3SO_2)_2NPh$, K_2CO_3, DMF, RT

(iv) HNR^1R^2, K_2CO_3, dioxane, microwave 80°C

(v) 2N NaOH

Route 5



(i) $ClCHR^4CHO$, $NaHCO_3$, H_2O, 50°C

(ii) $(tBuCO)_2O$, DMAP, 120°C

(iii) $POCl_3$, 110°C

(iv) 2N NaOH, 100°C

(v) TsCl, NaH, DMF, RT

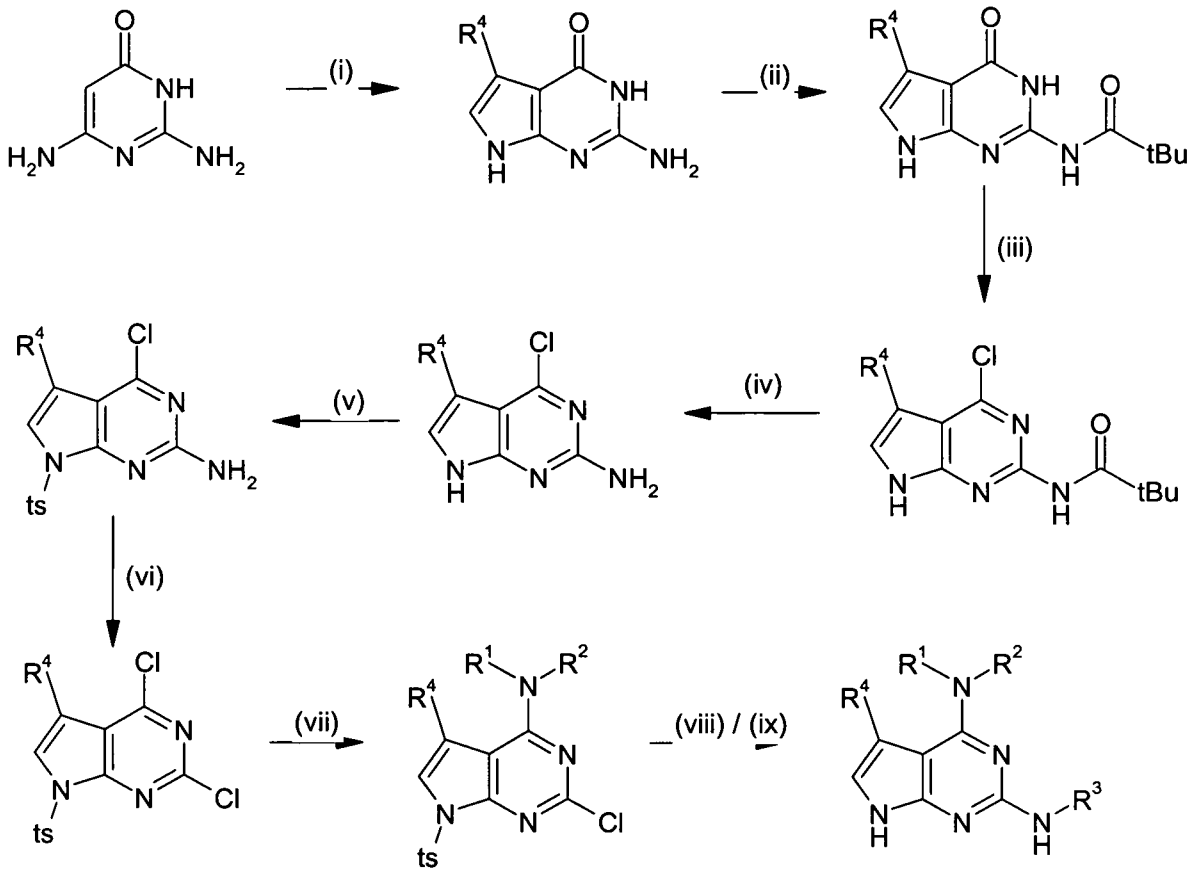
(vi) tBuONO, CH_2I_2, CuI, I_2, THF, 80°C

(vii) HNR^1R^2, IPA, 80°C

(viii) R^3NH_2, $Pd_2(dba)_3$, 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl, Cs_2CO_3, DMF, 90°C

(ix) NaOMe, MeOH

Route 6



(i) $ClCHR^4CHO$, $NaHCO_3$, H_2O, 50°C

(ii) $(tBuCO)_2O$, DMAP, 120°C

(iii) $POCl_3$, 110°C

(iv) 2N NaOH, 100°C

(v) TsCl, NaH, DMF, RT

(vi) t-BuONO, Me_3SiCl, $BnN(Et)_3Cl$, DCM.

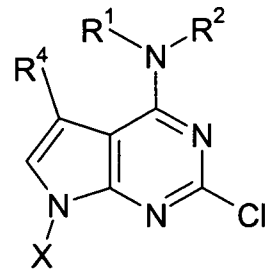
(vii) HNR^1R^2, IPA, 80°C

(viii) R^3NH_2, $Pd_2(dba)_3$, 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl, K_2CO_3, t-BuOH, microwave, 120°C

(ix) NaOMe, MeOH

Accordingly, in a further apect, the present invention provides a process for preparing a compound of formula (I) which process comprises:

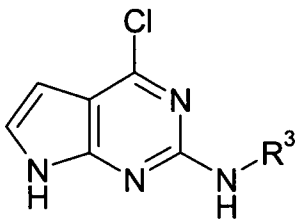
(i) reacting a compound of formula (II):



(II)

wherein X is H or a protecting group such as p-toluenesulphonyl, with an amine R^3NH_2 and thereafter, if present, removing the protecting group;

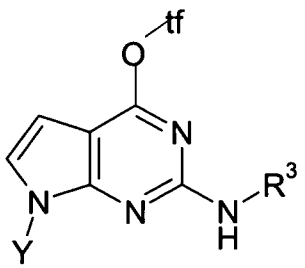
(ii) reacting a compound of formula (III):



(III)

with an amine R^1R^2NH;

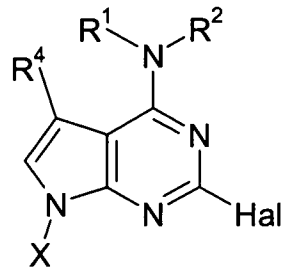
(iii) when R^4-H, reacting a compound of formula (IV):



(IV)

wherein Y is a protecting group such as triflate, with an amine HNR^1R^2 and thereafter removing the protecting group;

(iv) reacting a compound of formula (V):



(V)

wherein Hal is Cl or I, with an amine R^3NH_2 and thereafter removing the protecting group.

Certain embodiments of the present invention will now be illustrated by way of example only. The physical data given for the compounds exemplified is consistent with the assigned structure of those compounds.

EXAMPLES

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams);
l (liters);
µl (microliters);
M (molar);
MHz (megahertz);
mmol (millimoles);
min (minutes);
Rt (retention time);
MeOH (methanol);
TFA (trifluoroacetic acid);
THF (tetrahydrofuran);
DMSO (dimethylsulfoxide);
DCM (dichloromethane);
DMF (*N*,*N*-dimethylformamide);
IMS (Industrial methylated spirits);
Ac (acetyl);
TMS (trimethylsilyl);
DMAP (4-dimethylaminopyridine);
ATP (adenosine triphosphate);
DMEM (Dulbecco's modified Eagle medium);
HPLC (high pressure liquid chromatography);
TBAF (tetra-*n*-butylammonium fluoride);
HBTU (O-Benzotriazole-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluroniumhexafluoro phosphate).
HEPES (4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid);
DPPA (diphenylphosphoryl azide);

EDTA (ethylenediaminetetraacetic acid);
TMEDA (*N,N,N',N'*-tetramethyl-1,2-ethanediamine);
NBS (*N*-bromosuccinimide);
HATU (O-(7azabenzobenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate);
DIPEA (diisopropylethylamine);
dppf (1,1'-bis(diphenylphosphino)ferrocene);
NIS (*N*-iodsuccinimide);
PTFE ((poly)tetrafluoroethylene);
LC/MS (liquid chromatography – mass spectrometry);
mg (milligrams);
ml (milliliters);
psi (pounds per square inch);
mM (millimolar);
rt (room temperature);
h (hours);
IPA (isopropanol);
atm (atmosphere);
BSA (bovine serum albumin)
HRP (horseradish peroxidase);
MDAP (mass directed autoprep / preparative mass directed HPLC);
TBTU (*O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate)
PyBOP (Benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate)

All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted.

^{1}H NMR spectra were recorded using a Bruker DPX 400MHz, referenced to tetramethylsilane.
LC/MS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% HCO_2H and 0.01M ammonium acetate in water (solvent A) and 0.05% HCO_2H 5% water in acetonitrile (solvent B), using the following elution gradient 0.0-7min 0%B, 0.7-4.2min 100%B, 4.2-5.3min 0%B, 5.3-5.5min 0%B at a flow rate of 3ml/min. The mass spectra were recorded on a Fisons VG Platform

spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

"Mass directed autoprep" / "preparative mass directed HPLC" was conducted on a system such as; a Waters *FractionLynx* system comprising of a Waters 600 pump with extended pump heads, Waters 2700 autosampler, Waters 996 diode array and Gilson 202 fraction collector on a 10 cm 2.54 cm ID ABZ+ column, eluting with either 0.1% formic acid or trifluoroacetic acid in water (solvent A) and 0.1% formic or trifluoroacetic acid in acetonitrile (solvent B) using the appropriate elution gradient. Mass spectra were recored on Micromass ZMD mass spectrometer using electrospray positive and negative mode, alternate scans. The software used was *MassLynx* 3.5 with *OpenLynx* and *FractionLynx* optio or using equivalent alternative systems.

"Hydrophobic frits" refers to filtration tubes sold by Whatman. SPE (solid phase extraction) refers to the use of cartridges sold by International Sorbent Technology Ltd.

The Flashmaster II is an automated multi-user flash chromatography system, available from Argonaut Technologies Ltd, which utilises disposable, normal phase, SPE cartridges (2 g to 100 g). It provides quaternary on-line solvent mixing to enable gradient methods to be run. Samples are queued using the multi-functional open access software, which manages solvents, flow-rates, gradient profile and collection conditions. The system is equipped with a Knauer variable wavelength uv-detector and two Gilson FC204 fraction-collectors enabling automated peak cutting, collection and tracking.

Silica chromatography techniques include either automated (Flashmaster) techniques or manual chromatography on pre-packed cartridges (SPE) or manually-packed flash columns.

Microwave chemistry was typically performed in sealed vessels, irradiating with a suitable microwave reactor system, such as a Biotage Initiator™ Microwave Synthesiser.

When the name of a commercial supplier is given after the name of a compound or a reagent, for instance "compound X (Aldrich)" or "compound X / Aldrich", this means

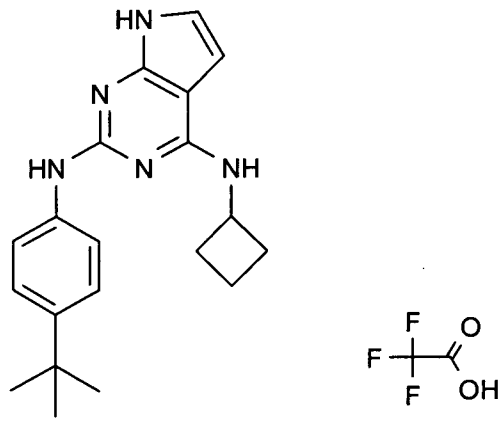
that compound X is obtainable from a commercial supplier, such as the commercial supplier named.

Similarly, when a literature or a patent reference is given after the name of a compound, for instance compound Y (EP 0 123 456), this means that the preparation of the compound is described in the named reference.

The names of the Examples have been obtained using the compound naming programme "ACD Name Pro 6.02".

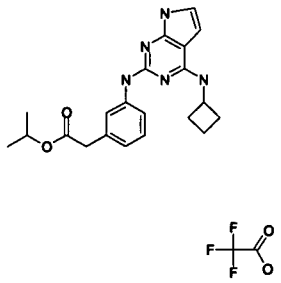
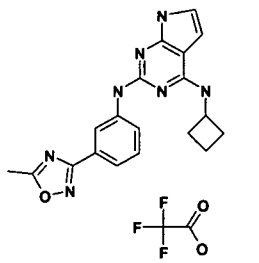
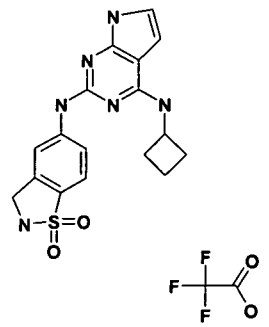
Example 1

N^4-cyclobutyl-N^2-[4-(1,1-dimethylethyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate



2-Chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (22.8mg) was suspended in IPA (2ml) and added to a microwaveable tube containing 4-*tert*-butylaniline (27.5mg, Aldrich). Aqueous hydrochloric acid (0.04ml) was added, the tube sealed and heated to 180°C by microwave irradiation for 150min. The reaction mixture was allowed to cool, applied directly to a SCX-2 cartridge (0.5g) that had been pre-conditioned with methanol. The column was washed with methanol (5ml) and the crude product was eluted with methanolic ammonia solution (2N, 2ml). The solution was evaporated to dryness, dissolved in DMSO (1ml) and purified by MDAP. The fractions containing product were evaporated to dryness to give N^4-cyclobutyl-N^2-[4-(1,1-dimethylethyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate (8.5mg). LC/MS; Rt 3.32min, MH^+ 336

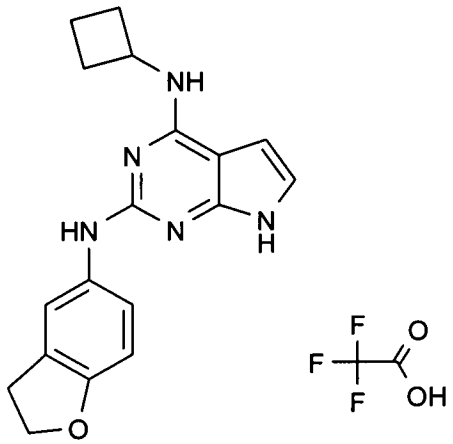
Similarly prepared were the following:

Example	Structure	Name	Amine Reagent / Source	LC/MS Rt (min)	LC/MS MH^+
2		1-methylethyl (3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)acetate trifluoroacetate*	methyl (3-aminophenyl)acetate* / DE2423536	3.10	380
3		N^4-cyclobutyl-N^2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amine / WO2004103998	3.10	362
4		N^4-cyclobutyl-N^2-(1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2,3-dihydro-1,2-benzisothiazol-5-amine 1,1-dioxide	2.69	371

*transesterification of methyl to isopropyl ester occurs during reaction in IPA.

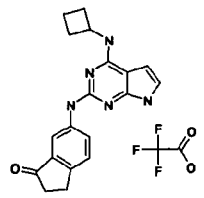
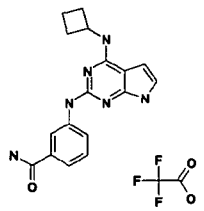
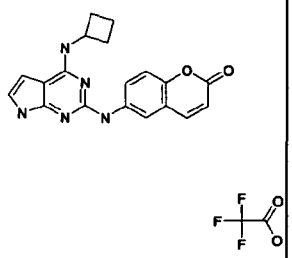
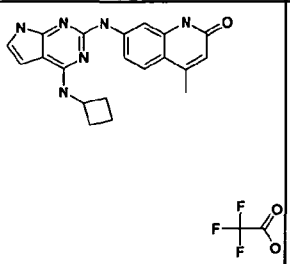
Example 5

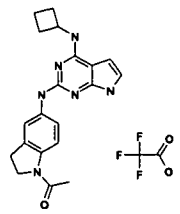
N^4-cyclobutyl-N^2-(2,3-dihydro-1-benzofuran-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate



2-Chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (22.8mg) was dissolved in DMF (0.5ml) and added to a microwaveable tube containing sodium t-butoxide (15mg). A solution of 2,3-dihydro-1-benzofuran-5-amine (20.3mg, Key Organics Limited/Bionet Research) in DMF (0.5ml) was added, followed by 2'-(dimethylamino)-2-biphenyl-palladium(II) chloride dinorbornylphosphine complex (10mg, Fluka). The tube was sealed and heated to 150°C by microwave irradiation for 60min. The reaction mixture was allowed to cool, evaporated to dryness, dissolved in methanol and applied to a SCX-2 cartridge (1g) that had been pre-conditioned with methanol. The column was washed with methanol (5ml) and the crude product was eluted with methanolic ammonia solution (2N, 2ml). The solution was evaporated to dryness, dissolved in DMSO and purified by MDAP. The fractions containing product were evaporated to dryness to give N^4-cyclobutyl-N^2-(2,3-dihydro-1-benzofuran-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate (0.05mg). LC/MS; Rt 2.76min, MH^+ 322

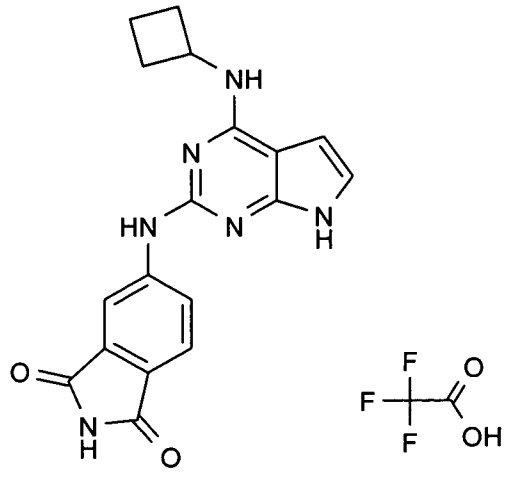
Similarly prepared were the following:

Example	Structure	Name	Amine Reagent / Source	LC/MS Rt (min)	LC/MS MH^+
6		6-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-2,3-dihydro-1*H*-inden-1-one trifluoroacetate	6-amino-2,3-dihydro-1*H*-inden-1-one / Journal of Medicinal Chemistry (2003), 46(3), 399-408	2.81	334
7		3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide trifluoroacetate	3-aminobenzamide / Aldrich	2.42	323
8		6-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-2*H*-chromen-2-one trifluoroacetate	6-amino-2*H*-chromen-2-one / J. Heterocyclic Chem, 23, 87 (1986)	2.83	348
9		7-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-4-methyl-2(1*H*)-quinolinone trifluoroacetate	7-amino-2-hydroxy-4-methylquinoline / Aldrich	2.86	361

10		N^2-(1-acetyl-2,3-dihydro-1*H*-indol-5-yl)-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	1-acetyl-5-amino-2,3-dihydro-(1H)-indole / Apollo Chem	2.62	363

Example 11

5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-1*H*-isoindole-1,3(2*H*)-dione trifluoroacetate



2-Chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (22.8mg), 4-aminophthalimide (49mg, Acros), cesium carbonate (65mg), bis(dibenzylideneacetone)palladium (6mg, Acros) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (6mg, Acros) were combined in a microwaveable tube with DMF (0.5ml). The tube was sealed and heated to 150°C by microwave irradiation for 30min. The reaction mixture was allowed to cool, then evaporated to dryness, dissolved in methanol and applied to a SCX-2 cartridge (1g) that had been pre-conditioned with methanol. The column was washed with methanol (5ml) and the crude product was eluted with methanolic ammonia solution (2N, 2ml). The solution was evaporated to dryness, dissolved in DMSO and purified by Mass Directed HPLC. The fractions containing product were evaporated to dryness to give 5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-1*H*-isoindole-1,3(2*H*)-dione trifluoroacetate (1.3mg). LC/MS; Rt 3.01min, MH^+ 349.

Similarly prepared were the following:

Example	Structure	Name	Amine Reagent/ Source	Reaction Time (minutes)	Isolation Method (a)	LC/MS R_t (min)	LC/MS MH^+
12		*N*⁴-cyclobutyl-*N*²-1*H*-indazol-5-yl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	5-Aminoindazole / Aldrich	30	(I)	2.64	320
13		*N*⁴-cyclobutyl-*N*²-(2-methyl-1*H*-benzimidazol-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	5-Amino-2-Methyl-Benzenimidazole / Avocado	30	(I)	2.15	334
14		*N*⁴-cyclobutyl-*N*²-1*H*-indazol-6-yl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	6-Aminoindazole / Aldrich	30	(I)	2.66	320

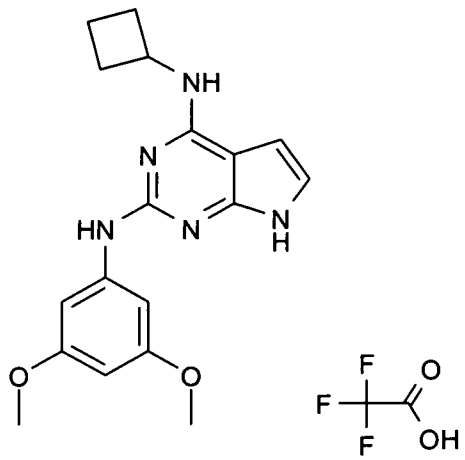
15		N^4-cyclobutyl-N^2-[4-(phenyloxy)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	4-Phenoxyaniline / Aldrich	20 (b)	(I)	3.40	372
16		4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide trifluoroacetate	4-Aminobenzamide / Aldrich	20 (b)	(I)	2.44	323
17		6-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-3,4-dihydro-1(2*H*)-naphthalenone trifluoroacetate	6-amino-3,4-dihydro-1(2*H*)-naphthalenone / Maybridge	30	(II)	3.15	348

18		N^4-cyclobutyl-N^2-{3-[(1-methylethyl)oxy]phenyl}-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	3-isopropoxy aniline / Maybridge	30	(II)	3.14	338

(a) Isolation Method: (I) SCX-2 then MDAP; (II) SCX-2 then MDAP. Compounds were then repurified, again by MDAP; (b) In these reactions only 1.5 equivalents of the amine reagent were used rather than the 3 equivalents described in the general procedure. 50mg of cesium carbonate was used rather than the 65mg described in the general procedure.

Example 19

N^2-[3,5-bis(methyloxy)phenyl]-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate



2-Chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (22.8mg), 3,5-dimethoxyaniline (46mg, Aldrich), cesium carbonate (65mg), bis(dibenzylideneacetone)palladium (6mg, Acros) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (6mg, Acros) were combined in a tube equipped with stirrer bar with DMF (1.0ml). The reaction mixture was heated to 110°C for 18h. The reaction was transferred to a microwaveable tube and bis(dibenzylideneacetone)palladium (6mg) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (6mg) were added. The tube was sealed and heated to 150°C by microwave irradiation for 60min. The reaction mixture was allowed to cool, then evaporated to dryness, dissolved in methanol and applied to a SCX-2 cartridge (1g) that had been pre-conditioned with methanol. The column was washed with methanol (5ml) and the crude product was eluted with methanolic ammonia solution (2N, 2ml). The solution was evaporated to dryness, dissolved in DMSO and purified by MDAP. The fractions containing product were evaporated to dryness to give

N^2-[3,5-bis(methyloxy)phenyl]-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate (3.5mg). LC/MS; Rt 2.99min, MH^+ 340.

Similarly prepared were the following:

5

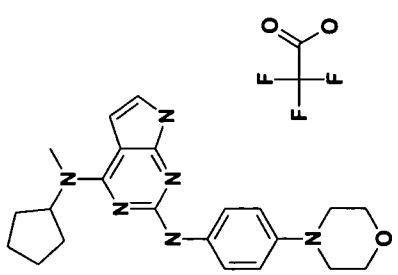
Example	Structure	Name	Pyrrolo[2,3-*d*]pyrimidine Starting Material	Amine Reagent / Source	Isolation Method (a)	LC/MS R_t (min)	LC/MS MH^+
20		N^4-cyclobutyl-N^2-[4-(1-methylethyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-Isopropylaniline / Aldrich	(I)	3.30	322
21		N^4-cyclobutyl-N^2-[4-(4-methyl-1-piperazinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-(4-Methylpiperazino)aniline / Apollo Chem	(I)	2.12	378

22		N^4-cyclobutyl-N^2-(4-cyclohexylphenyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-Cyclohexylaniline / Lancaster	(I)	3.80	362
23		N^4-cyclobutyl-N^2-(3-methylphenyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	m-Toluidine / Aldrich	(I)	3.05	294
24		N^4-cyclobutyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-Morpholinoaniline / Aldrich	(I)	2.64	365

25		3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzenesulfonamide trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	3-Aminobenzenesulfonamide / Avocado	(I)	2.55	359
26		N^4-cyclobutyl-N^2-{4-[(1-methylethyl)oxy]phenyl}-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-Isopropoxyaniline / TCI	(I)	3.02	338
27		N^4-cyclobutyl-N^2-6-quinolinyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	6-Aminoquinoline / Aldrich	(I)	2.64	331

28		*N*-(4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)-*N*-ethylacetamide trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	*N*-ethyl-*N*-[4-(methylamino)phenyl]acetamide / WO2004014382, WO2001009134	(I)	2.65	365
29		N^2-1,3-benzothiazol-6-yl-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1,3-benzothiazol-6-amine / Aldrich	(II)	2.86	337
30		N^4-cyclobutyl-N^2-(2-methyl-1,3-benzothiazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	2-methyl-1,3-benzothiazol-6-amine / ASDI Product	(II)	2.96	351

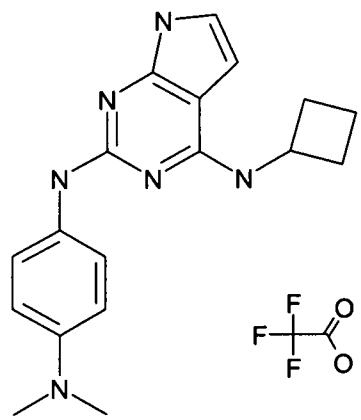
		trifluoroacetate		list			
31		N^4-(cyclobutylmethyl)-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	4-chloro-*N*-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine	(cyclobutylmethyl)amine / MicroChemistry Building Blocks	(I)	2.46	378.9
32		N^4-cyclopentyl-N^4-methyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	4-chloro-*N*-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine	N-methylcyclopentanamine hydrochloride / free base	(I)	2.65	392.8

			available from ASDI product List		
					

(a) Isolation Method: (I) SCX-2 then MDAP. (II) SCX-2 then MDAP. Compounds were then repurified, again by MDAP.

Example 33

N^4-cyclobutyl-N^2-[4-(dimethylamino)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate



2-Chloro-*N*-cyclobutyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (38mg) was was suspended in IPA (1.0ml) and treated with *N,N*-dimethyl-p-phenylenediamine (20.4mg, Aldrich) and hydrogen chloride in dioxane (4N, 30µl). The tube was sealed and heated by microwave irradiation to 170°C for 1h then at 180°C for 1h then allowed to cool to room temperature. The reaction mixture was evaporated to dryness and purified by MDAP. The product was deprotected by treating with dioxane (1ml) / sodium hydroxide solution (10M, 1ml) and heating to 80°C for 18h before partitioning between ethyl acetate and water. The organics were evaporated to dryness and purified by MDAP. The fractions containing product were evaporated to dryness to give N^4-cyclobutyl-N^2-[4-(dimethylamino)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate (9.2mg). LC/MS; Rt 2.38min, MH^+ 323.

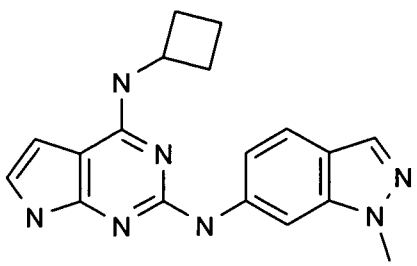
Similarly prepared were the following:

Example	Structure	Name	Starting Material	Amine Reagent/ Source	LC/MS MH^+	LC/MS Rt (min)
34		N^2-1*H*-1,2,3-benzotriazol-5-yl-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	5-Aminobenzotriazole / Lancaster	321	2.48
35		5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-1,3-dihydro-2*H*-benzimidazol-2-one trifluoroacetate	2-chloro-*N*-cyclobutyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	5-Aminobenzimidazolone / Fluorochem	336	2.28

36		*N*⁴-cyclobutyl-*N*²-[4-(1*H*-tetrazol-5-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-(1*H*-Tetrazol-5-yl)aniline / Butt Park	348	2.75
37		*N*⁴-cyclobutyl-*N*²-(2-methyl-1,3-benzothiazol-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	5-Amino-2-methylbenzothiazole / Avocado	351	2.85

Example 38

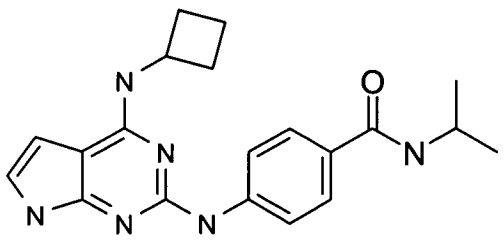
N^4-cyclobutyl-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



A mixture of 2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (50mg), 1-methyl-1*H*-indazol-6-ylamine (50mg, Fluorochem), bis(dibenzylideneacetone) palladium (0) (21mg), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (13mg) and cesium carbonate (110mg) in DMF (1ml) was heated in a sealed tube by microwave irradiation at 120°C for 30min. The mixture was reacted for a 120°C for a further 1h. Bis(dibenzylideneacetone) palladium (0) (10mg) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (7mg) were added to the reaction mixture which was heated at 150°C for 30min. The solvent was evaporated under vacuum. The residue was dissolved in methanol (0.5ml) and applied to an SCX-2 cartridge (1g) and the product eluted with methanol. The solution was evaporated, partially purified by MDAP and the impure product adsorbed onto Florisil and further purified by column chromatography on a silica cartridge (5g) eluting with a DCM / methanol gradient (0-25%) to give N^4-cyclobutyl-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2, 4-diamine (3mg) as a clear residue. LC/MS; Rt 2.7min, MH^+ 334.

Example 39

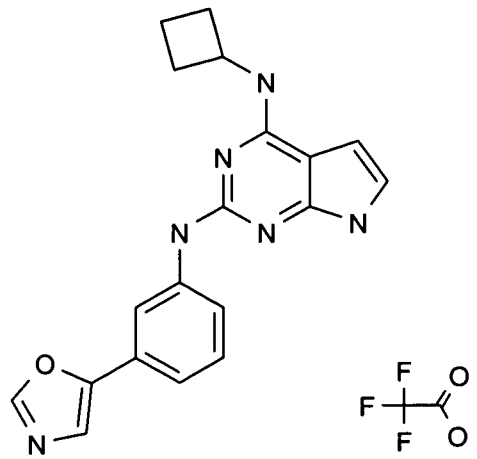
4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(1-methylethyl)benzamide



A mixture of 2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (120mg), 4-amino-*N*-(1-methylethyl)benzamide (144mg, Buttpark), bis(dibenzylideneacetone) palladium (0) (15.5mg), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (10.6mg) and cesium carbonate (263.2mg) in DMF (2ml) was heated in a sealed tube by microwave irradiation at 150°C for 30min. Further bis(dibenzylideneacetone) palladium (0) (7mg) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (5mg) was added to the reaction mixture and heating at 150°C continued for 30min. The reaction mixture was concentrated under vacuum and the residue suspended in methanol. The suspension was filtered through a pad of Celite and the solvent evaporated. The crude material was partitioned between ethyl acetate (50ml) and brine (50ml). The organic layer was evaporated and purified by chromatography on a silica cartridge (70g) eluting with an ethyl acetate / cyclohexane gradient (0-100%) to give, after evaporation of the solvents, 4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(1-methylethyl)benzamide as a brown gum (22.6mg). LC/MS; Rt 2.7min, MH^+ 365.

Example 40

N^4-cyclobutyl-N^2-[3-(1,3-oxazol-5-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate



2-Chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (22.8mg), [3-(1,3-oxazol-5-yl)phenyl]amine (48mg, Maybridge), cesium carbonate (65mg), bis(dibenzylideneacetone)palladium (10mg, Acros) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (10mg, Acros) were combined in a microwaveable tube with DMF (1.3ml). The tube was sealed and heated to 150°C by microwave irradiation at a normal absorption setting for 45min. The reaction mixture was concentrated and dissolved in water and extracted with DCM. The organic phase was separated, evaporated to dryness, the residue dissolved in DMSO and purified by MDAP. The fractions containing product were evaporated to dryness to give N^4-cyclobutyl-N^2-[3-(1,3-oxazol-5-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate (1.8mg). LC/MS; Rt 3.01min, MH^+ 346.89.

Similarly prepared were the following:

Example	Structure	Name	Starting Material	Amine Reagent/ Source	Isolation (a)	Reaction Time (min)	LC/MS MH^+	LC/MS Rt (min)
41		N^2-[3,4-bis(methyloxy)phenyl]-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	[3,4-bis(methyloxy)phenyl]amine / Aldrich	(II)	45	339.9	2.5
42		4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-aminobenzamide / Aldrich	(I)	45	323	2.34

43		N^4-cyclobutyl-N^2-3-pyridinyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	3-pyridinamine / Aldrich	(I)	90	280.9	2.17
44		*N*-(4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)-*N*-methylacetamide trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	*N*-(4-aminophenyl)-*N*-methylacetamide / Aldrich	(I)	45	350.9	2.43

45		N^4-cyclobutyl-N^2-4-pyridinyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-pyridinamine / Aldrich	(I)	90	280.9	2.19
46		3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenol trifluoroacetate (salt)	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	3-aminophenol / Aldrich	(II)	45	295.9	2.46
47		4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*,*N*-diethylbenzamide	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-amino-*N*,*N*-diethylbenzamide / MicroChemistry Building	(I)	90	379	2.75

		trifluoroacetate		Blocks				
48		N^4-cyclobutyl-N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amine / Maybridge	(I)	90	370	2.60
49		4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-methylbenzamide trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-amino-*N*-methylbenzamide / Park Research	(I)	90	337	2.51

50		ethyl 4-(4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)-1-piperazinecarboxylate trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	ethyl 4-(4-aminophenyl)-1-piperazinecarboxylate / Key Organics	(II)	90	435.8	2.83
51		N^4-cyclobutyl-N^2-(3,5-dimethylphenyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	(3,5-dimethylphenyl)amine / Aldrich	(I)	90	308	3.26

52		N^2-[3-chloro-4-(methyloxy)phenyl]-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	[3-chloro-4-(methyloxy)phenyl]amine / Aldrich	(II)	90	343.8	3
53		N^4-cyclobutyl-N^2-(4-methylphenyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	(4-methylphenyl)amine / Aldrich	(I)	90	294	3.05

54		N^4-cyclobutyl-N^2-{3-[(phenylmethyl)oxy]phenyl}-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	{3-[(phenylmethyl)oxy]phenyl}amine / Aldrich	(I)	90	386	3.49

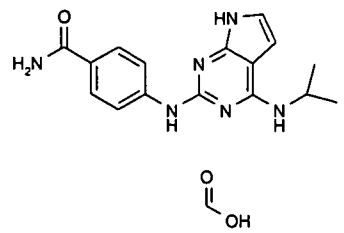
(a) Isolation Method:

(I) MDAP.

(II) MDAP. Compounds were then repurified by MDAP.

Example 55

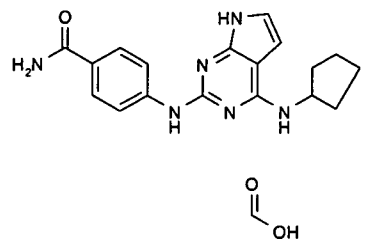
4-({4-[(1-Methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide formate



To a solution of 2-{[4-(aminocarbonyl)phenyl]amino}-7-[(trifluoromethyl)sulfonyl] -7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl trifluoromethanesulfonate (0.024g) in dioxane (1.5ml) was added potassium carbonate (15mg) and isopropylamine (0.005g). The suspension was heated in a sealed vial at 80°C by microwave irradiation for 10min. The mixture was treated with aqueous sodium hydroxide (2M, 0.75ml) and stirred vigorously for 4h. The mixture was treated with aqueous hydrochloric acid (2M, 0.75ml) and applied to a SCX-2 cartridge (10g, pre-conditioned with methanol). The cartridge was washed with methanol and eluted with 10% ammonia in methanol. The basic fractions were concentrated *in vacuo* and the residue purified by MDAP to give 4-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide formate as a white solid (0.010g). LC/MS: Rt 2.37min, MH^+ 311.

Example 56

4-{[4-(cyclopentylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide formate

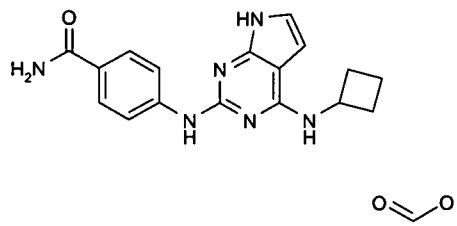


To a solution of 2-{[4-(aminocarbonyl)phenyl]amino}-7-[(trifluoromethyl)sulfonyl] -7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl trifluoromethanesulfonate (0.024g) in dioxane (1.5ml) was added potassium carbonate (15mg) and cyclobutanol (0.010g). The suspension was heated in a sealed vial at 80°C for 10min by microwave irradiation. The suspension was further heated to 120°C for 30min.

To the suspension was added cyclopentylamine (0.008g, Aldrich) and the mixture heated in a sealed vial at 80°C for 10min by microwave irradiation. The mixture was treated with aqueous sodium hydroxide (2M, 0.75ml) and stirred vigorously for 2.5h. The mixture was treated with aqueous hydrochloric acid (2M, 0.75ml) and applied to a SCX-2 cartridge (10g, pre-washed with methanol). The cartridge was washed with methanol and eluted with 10% ammonia in methanol. The basic fractions were concentrated *in vacuo* and the residue purified by MDAP to give 4-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide formate as a white solid (0.006g). LC/MS; Rt 2.59min, MH^+ 337.

Example 57

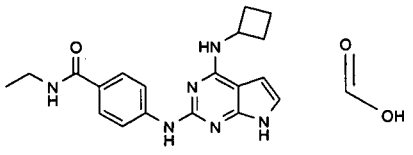
4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide formate



To a solution of 2-{[4-(aminocarbonyl)phenyl]amino}-7-[(trifluoromethyl)sulfonyl] -7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl trifluoromethanesulfonate (0.206g) in dioxane (4ml) was added potassium carbonate (80mg) and cyclobutylamine (0.048g, Aldrich). The suspension was heated to 70°C for 1h. The mixture was treated with aqueous sodium hydroxide (10M, 1ml) and stirred vigorously for 2.25h. The mixture was treated with aqueous hydrochloric acid (5M, 2ml) and applied to SCX-2 ion exchange cartridges (20g x2, pre-washed with methanol). The cartridges were washed with methanol and eluted with 10% ammonia in methanol. The basic fractions were concentrated *in vacuo* and the residue purified by chromatography on a silica cartridge (20g) eluting with 0-25% methanol in DCM with 1% triethylamine to give 4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide (0.0070g) as a yellow solid. The free base was dissolved in methanol (4ml) and acetonitrile (1ml). The solution was treated with formic acid (16mg). The solvent was removed *in vacuo* to give 4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino} benzamide formate as a yellow solid (0.0072g). LC/MS; Rt 2.32min, MH^+ 323.

Example 58

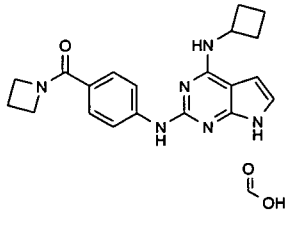
4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-ethylbenzamide formate



To a mixture of 2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.120g), cesium carbonate (0.350g), bis(dibenzylideneacetone) palladium (0.024g), 2-dicyclohexylphosphino-2'-(*N,N*-dimethyl-amino)biphenyl (0.016g) and 4-amino-*N*-ethylbenzamide (0.140g, Journal of Medicinal Chemistry (1984), 27(6), 779-82.) was added DMF (2ml). The mixture was heated in a sealed vial at 150°C for 15min by microwave irradiation. Further amounts of bis(dibenzylideneacetone) palladium (0.008g) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (0.005g) were added to the mixture and the reaction heated in a sealed vial at 150°C for 15min by microwave irradiation. The mixture was filtered through Celite and the residue washed with methanol. The filtrate was concentrated *in vacuo* and the residue purified by chromatography on a silica cartridge (50g) eluting sequentially with cyclohexane, cyclohexane / ethyl acetate (1:1) and ethyl acetate, to give, after evaporation of the solvents from appropriate fractions, a brown solid. The crude was further purified by MDAP to give 4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl] amino}-*N*-ethylbenzamide formate as a pale yellow gum (0.005g). LC/MS; Rt 2.64min, MH^+ 351.

Example 59

N^2-[4-(1-azetidinylcarbonyl)phenyl]-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine formate

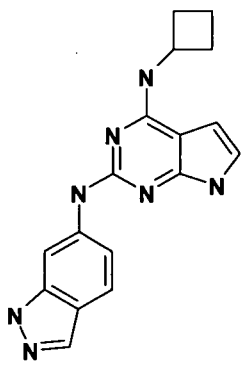


To a mixture of 2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.120g), cesium carbonate (0.350g), bis(dibenzylideneacetone) palladium (0.024g),

2-dicyclohexylphosphino-2'-(*N,N*-dimethyl-amino)biphenyl (0.016g) and 4-(1-azetidinylcarbonyl)aniline (0.140g) was added DMF (2ml). The mixture was heated in a sealed vial at 150°C for 15min by microwave irradiation. Further amounts of bis(dibenzylideneacetone) palladium (0.008g) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethyl-amino)biphenyl (0.005g) were added to the mixture and the reaction heated in a sealed vial at 150°C for 15min by microwave irradiation. The mixture was filtered through Celite and the residue washed with methanol. The filtrate was concentrated *in vacuo* and the residue purified by chromatography on a silica cartridge (50g) eluting sequentially with cyclohexane, cyclohexane / ethyl acetate (1:1), ethyl acetate and 10% methanol in ethyl acetate. Evaporation of the solvents from appropriate fractions left a yellow gum which was further purified by MDAP to give 4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-ethylbenzamide formate as a pale grey solid (0.016g). LC/MS; Rt 2.58min, MH^+ 363.

Example 60

N^4-cyclobutyl-N^2-1*H*-indazol-6-yl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



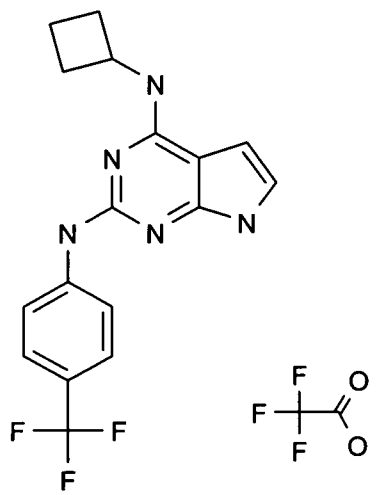
A mixture of 2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (111mg), cesium carbonate (325mg), tris(dibenzylideneacetone)bipalladium (50mg), 2-dicyclohexylphosphino-2'-(*N,N*-dimethyl-amino)biphenyl (50mg) and 1-[(4-methylphenyl)sulfonyl]-1*H*-indazol-6-amine (430mg) in DMF (4ml) was heated by microwave in a sealed vial at 150°C for 45min. The reaction was diluted with methanol and filtered through an aminopropyl SPE (10g), washing with methanol and ethyl acetate. The combined filtrate and washings were applied to a SCX-2 SPE (10g), the column washed with methanol / ethyl acetate and the product fraction eluted with methanol / 0.880 ammonia. The solvents were evaporated *in vacuo*, the

residue adsorbed onto silica and applied to a silica cartridge (10g). The cartridge was eluted with an ethyl acetate / cyclohexane gradient (12-100%) and the product fractions combined and reduced to dryness *in vacuo*. The residue was further purified using MDAP, and the solvents evaporated from the product fractions.

This material was dissolved in sodium methoxide solution (0.5M in methanol, 2ml) and heated at reflux for 2.5h. The reaction was quenched with water and the methanol evaporated *in vacuo*. The aqueous was extracted with chloroform, the extract washed with water, dried (hydrophobic frit) and reduced to dryness under vacuum. The residue was further purified by MDAP, the product fractions reduced to dryness *in vacuo*, and the residue converted to the free base by dissolution in methanol and filtration through an aminopropyl SPE (2g). Evaporation of the solvent gave N^4-cyclobutyl-N^2-1*H*-indazol-6-yl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine as a white solid (11.9mg). LC/MS; Rt 2.73min, MH^+ 320.

Example 61

N^4-cyclobutyl-N^2-[4-(trifluoromethyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate

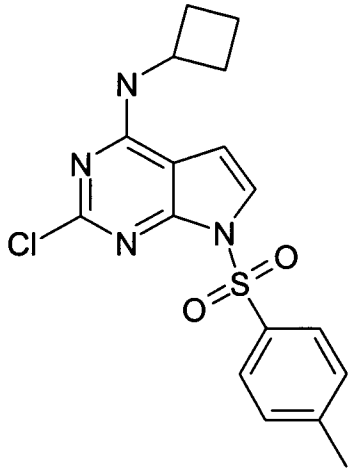


2-Chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (22.8mg) [4-(trifluoromethyl)phenyl]amine (48mg, Aldrich), cesium carbonate (65mg), bis(dibenzylideneacetone)palladium (10mg) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (8mg) were combined in a microwaveable tube with DMF (1.3ml). Nitrogen was allowed to bubble through the

suspension for 2min. The tube was sealed and heated at 150°C by microwave irradiation for 90min. The reaction mixture was concentrated, redissolved in water (2ml) and extracted with DCM (2ml). The organic phase was separated, evaporated to dryness, dissolved in DMSO and purified by MDAP. The fractions containing product were evaporated to dryness to N^4-cyclobutyl-N^2-[4-(trifluoromethyl)phenyl]-1*H*-pyrrolo [2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate (3.6mg). LC/MS; Rt 3.55min, MH^+ 348.

Intermediate 1

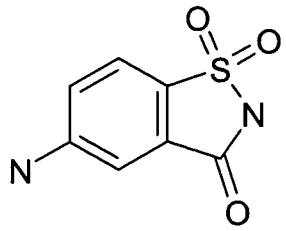
2-chloro-*N*-cyclobutyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



2-Chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (1.5g) was dissolved in DMF (30ml) under an inert atmosphere of nitrogen and the solution was cooled to 0°C. Sodium hydride (380mg, 60% in mineral oil) was added and the solution was stirred for 15min before treating with p-toluene sulphonyl chloride (2.2g, Aldrich). The solution was allowed to warm to room temperature over 2h before partitioning between DCM and saturated aqueous ammonium chloride solution. The organics were separated and dried (magnesium sulphate), concentrated *in vacuo* and purified by chromatography, eluting with a gradient of ethyl acetate in cyclohexane (0-100%) to give the title compound as an orange oil (1.5g). LC/MS; Rt 3.86, MH^+ 376.9

Intermediate 2

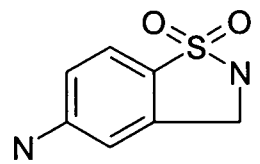
5-amino-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide



A vigorously stirred solution of 5-nitro-1,2-benzisothiazol-3(2*H*)-one-1,1-dioxide (1.99g, Journal of Heterocyclic Chemistry 1986, 23(4), 1253-5) in ethanol (80ml) was hydrogenated at room temperature and 1atm. of pressure using palladium on carbon catalyst (400mg) for 2 days. The mixture was filtered and the solvent was evaporated *in vacuo* before the residue was re-dissolved in ethanol (80ml) and was hydrogenated at room temperature and 1atm. of pressure using palladium on carbon catalyst (400mg) for a further one day. The mixture was filtered and the solvent was evaporated *in vacuo*, the residue was dissolved in methanol and adsorbed onto silica. The resulting solid was aplied to a silica cartridge (50g) and the cartridge eluted with a (1% triethylamine in methanol) / DCM gradient (0-15%). The required fractions were combined and the solvent was evaporated *in vacuo* to give 5-amino-1,2-benzisothiazol-3(2H)-one 1,1-dioxide as a brown oil (603mg). LC/MS; Rt 1.68min, $[M-H]^-$197.

Intermediate 3

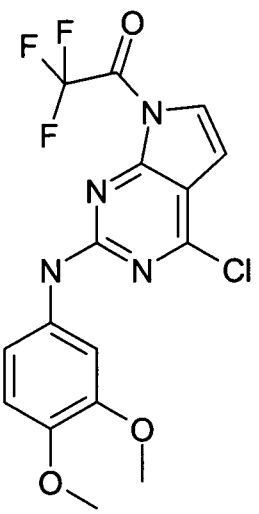
2,3-dihydro-1,2-benzisothiazol-5-amine-1,1-dioxide



Zinc dust (2.4g) was added portionwise to a stirred suspension of 5-amino-1,2-benzisothiazol-3(2*H*)-one-1,1-dioxide (820mg) in concentrated hydrochloric acid (10ml). The mixture was stirred at room temperature for 20h before saturated aqueous sodium hydrogen carbonate solution was added to the mixture until the pH of the solution was 8. The mixture was filtered and extracted with ethyl acetate (4x 150ml). The combined organic phases were dried (magnesium sulphate), filtered and the solvents evaporated *in vacuo* to give 2,3-dihydro-1,2-benzisothiazol-5-amine-1,1-dioxide as a yellow solid (230mg). LC/MS; Rt 0.82min, MH^+ 185.

Intermediate 4

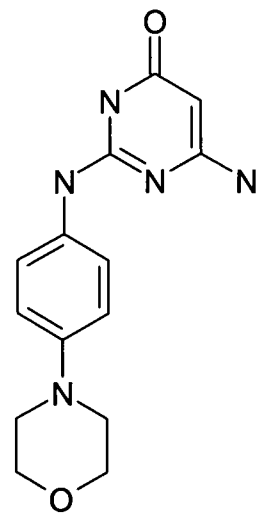
***N*-[3,4-bis(methyloxy)phenyl]-4-chloro-7-(trifluoroacetyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine**



N-[3,4-Bis(methyloxy)phenyl]-4-chloro-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (91.2mg) was suspended in chloroform (3ml) and treated with trifluoroacetic anhydride (186mg) and pyridine (100µl). The reaction was stirred at room temperature for 4h; the reaction was treated with trifluoroacetic anhydride (62mg) and stirred at room temperature for 16h. The reaction was washed with water (5ml) and the organic layer separated and the aqueous extracted with chloroform (3ml). The organic layer was separated and the combined organics concentrated. The crude was taken up in methanol (2ml) from which solid crashed out and was isolated by filtration and dried to give *N*-[3,4-bis(methyloxy)phenyl]-4-chloro-7-(trifluoroacetyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (42.5mg). LC/MS; Rt 3.17min, MH^+ 401.

Intermediate 5

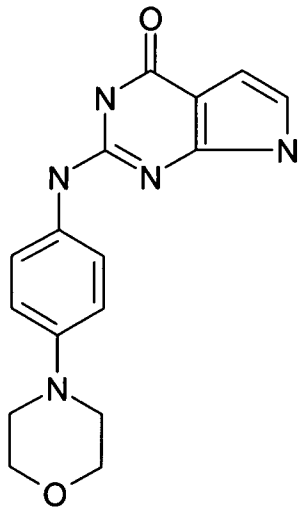
6-amino-2-{[4-(4-morpholinyl)phenyl]amino}-4(1*H*)-pyrimidinone



6-Amino-2-(methylthio)-4(1*H*)-pyrimidinone (3.0g, Pfaltz and Bauer Chemicals catalogue) and 4-morpholinoaniline (3.40g, Aldrich) were thoroughly pre-mixed then heated with vigorous stirring at 190°C under nitrogen for 3h. The resulting red-brown solid was allowed to cool to room temperature then triturated with methanol / water (65ml, 1:1) to give a powder which was collected by filtration *in vacuo* to give 6-amino-2-{[4-(4-morpholinyl)phenyl]amino}-4(1*H*)
-pyrimidinone as a grey-mauve solid (3.87g). LC/MS; Rt 2.1min, MH^+ 288.

Intermediate 6

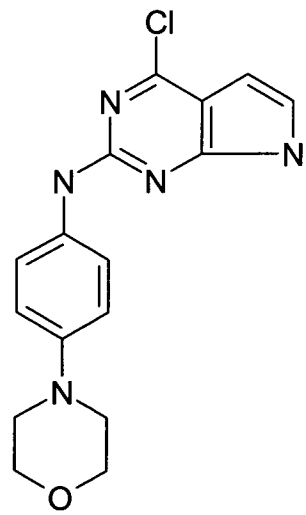
2-{[4-(4-morpholinyl)phenyl]amino}-1,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one



A mixture of 6-amino-2-{[4-(4-morpholinyl)phenyl]amino}-4(1*H*)-pyrimidinone (3.87g) in IPA / water (4:1, 42.5ml) was treated with sodium acetate (2.43g) then a 50% w/w aqueous solution of chloroacetaldehyde (2.22ml). The mixture was heated at 80°C for 30min. then allowed to cool to room temperature and concentrated *in vacuo*. Trituration with water (100ml) and filtration *in vacuo* gave a grey-mauve solid (4.13g). 1.75g of this solid was adsorbed onto Florisil and purified by chromatography on silica cartridges (2x 70g) eluting with a methanol / DCM gradient (0-15%) + 1% triethylamine over 60min. The appropriate fractions were combined and concentrated to give 2-{[4-(4-morpholinyl)phenyl]amino}-1,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one as a cream-pink solid (0.88g). LC/MS; Rt 2.4min, MH^+ 312.

Intermediate 7

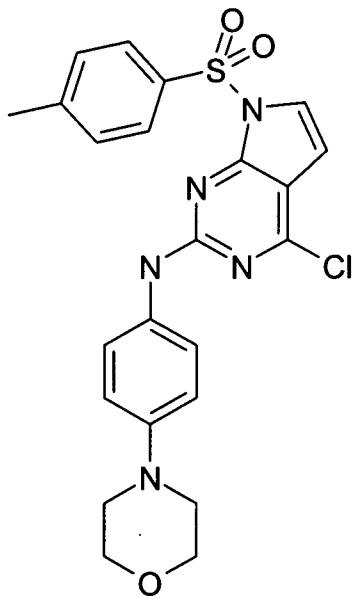
4-chloro-*N*-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine



A vigorously stirring slurry of 2-{[4-(4-morpholinyl)phenyl]amino}-1,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (0.86g) in phosphorus oxychloride (4ml) was heated in an oil bath set to 120°C for 1h. The reaction was then allowed to cool to room temperature, concentrated *in vacuo* and azeotroped with toluene. The residue was adsorbed onto Florisil and purified by chromatography on a silica cartridge (100g), eluting with a methanol / DCM gradient (0-15%) + 1% triethylamine over 40min. The appropriate fractions were combined and concentrated *in vacuo* to give 4-chloro-*N*-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine as a pale-yellow/cream solid (0.52g). LC/MS; Rt 3.1min MH^+ 330, 332.

Intermediate 8

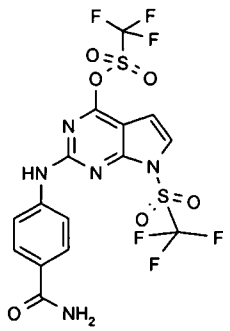
4-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-[4-(4-morpholinyl)phenyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine



4-Chloro-*N*-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (578mg) was suspended in DMF (12ml) and stirred at 5°C for 10mins. Sodium hydride (60% in mineral oil, 59mg) was added and the reaction stirred at 5°C for a further 5mins. Tosyl chloride (400mg) was added and the reaction allowed to warm to room temperature with stirring over 20mins. The reaction was poured onto aqueous ammonium chloride solution (50ml), diluted with water (50ml), extracted with chloroform (100ml) and DCM (100ml). The combined organics were dried (magnesium sulphate) and concentrated to a brown oil. The oil was purified by chromatography on a silica cartridge (20g), eluting with a methanol / DCM gradient (0-25%) over 30mins. The fractions were containing product were concentrated and the residue recrystallised from methanol to give 4-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-[4-(4-morpholinyl)phenyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (372mg). LC/MS; Rt 3.75min, MH^+ 484, 486.

Intermediate 9

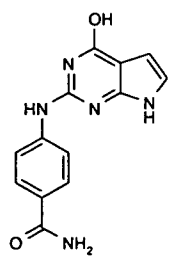
2-{[4-(Aminocarbonyl)phenyl]amino}-7-[(trifluoromethyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl trifluoromethanesulfonate



To a suspension of 4-[(4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino] benzamide (0.077g) in DMF (3ml) was added potassium carbonate (0.097g) and N-phenyltrifluoromethanesuphonamide (0.25g). The suspension was stirred at 20°C for 1.5h. A further amount of *N*-phenyltrifluoromethanesuphonamide (0.064g) and potassium carbonate (0.024g) was added to the mixture and stirred at 20°C for 3.5h. The mixture was partitioned between ethyl acetate (30ml) and water (20ml). The phases were separated and the organic phase washed with water (2x 15ml). The combined aqueous washings were extracted with ethyl acetate (20ml) and the second ethyl acetate extract washed with water (10ml). The combined organic extracts were dried (magnesium sulphate), filtered and the solvent removed *in vacuo*. The residue was adsorbed onto silica and purified by chromatography on a silica cartridge (20g), eluting with an ethyl acetate / cyclohexane gradient (0-100%) over 30min to give, after evaporation of the solvent from appropriate fractions, 2-{[4-(aminocarbonyl)phenyl]amino}-7-[(trifluoromethyl)sulfonyl] -7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl trifluoromethanesulfonate (0.050g). LC/MS: Rt 3.50min, MH^+ 534.

Intermediate 10

4-[(4-Oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino]benzamide

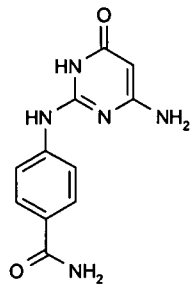


To a suspension of 4-[(4-amino-6-oxo-1,6-dihydro-2-pyrimidinyl)amino]benzamide (0.325g) in IPA (3ml) and water (1ml) was added sodium acetate (0.240g). To the

mixture was added chloroacetaldehyde (0.22ml, 50% in water). The suspension was heated to 80°C for 20min. The mixture, at room temperature, was diluted with water (30ml) and the resulting suspension stirred for 15min. The suspension was filtered and the residue washed with water (10ml). The crude was further purified by chromatography on a silica cartridge (50g), eluting with a methanol / DCM gradient (0-30%) + 1% triethylamine to give, after evaporation of the solvents from appropriate fractions, 4-[(4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl) amino]benzamide (0.132g) as a white solid. LC/MS: Rt 2.1min, MH^+ 270.

Intermediate 11

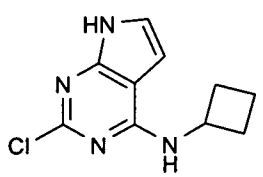
4-[(4-Amino-6-oxo-1,6-dihydro-2-pyrimidinyl)amino]benzamide



A mixture of 6-amino-2-(methylthio)-4(1*H*)-pyrimidinone (1.023g, Salor) and 4-aminobenzamide (1.0g, Acros) was shaken at room temperature and then stirred at 190°C for 26h. The residue was adsorbed onto silica using DCM / methanol (1:1, 100ml). The crude product was purified by chromatography on a silica cartridge (100g), eluting with a methanol / DCM gradient (0-25%) and then with 50% methanol / DCM with 1% triethylamine. Evaporation of the solvent from appropriate fractions gave 4-[(4-amino-6-oxo-1,6-dihydro-2-pyrimidinyl)amino]benzamide (0.340g) as a yellow solid. LC/MS: Rt 1.8min, MH^+ 246.

Intermediate 12

2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

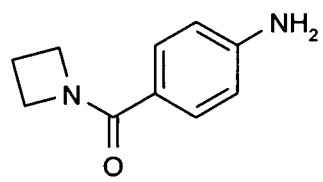


To a suspension of 2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (2.0g, Pharm Lab Product List) in IPA (10ml) was added cyclobutylamine (1.4ml). The mixture was

heated in a sealed vial at 100°C by microwave irradiation for 30mins. A further portion of cyclobutylamine (1ml) was added to the mixture and heated in a sealed vial at 100°C by microwave irradiation for 30mins. The mixture was partitioned between ethyl acetate (250ml) and saturated aqueous sodium hydrogen carbonate (75ml). The phases were separated and the organic phase washed with saturated sodium hydrogen carbonate (2x 75ml), dried (magnesium sulphate) and filtered. The solvent was removed *in vacuo* to give 2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (2.34g) as a pale brown solid. LC/MS; Rt 2.85min, MH^+ 223.

Intermediate 13

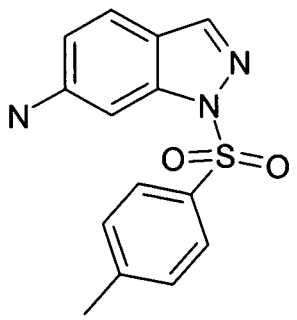
4-(1-azetidinylcarbonyl)aniline



To a slight suspension of 4-aminobenzoic acid (0.4g, Aldrich) in DMF (5ml) was added 1-hydroxybenzotriazole (0.410g) and dicyclohexylcarbodiimide (0.61g). The mixture was stirred at 20°C for 5min and then treated with azetadine (0.171g). The suspension was stirred overnight. The suspension was filtered and the residue washed with DMF (2-3ml). The filtrate was applied to a SCX-2 cartridge (50g, pre-washed with methanol). The cartridge was washed with methanol and eluted with 10% ammonia in methanol. The basic fractions were concentrated *in vacuo* and then applied to an aminopropyl cartridge (20g, pre-washed with methanol). The cartridge was washed with methanol and the methanol fractions concentrated *in vacuo* to give 4-(1-azetidinylcarbonyl)aniline (0.479g). LC/MS; Rt 1.83min, MH^+ 177.

Intermediate 14

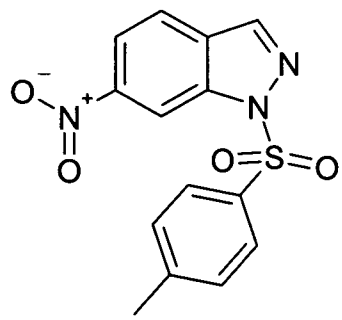
1-[(4-methylphenyl)sulfonyl]-1*H*-indazol-6-amine



1-[(4-methylphenyl)sulfonyl]-6-nitro-1*H*-indazole (5.3g) in ethanol (~200ml) was hydrogenated over palladium on carbon (10%, wet, 0.53g) for 4h under 1atm. of hydrogen. A further portion of palladium on carbon (10%, wet, 0.53g) was added to the reaction and hydrogenation continued for 72h. The reaction was filtered through Celite, and the residue washed with ethanol, ethyl acetate and DMF. The combined filtrate and washings were reduced to dryness under vacuum, the residue dissolved in methanol / ethyl acetate and applied to a SCX-2 SPE (70g). The cartridge was washed with methanol and ethyl acetate and the product eluted with methanol / ethyl acetate / 0.880 ammonia. The product fraction was reduced to dryness under vacuum, the residue dissolved in ethyl acetate and filtered through a silica cartridge (10g) washing with ethyl acetate. The solvent was evaporated from the combined filtrate / washings *in vacuo* and the residue triturated with ether to give 1-[(4-methylphenyl)sulfonyl]-1*H*-indazol-6-amine as a beige solid (4.0g). LC/MS; Rt 3.06min, MH^+ 288.

Intermediate 15

1-[(4-methylphenyl)sulfonyl]-6-nitro-1*H*-indazole

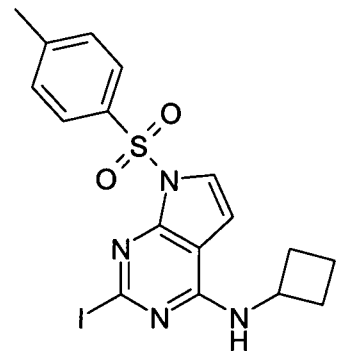


Sodium hydride (0.8g, 60% in mineral oil) was added in portions to a solution of 6-nitroindazole (3.26g, Aldrich) in DMF (80ml). Tosyl chloride (3.82g, Aldrich) was added to the reaction and the mixture stirred at room temperature for 1h. The reaction was diluted with water and the precipitate filtered off, washed with water and

dried at 50°C under vacuum to give 1-[(4-methylphenyl)sulfonyl]-6-nitro-1*H*-indazole as a beige solid (5.3g). LC/MS; Rt 3.50min, MH^+ 318.

Intermediate 16

5 *N*-cyclobutyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

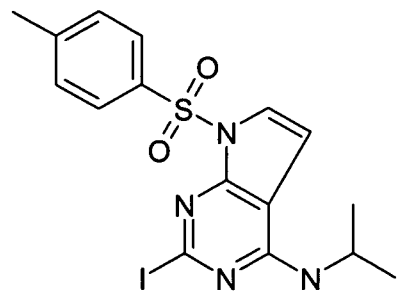


4-Chloro-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (3.0g) was
10 suspended in ethanol (65ml) and treated with cyclobutylamine (1.0ml, Aldrich) and diisopropylethlamine (1.6ml). The mixture was heated to 80°C for 2h, allowed to cool and evaporated to dryness. The residue was partitioned between DCM and water and the organic layer reduced to dryness *in vacuo* to give the title compound (3.2g). LC/MS; Rt 4.04min, MH^+ 468.89.

15

Intermediate 17

2-Iodo-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

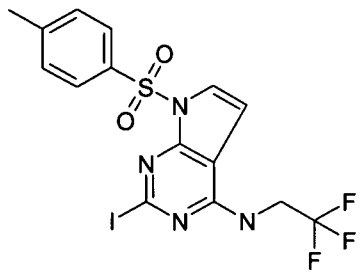


20 4-Chloro-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.3g) was suspended in ethanol (20ml) and treated with isopropylamine (360mg, Aldrich) and DIPEA (10mmol) and the mixture was heated at 80°C for 3h. The reaction was reduced to dryness and the residue purified by chromatography on a silica cartridge,

eluting with an ethyl acetate / DCM gradient (0-100%). Combination of the appropriate fractions and evaporation of the solvents gave the title compound (950mg). LC/MS; Rt 3.88min, MH^+ 456.9.

Intermediate 18

2-Iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



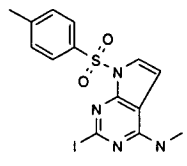
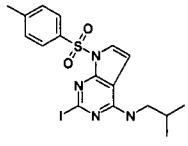
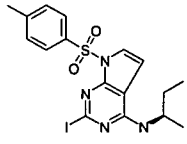
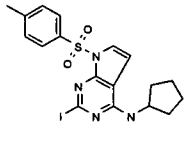
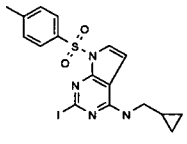
4-Chloro-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.3g) was suspended in ethanol (20ml) and treated with 2,2,2-trifluorethylamine (600mg, Aldrich) and DIPEA (10mmol) and the mixture was heated at 80°C for 6h. 2,2,2-Trifluorethylamine (2ml) and DIPEA (2ml) were added and heating continued at 90°C for 18h. The reaction was reduced to dryness and the residue purified by chromatography on a silica cartridge, eluting with an ethyl acetate / DCM gradient (0-100%). Combination of the appropriate fractions and evaporation of the solvents gave the title compound (1.21g). LC/MS; Rt 3.80min, MH^+ 496.9

Method 1:

4-Chloro-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (310mg) was suspended in ethanol and treated with amine (2mmol) and DIPEA (3mmol) and the mixture was heated at 80°C for 3h. The reaction was reduced to dryness and the residue purified by chromatography on a silica cartridge, eluting with an ethyl acetate / DCM gradient (0-100%). Combination of the appropriate fractions and evaporation of the solvents gave the desired product

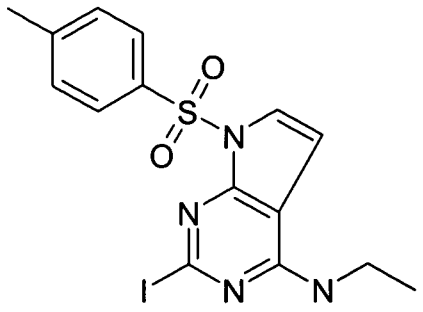
The following compounds were prepared using Method 1:

Intermediate	Structure	Name	Amine / source	LC/MS Rt (min)	LC/MS MH^+

19		2-iodo-*N*-methyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	Methylamine / Aldrich	3.60	428.9
20		2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2-methylpropyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	Isobutylamine / Aldrich	4.09	470.83
21		2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-[(1*R*)-1-methylpropyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	(*R*)-sec Butylamine / Aldrich	4.04	470.82
22		*N*-cyclopentyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	Cyclopentylamine / Aldrich	4.15	482.81
23		*N*-(cyclopropylmethyl)-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	(Cyclopropylmethyl)amine / Aldrich	3.91	468.9

Intermediate 24

***N*-Ethyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amin**

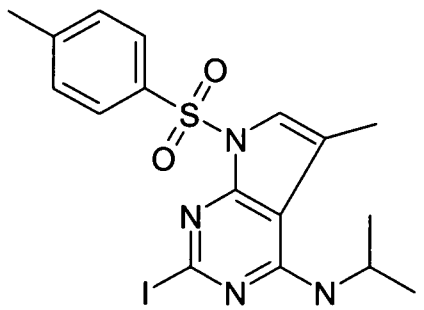


e

4-Chloro-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (300mg) was suspended in ethanol (5ml) and treated with ethylamine (1ml, Aldrich) and DIPEA (1ml) and the mixture was heated at 80°C for 2h. The reaction was reduced to dryness and the residue purified by chromatography on a silica cartridge (20g), eluting with an ethyl acetate / cyclohexane gradient (0-100%). Combination of the appropriate fractions and evaporation of the solvents gave the title compound. LC/MS; Rt 3.82min, MH^+ 442.78.

Intermediate 25

2-iodo-5-methyl-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

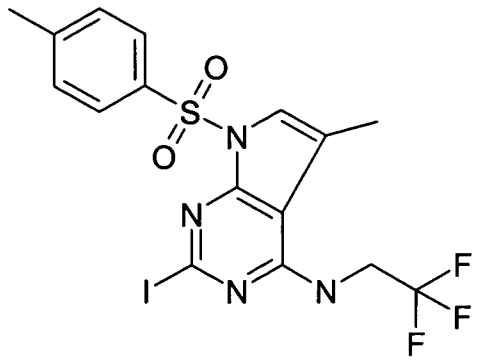


4-Chloro-2-iodo-5-methyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.0g) was suspended in ethanol (20ml), treated with isopropylamine (3ml, Aldrich) and DIPEA (1ml) and heated at 80°C for 2h. The volatiles were evaporated and the residue purified by chromatography on a silica cartridge, eluting with an ethyl acetate / cyclohexane gradient (0-100%). Evaporation of the solvents from the appropriate fractions gave the title compound (860mg). LC/MS; Rt 3.92min, MH^+ 470.9.

Intermediate 26

2-iodo-5-methyl-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrol

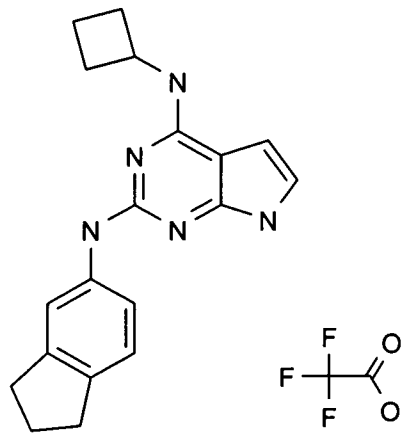
o[2,3-*d*]pyrimidin-4-amine



4-Chloro-2-iodo-5-methyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.0g) was suspended in ethanol (20ml), treated with 2,2,2-trifluorethylamine (3ml, Aldrich) and DIPEA (1ml) and heated at 80°C for 2h and then at 90°C for 42h. The volatiles were evaporated and the residue purified by chromatography on a silica cartridge, eluting with an ethyl acetate / cyclohexane gradient (0-100%). Evaporation of the solvents from the appropriate fractions gave the title compound (740mg). LC/MS; Rt 3.83min, MH^+ 511.

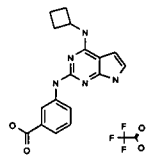
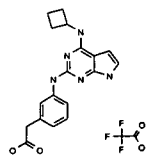
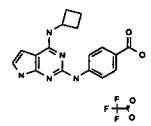
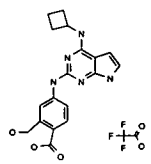
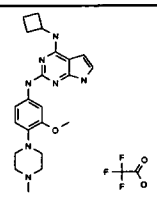
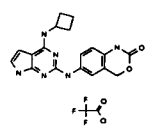
Example 62.

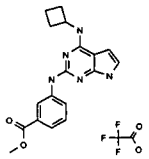
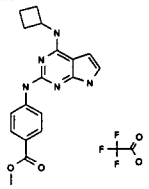
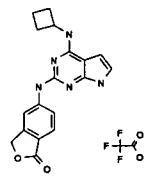
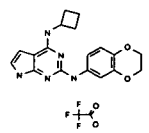
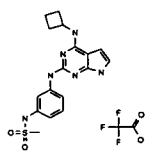
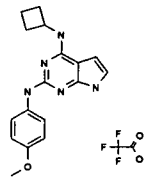
N^4-cyclobutyl-N^2-(2,3-dihydro-1*H*-inden-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate



N-Cyclobutyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (47mg), 5-aminoindan (15mg, Aldrich), cesium carbonate (85mg), bis(dibenzylideneacetone)palladium (2.3mg, Acros) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (2.3mg, Acros) were combined in a tube equipped with stirrer bar with DMF (1.0ml). The reaction mixture was heated to 100°C for 18h. The reaction mixture was allowed to cool and evaporated to dryness. The residue was partitioned between water (3ml) and DCM (3ml). The organic layer was separated and evaporated to dryness and purified by MDAP then treated with sodium methoxide in methanol (0.5N, 0.5ml) and heated to 80°C for 3h and allowed to cool to room temperature. The solution was evaporated to dryness, dissolved in DMSO and purified by MDAP. The fractions containing product were evaporated to dryness to give the title compound (1.9mg). LC/MS; Rt 3.25min, MH^+ 320.

Similarly prepared were the following:

Example	Structure	Name	Amine Reagent / Source	Method (a)	LCMS Rt (min)	LCMS MH^+
63		3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoic acid trifluoroacetate	Methyl 3-Aminobenzoate / Acros	II	2.7	324
64		(3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)acetic acid trifluoroacetate	Methyl (3-aminophenyl)acetate / WO 9301167	II	2.58	338
65		4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoic acid trifluoroacetate	Methyl 4-aminobenzoate / Aldrich	II	2.8	324
66		4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-2-(hydroxymethyl)benzoic acid trifluoroacetate (salt)	5-Aminophthalide / Asinex	II	2.58	354
67		N^4-cyclobutyl-N^2-[3-(methyloxy)-4-(4-methyl-1-piperazinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	[3-Methoxy-4-(4-methylpiperazin-1-Yl)phenyl]amine / WO 9827081	I	2.13	408
68		6-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-1,4-dihydro-2*H*-	6-Amino-1,4-Dihydro-2h-3,1-Benzoxazin-2-One / Key	I	2.46	351

		3,1-benzoxazin-2-one trifluoroacetate	Organics			
69		methyl 3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoate trifluoroacetate	Methyl 3-Aminobenzoate / Acros	I	3.01	338
70		methyl 4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoate trifluoroacetate	Methyl 4-aminobenzoate / Aldrich	I	3.14	338
71		5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-2-benzofuran-1(3*H*)-one trifluoroacetate	5-Aminophthalide / Asinex	I	2.91	336
72		N^4-cyclobutyl-N^2-(2,3-dihydro-1,4-benzodioxin-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	3,4-Ethylenedioxyaniline / Aldrich	III	2.69	338
73		*N*-(3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)methanesulfonamide trifluoroacetate	N-(3-Aminophenyl)methanesulfonamide / Aldrich	III	2.51	373
74		N^4-cyclobutyl-N^2-[4-(methyloxy)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamin	p-Anisidine / Aldrich	III	2.71	310

		e trifluoroacetate				

(a) Method:

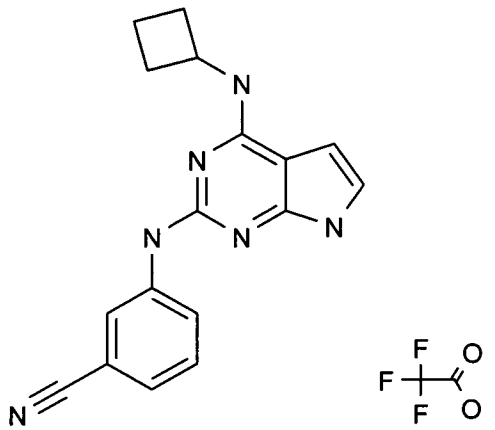
(I) As described above

(II) These compounds were formed when the ester functionality was hydrolysed during the reaction conditions.

(III) The reaction was carried out for 72h rather than the 18h described above, and worked up by passing through a plug of silica (eluting with 2:1 DCM / methanol), rather than the aqueous workup described above.

Example 75

3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzonitrile trifluoroacetate



N-Cyclobutyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.1 mmol, 47mg), 3-aminobenzonitrile (18mg, Aldrich), cesium carbonate (85mg), bis(dibenzylideneacetone)palladium (2.3mg, Acros) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (2.3mg, Acros) were combined in a tube equipped with stirrer bar with DMF (1.0ml). The reaction mixture was heated to 100°C for 18h. The reaction mixture was allowed to cool, evaporated to dryness, then suspended in methanol (2ml) and treated with sodium methoxide solution (2N, 0.5ml) and heated to 70°C for 4h and allowed to cool to room temperature. The solution was diluted with DCM and passed through a plug of silica, evaporated to dryness, dissolved in DMSO and purified by MDAP. The fractions containing product were evaporated to dryness to give the title compound (23.3mg). LC/MS; Rt 3.11min MH^+ 305.

Similarly prepared were the following:

Example	Structure	Name	Amine Reagent / Source	LCMS Rt (min)	LCMS MH^+
76		N^4-cyclobutyl-N^2-[3-(trifluoromethyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	3-Aminobenzotrifluoride / Aldrich	3.47	348
77		N^4-cyclobutyl-N^2-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	[4-(3-Methyl-1,2,4-oxadiazol-5-yl)phenyl]amine / Journal of Heterocyclic Chemistry (1980), 17(6), 1273-5	3.28	362

78		5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-2-[2-(dimethylamino)ethyl]-1*H*-isoindole-1,3(2*H*)-dione trifluoroacetate	5-Amino-2-[2-(dimethylamino)ethyl]-1H-isoindole-1,3(2H)-dione Hydrochloride / WO 2003004467	2.38	420
79		N^4-cyclobutyl-N^2-{2-[(dimethylamino)methyl]-1,3-benzoxazol-5-yl}-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-[(Dimethylamino)methyl]-1,3-benzoxazol-5-amine Hydrochloride	2.16	378

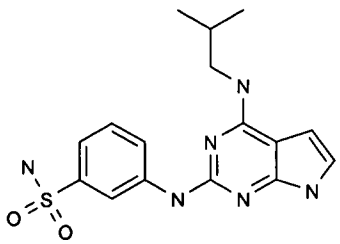
80		N^4-cyclobutyl-N^2-[4-(1,3-oxazol-2-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	4-(1,3-Oxazol-2-yl)Aniline / Journal of Organic Chemistry (1977), 42(19), 3208-9	3.01	347
81		5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-1,3-dimethyl-1,3-dihydro-2*H*-benzimidazol-2-one trifluoroacetate	5-Amino-1,3-Dimethyl-1,3-Dihydro-2h-Benzimidazol-2-One / Journal of Heterocyclic Chemistry (1992), 29(5), 1069-76	2.5	364

82		N^4-cyclobutyl-N^2-(2-methyl-1,3-benzoxazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-Methyl-1,3-benzoxazol-6-amine / Key Organics Limited/Bionet Research	2.71	335
83		N^4-cyclobutyl-N^2-[4-(1,3-oxazol-5-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	4-(1,3-Oxazol-5-yl)aniline / Acros	2.86	347
84		N^2-(4-chlorophenyl)-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	4-Chloroaniline / Aldrich	3.19	314

85		*N*-(5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-3-pyridinyl)acetamide trifluoroacetate	N-(5-Amino-3-pyridinyl)acetamide	2.28	338
86		N^4-cyclobutyl-N^2-(1,2-dimethyl-1*H*-benzimidazol-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	1,2-Dimethyl-1H-benzimidazol-5-amine / Chemstep	2.07	348

Example 87

3-({4-[(2-methylpropyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzenesulfonamide trifluoroacetate



2-Iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2-methylpropyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.1mmol, 43mg), 3-aminobenzenesulfonamide (34mg, Acros), cesium carbonate (96mg), bis(dibenzylideneacetone)palladium (6mg, Acros) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (6mg, Acros) were combined in DMF (2.0ml). The reaction mixture was heated to 80°C for 3h. The reaction mixture was allowed to cool, filtered through Celite, the Celite washed with DMF and the combined filtrate and washings evaporated to dryness. The residue was heated with sodium methoxide solution (2N, 0.5ml) at 80°C for 2h and allowed to cool to room temperature. The solution was evaporated to dryness, the residue dissolved in DMSO and purified by MDAP. The fractions containing product were evaporated to dryness to give the title compound (8.7mg). LC/MS; Rt 2.49min, MH^+ 361.

Similarly prepared were the following:

Example	Structure	Name	Starting Material	Amine Reagent/ Source	LC/MS Rt (min)	LC/MS MH^+
88		N^4-methyl-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-*N*-methyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1-Methyl-1*H*-indazol-6-amine / Pharm Lab Product List	2.32	294
89		N^2-(1-methyl-1*H*-indazol-6-yl)-N^4-[(1*R*)-1-methylpropyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-[(1*R*)-1-methylpropyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1-Methyl-1*H*-indazol-6-amine / Pharm Lab Product List	2.64	336
90		*N*-methyl-4-[(4-{[(1*R*)-1-methylpropyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino]benzamide trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-[(1*R*)-1-methylpropyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-Amino-*N*-methylbenzamide / Asinex	2.40	339

91		N^4-cyclopentyl-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	*N*-cyclopentyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1-Methyl-1*H*-indazol-6-amine / Pharm Lab Product List.	2.74	348
92		4-{[4-(ethylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-methylbenzamide trifluoroacetate	*N*-ethyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-Amino-*N*-methylbenzamide / Asinex	2.17	311
93		N^2-1,3-benzothiazol-6-yl-N^4-(cyclopropylmethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	*N*-(cyclopropylmethyl)-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	6-Aminobenzothiazole / Aldrich	2.67	337

94		4-({4-[(cyclopropylmethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-methylbenzamide trifluoroacetate	*N*-(cyclopropylmethyl)-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-Amino-*N*-methylbenzamide / Asinex	2.37	337
95		*N*-methyl-4-({4-[(2-methylpropyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2-methylpropyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-Amino-*N*-methylbenzamide / Asinex	2.45	339
96		N^2-(3-methyl-1*H*-indazol-6-yl)-N^4-(2-methylpropyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2-methylpropyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	3-Methyl-1*H*-indazol-6-amine Hydrochloride / WO 2002059110	2.73	336

97		N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-N^4-[(1*R*)-1-methylpropyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-[(1*R*)-1-methylpropyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1,3-dihydro-2-benzothiophen-5-amine 2,2-dioxide / Maybridge	2.56	372
98		N^2-(3-methyl-1*H*-indazol-6-yl)-N^4-[(1*R*)-1-methylpropyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-[(1*R*)-1-methylpropyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	3-Methyl-1H-indazol-6-amine Hydrochloride / WO 2002059110	2.70	336
99		N^2-1,3-benzothiazol-6-yl-N^4-cyclopentyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	*N*-cyclopentyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	6-Aminobenzothiazole / Aldrich	2.94	351

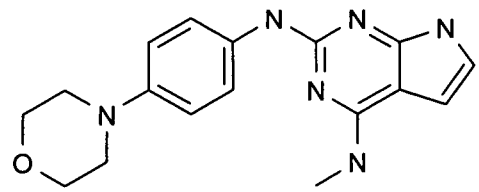
100		3-{[4-(cyclopentylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzenesulfonamide trifluoroacetate	*N*-cyclopentyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	3-Aminobenzenesulfonamide / Acros	2.61	373
101		4-{[4-(cyclopentylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-methylbenzamide trifluoroacetate	*N*-cyclopentyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-Amino-*N*-Methylbenzamide / Asinex	2.57	351
102		N^4-ethyl-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	*N*-ethyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1-Methyl-1*H*-indazol-6-amine / Pharm Lab Product List.	2.50	308

103		N^2-1,3-benzothiazol-6-yl-N^4-ethyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	*N*-ethyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	6-Aminobenzothiazole / Aldrich	2.52	311
104		N^4-(cyclopropylmethyl)-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	*N*-(cyclopropylmethyl)-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1-Methyl-1*H*-indazol-6-amine / Pharm Lab Product List.	2.7	334
105		3-({4-[(cyclopropylmethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzenesulfonamide trifluoroacetate	*N*-(cyclopropylmethyl)-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	Methyl 3-aminobenzoate / Acros	2.48	359

106		N^4-(cyclopropylmethyl)-N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	*N*-(cyclopropylmethyl)-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1,3-dihydro-2-benzothiophen-5-amine 2,2-dioxide / Maybridge	2.51	370

Example 107

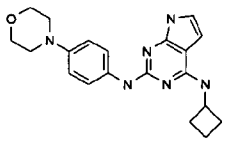
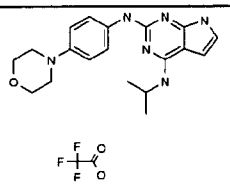
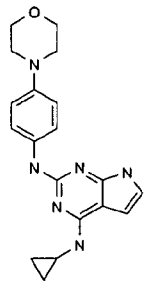
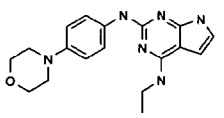
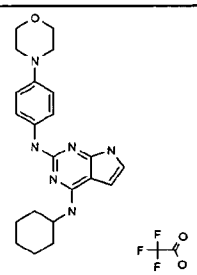
N^4-methyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamin e

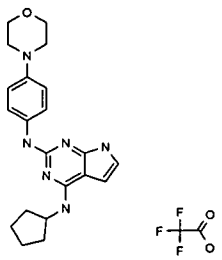


4-Chloro-*N*-[4-(4-morpholinyl)phenyl]-7-[(trifluoromethyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]p yrimidin-2-amine (46.1mg) was suspended in IPA (2ml) and treated with methylamine (4.6mg, Acros) and DIPEA (17µl). The reaction was stirred at 80°C under reflux conditions for 16h. The reaction was concentrated and redissolved in dioxane (1ml) and aqueous sodium hydroxide (2M, 1ml); the resulting biphasic mixture was stirred vigorously at 25°C for 16h. The reaction was treated with hydrochloric acid (2M, 1ml), a precipitate formed which was isolated by filtration and dried (purification method A) to give N^4-methyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (1.4mg). LC/MS; Rt 2.19min, MH^+ 324.91.

The following compounds were prepared in a similar manner, and purified using either the purification method above (Method A) or Method B (below).

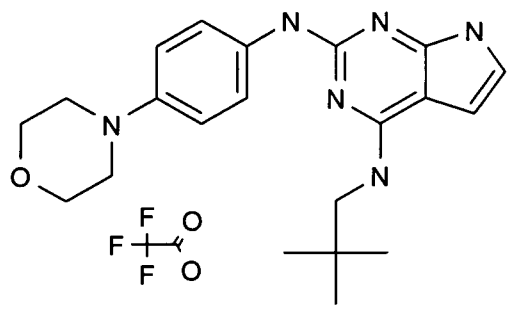
For some examples the solid was impure and for these the product was assumed to be in the filtrate. The filtrate was applied to a SCX-2 SPE that had been pre-conditioned with methanol. The column was washed with methanol (1500µl) and the product eluted with 2M ammonia / methanol (1500µl) and concentrated to give impure product. This was combined with the impure solid, dissolved in 1:1 DMSO: methanol and purified by MDAP. The fractions containing pure product were evaporated to dryness to give the desired compound (Purification method B).

Example	Structure	Name	Amine Reagent/ Source	Isolation Method	LC/MS R_t (min)	LC/MS MH^+
108		N^4-cyclobutyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine	Cyclobutylamine / Aldrich	A	2.52	364.56
109		N^4-(1-methylethyl)-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	(1-methylethyl)amine / Aldrich	B	2.50	353
110		N^4-cyclopropyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine	Cyclopropylamine / Aldrich	A	2.26	350.87
111		N^4-ethyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine	Ethylamine / Aldrich	B	2.38	339
112		N^4-cyclohexyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	Cyclohexylamine / Aldrich	B	2.85	393

113		N^4-cyclopentyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	Cyclopentyl amine / Aldrich	B	2.70	379

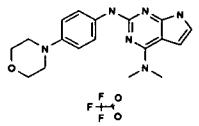
Example 114

N^4-(2,2-dimethylpropyl)-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate



4-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-[4-(4-morpholinyl)phenyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (48.2mg) was suspended in IPA (2ml) and treated with (2,2-dimethylpropyl)amine (13.05mg, Fluorochem) and DIPEA (17µl). The reaction was stirred at 25°C for 16h. The reaction was concentrated and the residue redissolved in sodium methoxide (0.5M, 1ml) and stirred 25°C for 72h, and then at 60°C for 2h. The reaction was concentrated and the residue purified by MDAP. The fractions containing product were evaporated to dryness to give the title compound (6.3mg). LC/MS; Rt 2.71min, MH^+ 381.

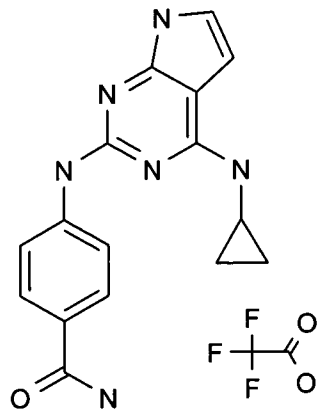
Similarly prepared was the following:

Example	Structure	Name	Starting Material	Amine Reagent/ Source	LC/MS Rt (min)	LC/MS MH^+
115		N^4,N^4-dimethyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	4-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-[4-(4-morpholinyl)phenyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine	dimethylamine/ Aldrich	2.31	339

Example 116

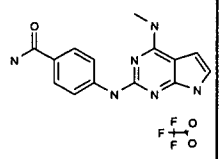
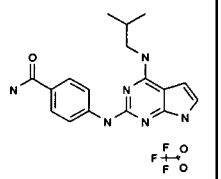
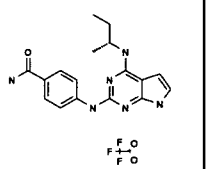
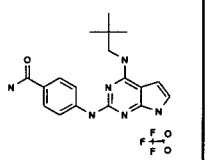
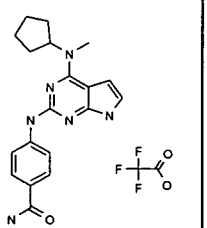
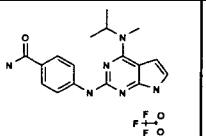
4-{[4-(cyclopropylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide

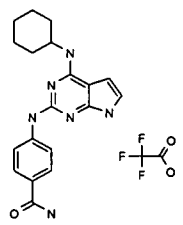
trifluoroacetate



2-{[4-(Aminocarbonyl)phenyl]amino}-7-[(trifluoromethyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]py rimidin-4-yl trifluoromethanesulfonate (853mg) was suspended in IPA (16ml) and an aliquot (1ml) of this mixture treated with cyclopropylamine (8.5mg, Aldrich) in IPA (1ml) and DIPEA (17µl). The reaction was stirred at 80°C under reflux conditions for overnight. The reaction was concentrated and the residue dissolved in dioxane (1ml) and sodium hydroxide (2M, 1ml) the resulting biphasic mixture was stirred vigorously at room temperature for ~72h. The reaction was neutralised with hydrochloric acid (2N), and extracted with ethyl acetate (2ml). The organic phase was concentrated and the residue purified by MDAP. The fractions containing product were evaporated to dryness to give the title compound (6.8mg)
LC/MS; Rt 2.26min, MH^+ 309.

The following compounds were prepared in a similar manner

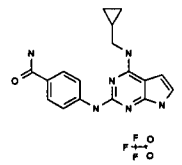
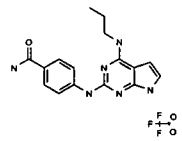
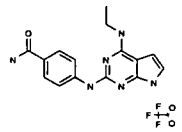
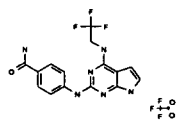
Example	Structure	Name	Amine Reagent / Source	LC/MS Rt (min)	LC/MS MH^+
117		4-{[4-(methylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide trifluoroacetate	methylamine / Acros	2.03	283
118		4-({4-[(2-methylpropyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	(2-methylpropyl)amine / Aldrich	2.39	325
119		4-[(4-{[(1*R*)-1-methylpropyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino]benzamide trifluoroacetate	[(1*S*)-1-methylpropyl]amine / Acros	2.34	325
120		4-({4-[(2,2-dimethylpropyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	(2,2-dimethylpropyl)amine / Fluorochem	2.51	339
121		4-({4-[cyclopentyl(methyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	*N*-methylcyclopentylamine / ASDI-Inter	2.66	351
122		4-({4-[methyl(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}ami	*N*-methyl-2-propylamine / Aldrich	2.39	325

		no)benzamide trifluoroacetate			
123		4-{[4-(cyclohexylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide trifluoroacetate	cyclohexylamine/ Aldrich	2.56	351

Method 2:

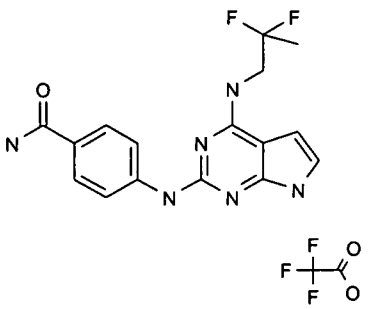
2-{[4-(Aminocarbonyl)phenyl]amino}-7-[(trifluoromethyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl trifluoromethanesulfonate (1190mg, 60% purity) was suspended in IPA (17ml). An aliquot (1ml) of this mixture was treated with a solution of the amine (0.15mmol) in IPA (1ml) and DIPEA (17µl). The reaction was stirred at 80°C under reflux conditions for overnight. The reaction was concentrated under a stream of nitrogen and the residue dissolved in dioxane (1ml) and sodium hydroxide (2M, 1ml) the resulting biphasic mixture was stirred vigorously at 25°C for ~72h. The dioxane phase was isolated and concentrated. The residue was purified by MDAP. Appropriate fractions were evaporated to dryness to give the desired product.

The following compounds were prepared using Method 2:

Example	Structure	Name	Amine Reagent / Source	LC/MS Rt (min)	LC/MS MH^+
124		4-({4-[(cyclopropylmethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	(cyclopropylmethyl)amine / Aldrich	2.30	323
125		4-{[4-(propylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide trifluoroacetate	1-propylamine / Aldrich	2.24	311
126		4-{[4-(ethylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide trifluoroacetate	Ethylamine / Aldrich	2.12	297
127		4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	(2,2,2-trifluoroethyl)amine / Aldrich	2.51	351

Example 128

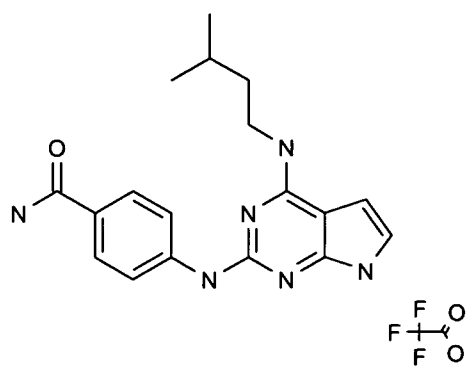
4-({4-[(2,2-Difluoropropyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate



2-{[4-(Aminocarbonyl)phenyl]amino}-7-[(trifluoromethyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl trifluoromethanesulfonate (312mg) was suspended in IPA (17ml). An aliquot (1ml) of this mixture was treated with a solution of the (2,2-difluoropropyl)amine (14.3mg, Oakwood Products) in IPA (1ml) and DIPEA (17µl). The reaction was stirred at 80°C under reflux conditions for 18h. The reaction was concentrated and the residue dissolved in dioxane (1ml) and sodium hydroxide (2M, 1ml) the resulting biphasic mixture was stirred vigorously at 25°C for ~90h. The dioxane phase was isolated and concentrated. The residue was purified by MDAP. Appropriate fractions were evaporated to dryness to give the title compound. LC/MS; Rt 2.43min, MH^+ 347.

Example 129

4-({4-[(3-methylbutyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate



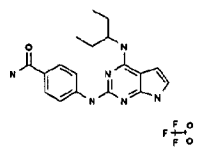
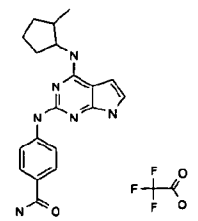
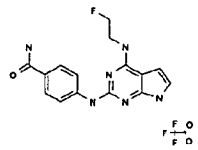
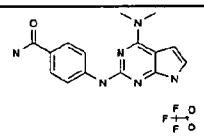
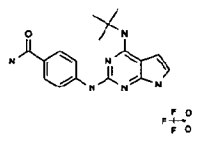
2-{[4-(Aminocarbonyl)phenyl]amino}-7-[(trifluoromethyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl trifluoromethanesulfonate (2.7g, impure ~4.2mmol) was suspended in

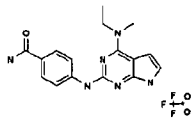
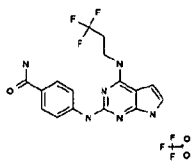
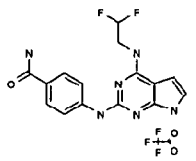
IPA (42ml). An aliquot (1ml) of this mixture was treated with (3-methylbutyl)amine (13.1mg, Aldrich) in IPA (1ml) and DIPEA (17µl). The reaction was stirred at 80°C under reflux conditions for ~72h. The reaction was concentrated (vacuum centrifuge), the residue dissolved in methanol (1.5ml) and treated with sodium methoxide in methanol (0.5M, 0.5ml) the resulting solution was stirred at 80°C overnight. The reaction was concentrated (vacuum centrifuge) and the residue purified by MDAP. The fractions containing product were evaporated to dryness to give the title compound (13.8mg) (Purification method 1). LC/MS; Rt 2.63min, MH^+ 339.

The following compounds were prepared in a similar manner, and purified using either the purification method above (Purification method 1) or Purification method 2 (below).

Purification method 2

After deprotection with sodium methoxide, conversion to the deprotected species was incomplete. The reaction was concentrated and the residue redissolved in dioxane (1ml) and sodium hydroxide (2M, 1ml). The reaction was stirred vigorously for 16h. The dioxane phase was isolated, concentrated and the residue purified by MDAP. The appropriate fractions were evaporated to dryness to give the desired product.

Example	Structure	Name	Amine Reagent/ Source	Purification	LC/MS Rt (min)	LC/MS MH^+
130		4-({4-[(1-ethylpropyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	(1-ethylpropyl)amine / Aldrich	1	2.52	339
131		4-({4-[(2-methylcyclopentyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	[(1*R*,2*R*)-2-methylcyclopentyl]amine hydrochloride / Journal of Organic Chemistry (2002), 67(12), 4115-4121.	2	2.62	351
132		4-({4-[(2-fluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	(2-fluoroethyl)amine hydrochloride / Aldrich	1	2.21	315
133		4-{[4-(dimethylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide trifluoroacetate	Dimethylamine / Aldrich	2	2.23	297
134		4-({4-[(1,1-dimethylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzami	(1,1-dimethylethyl)amine / Aldrich	1	2.48	325

		de trifluoroacetate				
135		4-({4-[ethyl(methyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	*N*-methylethylamine / Aldrich	1	2.34	311
136		4-({4-[(3,3,3-trifluoropropyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	(3,3,3-trifluoropropyl)amine hydrochloride / Apollo	2	2.53	365
137		4-({4-[(2,2-difluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	(2,2-difluoroethyl)amine / Apollo	1	2.39	333

Method 3:

2-Iodo starting material (0.1mmol) was suspended in DMF (2ml) and treated with aniline (0.15mmol), cesium carbonate (97.5mg), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (5.8mg) and bis(dibenzylideneacetone) palladium (5.75mg) the reaction was stirred at 80°C under nitrogen for 2h. The reaction was filtered through Celite, concentrated and the resulting gum redissolved in sodium methoxide in methanol (0.5M, 2ml) and stirred at 60°C for 16h. The reaction was concentrated and the residue purified by MDAP. The fractions containing product were evaporated to dryness to give the title compound.

The following were prepared using Method 3:

Example	Structure	Name	2-Iodo Starting Material	Amine Reagent / Source	LC/MS Rt (min)	LC/MS MH^+
138		N^4-(1-methylethyl)-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-Iodo-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1-methyl-1H-indazol-6-amine / Pharm Lab Product List.	2.71	322
139		N^4-cyclobutyl-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	*N*-cyclobutyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1-methyl-1*H*-indazol-6-amine / Pharm Lab Product List.	2.87	334

Method 4:

A mixture of 2-iodo-N-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (45.8mg), aniline (0.15mmol), cesium carbonate (97.5mg), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (5.8mg) and bis(dibenzylideneacetone) palladium (5.8mg) was suspended in DMF (2ml) and the reaction was stirred at 80°C under nitrogen for 4h. The reaction was filtered through Celite and the filtrate concentrated. The resulting gum was treated with aniline (0.15mmol), cesium carbonate (130mg), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (5.8mg) and bis(dibenzylacetone)palladium (5.8mg) in DMF (2ml) and the reaction was stirred at 80°C under nitrogen for 2h. The reaction was filtered through Celite and concentrated. The residue was dissolved in methanol (1ml), treated with sodium methoxide in methanol (0.5M, 1ml) and stirred at 60°C overnight. The reaction was concentrated and the residue purified by MDAP. The fractions containing product were evaporated to dryness to give the desired compound.

The following were prepared using Method 4:

Example	Structure	Name	Amine Reagent / Source	LC/MS Rt (min)	LC/MS MH^+
140		N2-1,3-benzothiazol-6-yl-N4-(1-methylethyl)-1H-pyrrolo[2,3-d]pyrimidine-2,4-diamine trifluoroacetate	1,3-benzothiazol-6-amine / Lancaster	2.58	325
141		4-({4-[(1-methylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	4-aminobenzamide / Aldrich	2.22	311
142		N-ethyl-N-[4-({4-[(1-methylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]acetamide trifluoroacetate	N-(4-aminophenyl)-N-ethylacetamide / Key Organics	2.44	353
143		N-methyl-N-[4-({4-[(1-methylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]acetamide trifluoroacetate	N-(4-aminophenyl)-N-methylacetamide / Aldrich	2.33	339

Method 5:

The 2-iodo pyrrolo[2,3-*d*]pyrimidin-4-amine starting material (2.0mmol) was suspended in DMF (20ml). An aliquot (1ml) of this mixture was treated with a solution of the aniline (0.2mmol) in DMF (1ml), cesium carbonate (97.5mg), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (5.8mg) and bis(dibenzylideneacetone) palladium (5.8mg). The reaction was stirred at 80°C under nitrogen for 3h. The reaction was filtered through Celite, concentrated (vacuum centrifuge) and the residue dissolved in methanol (1ml), treated with sodium methoxide in methanol (0.5M, 500µl) and stirred at 60°C overnight. The reaction was concentrated and purified using MDAP. The appropriate fractions were reduced to dryness to give the title compound.

The following were prepared using Method 5:

Example	Structure	Name	Starting Material	Amine Reagent / Source	Purification	LC/MS Rt (min)	LC/MS MH+
144		3-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzenesulfonamide trifluoroacetate	2-iodo-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	3-aminobenzenesulfonamide / Pfaltz and Bauer	A	2.32	347
145		N^2-(1-acetyl-2,3-dihydro-1*H*-indol-5-yl)-N^4-(1-methylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1-acetyl-2,3-dihydro-1*H*-indol-5-amine / Apollo	A	2.43	351
146		N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-N^4-(1-methylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine	2-iodo-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amine / Maybridge	A	2.38	358

147		6-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-1,4-dihydro-2*H*-3,1-benzoxazin-2-one trifluoroacetate	2-iodo-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	6-amino-1,4-dihydro-2*H*-3,1-benzoxazin-2-one / Key Organics	A	2.29	339
148		1-[4-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]-2-pyrrolidinone trifluoroacetate	2-iodo-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1-(4-aminophenyl)-2-pyrrolidinone / Chemical Block ltd	A	2.4	351
149		N^2-1,3-benzothiazol-6-yl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1,3-benzothiazol-6-amine / Lancaster	A	2.92	365

150		3-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzenesulfonamide trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	3-aminobenzenesulfonamide / Fluka	A	2.64	387
151		N^2-(1-acetyl-2,3-dihydro-1*H*-indol-5-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1-acetyl-2,3-dihydro-1*H*-indol-5-amine / Apollo	A	2.6	391
152		N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amine / Maybridge	A	2.68	398
153		N^2-(1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]py	2,3-dihydro-1,2-benzisothiazol-6-amine-1,1-dioxide /	A	2.66	399

		[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	rimidin-4-amine	Manchester Organics			
154		*N*-methyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-amino-*N*-methylbenzamide / Park research	A	2.59	365
155		6-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-1,4-dihydro-2*H*-3,1-benzoxazin-2-one trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	6-amino-1,4-dihydro-2*H*-3,1-benzoxazin-2-one / Key Organics	A	2.47	379
156		1-[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]-2-pyrrolidinone trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1-(4-aminophenyl)-2-pyrrolidinone / Chemical Block Ltd	A	2.62	391

157		N^4-(1-methylethyl)-N^2-6-quinolinyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	6-quinolinamine / Aldrich	B	2.37	319
158		4-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-[2-(methyloxy)ethyl]benzamide trifluoroacetate	2-iodo-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-amino-*N*-[2-(methyloxy)ethyl]benzamide / Park Research	B	2.33	369
159		N^2-(1-methyl-1*H*-indazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1-methyl-1*H*-indazol-6-amine / Pharm Lab Product List.	B	2.85	362
160		N^2-6-quinolinyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	6-quinolinamine / Aldrich	B	2.54	359

161		*N*-methyl-*N*-[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetamide trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	*N*-(4-aminophenyl)-*N*-methylacetamide / Aldrich	B	2.6	379
162		6-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-3,4-dihydro-1(2*H*)-naphthalenone trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	6-amino-3,4-dihydro-1(2*H*)-naphthalenone / Maybridge	B	3.1	376
163		N^2-(3-methyl-1*H*-indazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	3-methyl-1*H*-indazol-6-amine hydrochloride / WO 2002059110 A1	B	2.75	362

164		*N*-propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	2-iodo-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-amino-*N*-propylbenzamide / Park Research	B	2.87	393

Purification:

(A) MDAP

(B) Purified by 2 sequential MDAPs

Method 6:

2-Iodo starting material (0.1mmol) was suspended in DMF (2ml) and treated with aniline (0.2mmol), cesium carbonate (97.5mg), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (5.8mg) and bis(dibenzylideneacetone)palladium (5.75mg) the reaction was stirred at 80°C under nitrogen for 2h. The reaction was filtered through Celite, concentrated and the resulting gum redissolved in methanol (1.5ml) and sodium methoxide in methanol (0.5M, 500µl) and stirred at 80°C for 2h. The reaction was concentrated and the residue purified by MDAP. The fractions containing product were evaporated to dryness to give the title compound.

The following were prepared using Method 6:

Example	Structure	Name	2-Iodo Starting Material	Amine Reagent / Source	Purification	LC/MS Rt (min)	LC/MS MH^+
165		N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-5-methyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-5-methyl-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amine / Maybridge	A	2.86	412
166		*N*-methyl-4-({5-methyl-4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	2-iodo-5-methyl-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-amino-N-methylbenzamide / Park research	A	2.79	379
167		N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-5-methyl-N^4-(1-methylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine	2-iodo-5-methyl-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amine / Maybridge	B	2.68	372

		diamine trifluoroacetate					
168		5-methyl-N^4-(1-methylethyl)-N^2-(3-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-5-methyl-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	3-methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indazol-6-amine	B	2.78	336
169		*N*-methyl-4-({5-methyl-4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	2-iodo-5-methyl-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-amino-*N*-methylbenzamide / Park research	B	2.61	339
170		N^2-1,3-benzothiazol-6-yl-5-methyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-iodo-5-methyl-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	1,3-benzothiazol-6-amine / Lancaster	B	3.18	379

171		4-({5-methyl-4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate	2-iodo-5-methyl-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	4-aminobenzamide / Aldrich	B	2.78	365
172		*N*-methyl-*N*-[4-({5-methyl-4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetamide trifluoroacetate	2-iodo-5-methyl-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	*N*-(4-aminophenyl)-*N*-methylacetamide / Aldrich	B	2.86	393

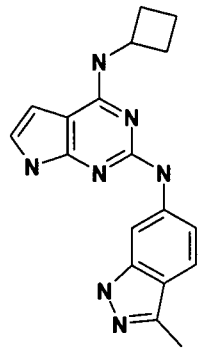
Purification:

(A) MDAP

(B) Purified by 2 sequential MDAP.

Example 173

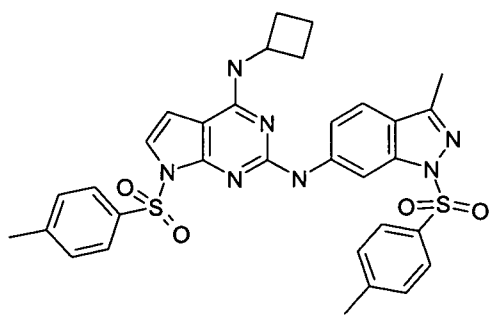
N^4-cyclobutyl-N^2-(3-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



N^4-Cyclobutyl-N^2-{3-methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indazol-6-yl}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (120mg) was dissolved in sodium methoxide in methanol (0.5M, 6ml) and the mixture heated at reflux under nitrogen for 2.5h. The cooled reaction was diluted with water and the solid precipitate filtered off and washed with water. The solid was dissolved in methanol, applied to a SCX-2 SPE (2g), the column washed with methanol and ethyl acetate and the product eluted with methanol / 0.880 ammonia. The basic fraction was concentrated *in vacuo* and the residue dissolved in ethyl acetate and filtered through a silica SPE (0.5g) washing with further ethyl acetate. The combined filtrate and washings were reduced to dryness *in vacuo* to give the title compound as an off-white solid (33mg). LC/MS; Rt 2.71min, MH^+ 334.

Intermediate 27

N^4-cyclobutyl-N^2-{3-methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indazol-6-yl}-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

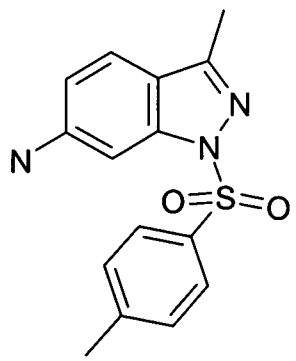


N-Cyclobutyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

(94mg), 3-methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indazol-6-amine (55mg), tris(dibenzylideneacetone)dipalladium (9mg) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (5.9mg) were mixed in dry DMF (2ml), the mixture degassed, cesium carbonate (130mg) added and the de-gassing repeated. The reaction was heated at 80°C for 1.5h, the cooled reaction diluted with ethyl acetate (~5ml) and applied to an SCX-2 SPE (5g). The cartridge was washed with ethyl acetate and methanol and the product eluted with methanol / 0.880 ammonia and ethyl acetate / methanol / 0.880 ammonia. The basic fractions were reduced to dryness *in vacuo* and the residue dissolved in chloroform and applied to a silica cartridge (1g). The cartridge was eluted with chloroform and then ethyl acetate, the fractions combined and the solvents evaporated *in vacuo* to give the title compound as a beige glass (120mg). LC/MS; Rt 4.14min, MH^+ 642.

Intermediate 28

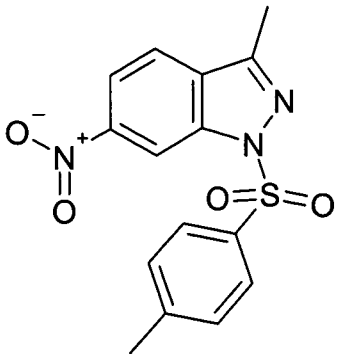
3-methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indazol-6-amine



3-Methyl-1-[(4-methylphenyl)sulfonyl]-6-nitro-1*H*-indazole (0.7g) and palladium on carbon (10%, wet, 70mg) were hydrogenated under 1atm. of hydrogen in ethanol (~75ml) for 20h. The reaction was left at room temperature for 5 days, filtered through Celite and the residue washed with ethanol and ethyl acetate. The combined filtrate and washings were reduced to dryness under vacuum to give 3-methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indazol-6-amine as a beige solid. NMR; [D_6-DMSO] δH 7.68,(2H, d), 7.38-7.33,(3H, m), 7.14,(1H, d), 6.63,(1H, dd), 2.32,(3H, s), 2.30,(3H, s).

Intermediate 29

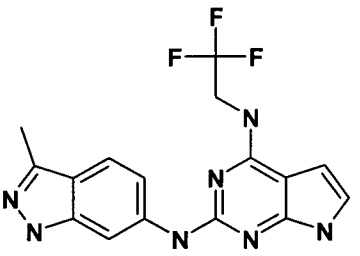
3-methyl-1-[(4-methylphenyl)sulfonyl]-6-nitro-1*H*-indazole



Sodium hydride (60% in mineral oil, 106mg) was added to a solution of 3-methyl-6-nitro-1*H*-indazole (468mg, WO 2002059110 A1) in DMF (15ml). The reaction was stirred at room temperature for 5min, tosyl chloride (505mg) added and stirring continued for 1h. The reaction was diluted with water, the solid isolated by filtration and washed with water and then methanol to give the desired product as a pale yellow solid (714mg). NMR; [D_6-DMSO] δH 8.83,(1H, d), 8.24,(1H, dd), 8.11,(1H, d), 7.87,(2H, d), 7.41,(2H, d), 2.55,(3H, s), 2.34,(3H, s).

Example 174

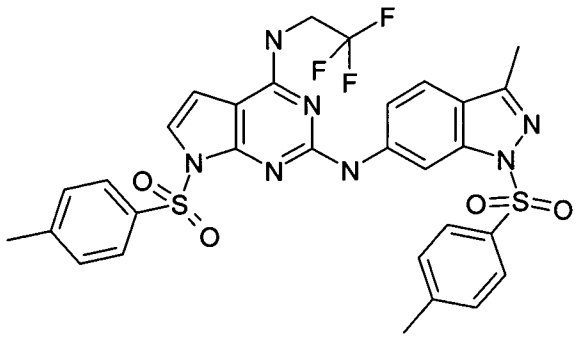
N^2-(3-methyl-1*H*-indazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



N^2-{3-Methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indazol-6-yl}-7-[(4-methylphenyl)sulfonyl]-N^4-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (190mg) in sodium methoxide in methanol (0.5M, 2ml) was heated at 80°C for 1.25h. The methanol was evaporated under vacuum, the residue triturated with water and the resulting solid isolated by filtration. The solid was adsorbed onto silica, applied to a silica cartridge (5g) and eluted with an ethyl acetate / cyclohexane gradient (10-100%). The product fractions were reduced to dryness *in vacuo* and the residue dried at 40°C under vacuum to give the title compound as a brown glass (50mg). LC/MS; Rt 2.84min, MH^+ 362.

Intermediate 30

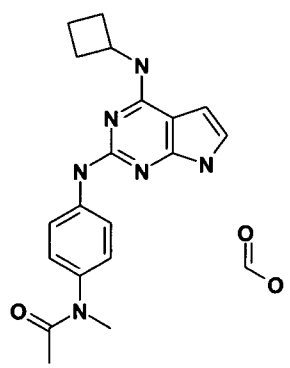
***N*^{2}-{3-methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indazol-6-yl}-7-[(4-methylphenyl) sulfonyl]-*N*^{4}-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine**



2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 3-methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indazol-6-amine (92mg), tris(dibenzylideneacetone)dipalladium (12mg), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (6mg) and potassium carbonate (50mg) were mixed in t-butanol (4ml). The reaction was heated in a sealed vial by microwave irradiation at 120°C for 40min, the cooled reaction diluted with methanol and applied to an SCX-2 SPE (5g). The cartridge was washed with methanol and the product eluted with methanol / 0.880 ammonia. The basic fraction was reduced to dryness *in vacuo* to give the title compound (190mg, 84% pure by LC/MS) which was used without further purification. LC/MS; Rt 4.02min, MH^+ 670.

Example 175

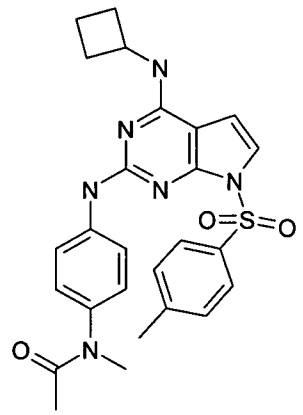
***N*-(4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)-*N*-methylacetamide**



A mixture of *N*-[4-({4-(cyclobutylamino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]-*N*-methylacetamide (315mg, Salor) in anhydrous methanol (5ml) was treated with a solution of sodium methoxide in methanol (0.5M, 3.2ml). The reaction mixture was heated in a sealed vial by microwave irradiation at 120°C for 30min. The solvent was evaporated and the residue purified by MDAP. Product containing fractions were combined and evaporated to give the title compound (92mg). LC/MS; Rt 2.3min, MH^+ 351.

Intermediate 31

***N*-[4-({4-(cyclobutylamino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]-*N*-methylacetamide**

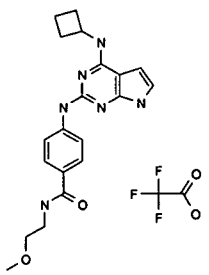
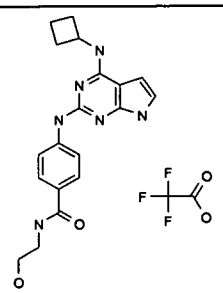
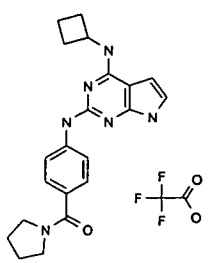


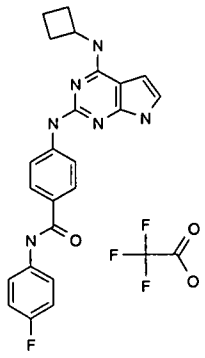
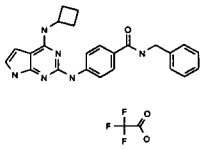
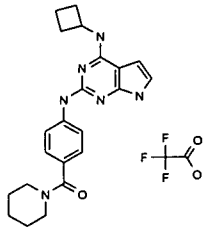
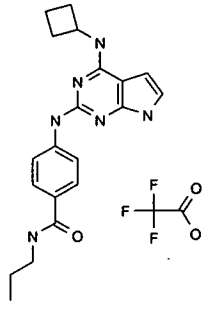
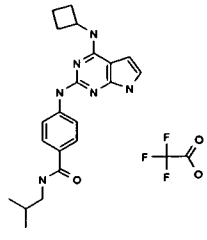
A mixture of *N*-cyclobutyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (445mg), *N*-(4-aminophenyl)-*N*-methylacetamide (311mg, Salor) in anhydrous DMF (5ml) was treated with cesium carbonate (930mg), bis(dibenzylidineacetone)palladium (58mg) and 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (59mg) and the resulting mixture stirred at 80°C for 2h. The reaction mixture was evaporated and the residue partitioned between ethyl acetate and water. The organic layer was dried (magnesium sulphate) and the solvent evaporated. The residue was triturated with methanol and the solid isolated by filtration to give the title compound (335mg). LC/MS; Rt 3.6min, MH^+ 505.

Method 7:

A mixture of 4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoic acid (258mg), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (334mg), DIPEA (0.416ml) in anhydrous DMF (2ml) was left to react. One eighth of the activated ester mixture was added to a suspension of amine (0.15mM) in DMF (0.25ml) and the reaction was left at room temperature overnight. The solvent was evaporated (vacuum centrifuge) and the residue dissolved in chloroform. The solution was loaded onto an aminopropyl SPE cartridge (1g) and eluted with 20% methanol in ethyl acetate. The solvent was evaporated and the residue purified by preparative HPLC.

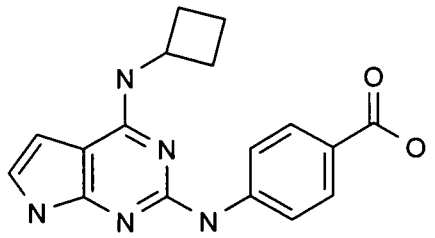
The following examples were prepared using Method 7:

Example	Structure	Name	Amine Reagent/ Source	LC/MS Rt (min)	LC/MS MH^+
176		4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-[2-(methyloxy)ethyl]benzamide trifluoroacetate	2-methoxyethylamine / Aldrich	2.48	381
177		4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(2-hydroxyethyl)benzamide trifluoroacetate (salt)	Ethanolamine / Aldrich	2.33	367
178		N^4-cyclobutyl-N^2-[4-(1-pyrrolidinylcarbonyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	Pyrrolidine / Aldrich	2.61	377

179		4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(4-fluorophenyl)benzamide trifluoroacetate	4-fluoroaniline / Aldrich	3.22	417
180		4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(phenylmethyl)benzamide trifluoroacetate	Benzylamine / Aldrich	2.99	413
181		N^4-cyclobutyl-N^2-[4-(1-piperidinylcarbonyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	Piperidine / Aldrich	2.77	391
182		4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-propylbenzamide trifluoroacetate	n-propylamine / Aldrich	2.71	365
183		4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(2-methylpropyl)benzamide trifluoroacetate	Isobutylamine / Aldrich	2.86	379

Example 184

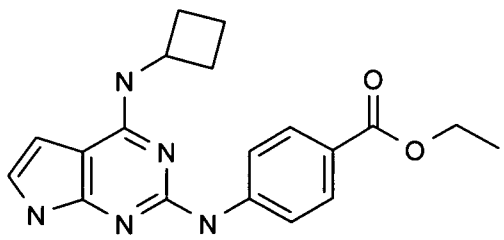
4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoic acid



A mixture of ethyl 4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoate (1.79g) and sodium hydroxide solution (2N, 3.2ml) in ethanol (26ml) was stirred at 40°C overnight. Further sodium hydroxide solution (2N, 0.96ml) was added to the reaction mixture and heating continued for a further 24h. The reaction mixture was acidified to pH7 with hydrochloric acid (1N) and the resulting precipitate isolated by filtration to give the title compound as a brown solid (0.802g). LC/MS; Rt 2.79min, MH^+ 324.

Intermediate 32

Ethyl 4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoate



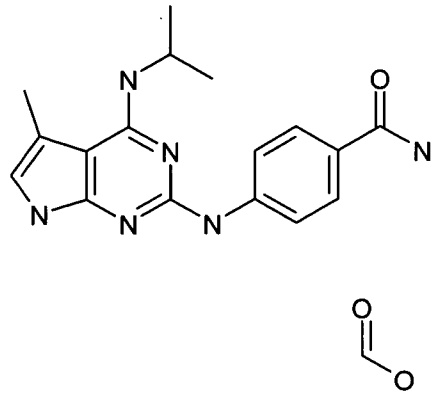
A mixture of 2-chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (2.5g), ethyl-4-aminobenzoate (2.23g), bis(dibenzylideneacetone) palladium (0) (0.323g), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (0.22g), cesium carbonate (4.4g) in DMF (50ml) was divided between 3 separate tubes which were each sealed and then heated using a microwave oven at 150°C for 45min. The reaction mixtures were combined and the DMF evaporated *in vacuo*. The residue was suspended in methanol and filtered through a pad of Celite. The filtrate was evaporated and the residue partitioned between ethyl acetate (150ml) and brine (150ml). The organic layer was separated, concentrated and the residue purified on a silica column eluting with cyclohexane / ethyl acetate gradient (0-100%) to give the

title compound as an amber solid (1.79g). LC/MS; Rt 3.4min, MH^+ 352.

Example 185

Formic acid -

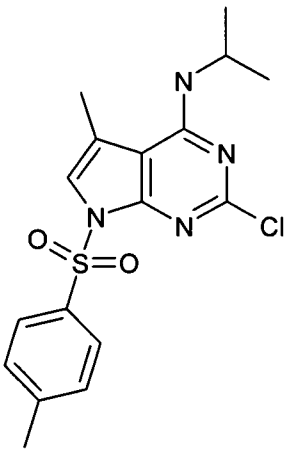
4-({5-methyl-4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide



A mixture of 2-chloro-5-methyl-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (199mg), 4-aminobenzamide (86mg), bis(dibenzylideneacetone) palladium (0) (15mg), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (10mg) and cesium carbonate (206mg) in DMF (3.5ml) was degassed by bubbling nitrogen through the mixture for 10min. The vessel was sealed and heated at 150°C for 45min by microwave irradiation. The solvent was evaporated under vacuum and the residue suspended in methanol. The suspension was filtered through a silica cartridge (0.5g) and the cartridge washed with methanol. The solvents were evaporated and the residue dissolved in sodium methoxide solution in methanol (0.5M, 2ml). The solution was heated at 80°C for 1h and the methanol removed by evaporation. The residue was purified by preparative HPLC to give the title compound as an oil (24mg). LC/MS; Rt: 2.54min, MH^+ 325.

Intermediate 33

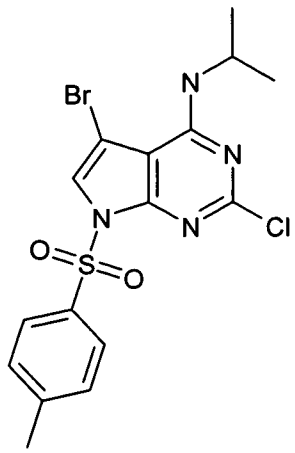
2-chloro-5-methyl-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



A mixture of 5-bromo-2-chloro-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (1.02g), potassium carbonate (0.95g), methyl boronic acid (0.41g) and 1,1' Bis(diphenylphosphino)ferrocenedichloropalladium (II) (279mg) in DMF (30ml) was heated at 90°C under nitrogen for 2h. Further methyl boronic acid (273mg) was added to the reaction mixture and heating continued at 65°C for 15h. The reaction temperature was raised to 80°C for 1h. Further methyl boronic acid (273mg) and potassium carbonate (0.63g) was added to the reaction mixture and heating continued for 1h. The solvent was evaporated and the residue partitioned between chloroform and saturated aqueous sodium bicarbonate. The aqueous was extracted with chloroform, the organics combined and washed with water. The organic layer was separated and adsorbed onto Florisil. The crude material was purified by chromatography on a silica cartridge (100g), eluting with an ethyl acetate / cyclohexane gradient (0-50%). The solvents were evaporated from the appropriate fractions to give the title compound as a yellow / white powder (398mg). LC/MS; Rt: 3.74min, MH^+ 379, 381.

Intermediate 34

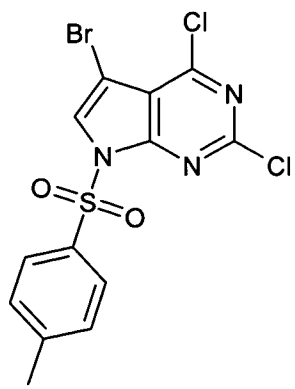
5-bromo-2-chloro-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



A mixture of 5-bromo-2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (2g) in ethanol (25ml) was heated at 80°C with isopropylamine (0.49ml) and DIPEA (1.66ml) for 1.75h. The solvent was evaporated and the residue partitioned between chloroform and water. The aqueous was extracted with chloroform and the organics combined. The solvent was evaporated, the residue adsorbed onto Florisil and was purified purified by chromatography on a silica cartridge (100g), eluting with an ethyl acetate / cyclohexane gradient (0-50%). Evaporation of the solvents from the appropriate fractions gave the title compound as a yellow / white powder (1.81g). LC/MS; Rt: 3.94min.

Intermediate 35

5-bromo-2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine



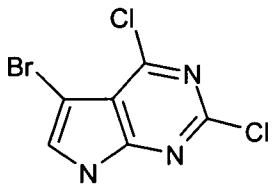
A mixture of 5-bromo-2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (3.73g) in DCM (100ml) was stirred with DIPEA (4.9ml) and 4-(dimethylamino)pyridine (0.17g) so a

solution formed. p-Toluenesulphonylchloride (2.9g) was added and the reaction stirred for 1h. Hydrochloric acid (1M) was added to the reaction mixture and the organic phase separated. The aqueous was extracted with DCM, the organics combined and washed with brine. The DCM was evaporated and the residue triturated with methanol. The solid was isolated by filtration to give the title compound (3.67g). LC/MS; Rt 3.91min.

The filtrate was concentrated by evaporation and the residue adsorbed from acetone onto Florisil. The crude material was purified by chromatography on a silica cartridge (100g) eluting with an ethyl acetate / cyclohexane gradient (0-100%). The solvents were evaporated to give a further portion of the title compound as a white solid (374mg). LC/MS; Rt 3.94min.

Intermediate 36

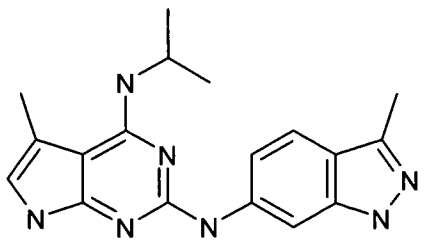
5-bromo-2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine



A mixture of 2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (2.75g, Pharma Lab Product List) in DMF (60ml) was stirred with *N*-bromosuccinimide (2.6g) for 16h at room temperature. The solvent was evaporated and the residue partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, the organics combined and washed with brine. The solvent was evaporated to give the title compound as a brown solid (3.73g). LC/MS; Rt 3.23min.

Example 186

5-methyl-N^4-(1-methylethyl)-N^2-(3-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

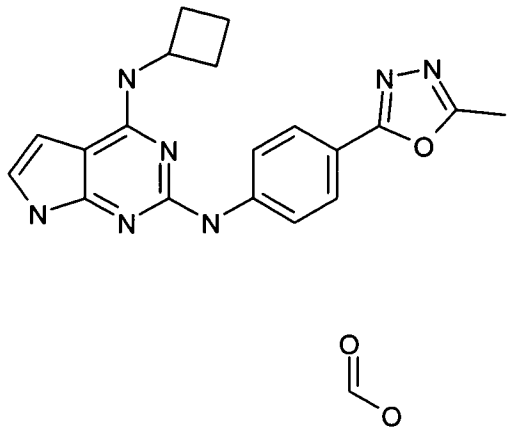


A mixture of 2-chloro-5-methyl-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (91mg), 3-methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indazol-6-amine (69mg), bis(dibenzylideneacetone) palladium (0) (6.9mg), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (4.7mg) and cesium carbonate (78.4mg) in DMF (1.7ml) was heated in a sealed vessel at 150°C for 45min by microwave irradiation. Bis(dibenzylideneacetone) palladium (0) (3mg) was added and the reaction heated for a further 20min. The contents of the vessel were transferred to a new vessel and DMF (0.2ml) added. The solution was degassed by bubbling nitrogen through the solution for 10min and then the vessel sealed. The reaction was heated at 150°C for 20min by microwave irradiation. The solvent was evaporated and the residue suspended in methanol. The suspension was passed through a silica cartridge (0.5g) and the filtrate evaporated. The residue was purified by preparative HPLC and the solvent evaporated.

Deprotection was achieved by heating the compound in a sodium methoxide solution in methanol (0.5M, 1ml) and methanol (1ml) at 60°C for 15h. The solvent was evaporated and the residue purified by preparative HPLC. The solvent was evaporated and a portion of the white solid dissolved in deuterated DMSO (0.94ml). The solution was applied to a pre-conditioned aminopropyl cartridge (0.5g) and eluted with methanol. The filtrate was reduced to dryness (vacuum centrifuge) and the residue dissolved in methanol. The solution was applied to a pre-conditioned SCX-2 cartridge (0.5g), washed with methanol and then the compound eluted with 2N ammonia in methanol solution. The same procedure was carried out with the remaining white solid sample but loaded onto the aminopropyl cartridge in methanol. The two solutions were combined and evaporation of solvent afforded the title compound as a solid (8.4mg). LC/MS; Rt: 2.85min, MH^+ 336.

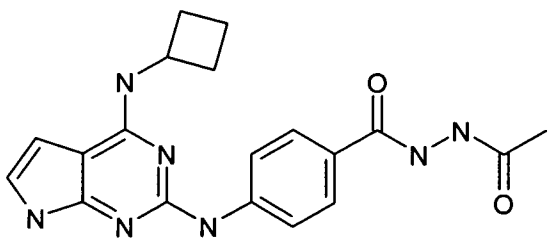
Example 187

Formic acid - N^4-cyclobutyl-N^2-[4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



N'-Acetyl-4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzohydrazide (35mg) and Burgess reagent (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt, 44mg) were combined in THF (1.2ml) and stirred at 70°C for 4h. The reaction mixture was removed from heat and the solvent evaporated *in vacuo*. The residue was purified by preparative HPLC and the fractions evaporated to give a yellow solid (20mg). LC/MS; Rt 2.87min, MH^+ 362.

Intermediate 37
N'-acetyl-4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzohydrazide

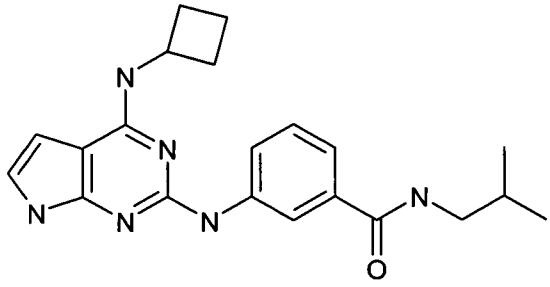


A mixture of 4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoic acid (100mg), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (129mg) and DIPEA (0.162ml) in DMF (0.5ml) was stirred for 10min. Acetic hydrazide (25mg) in DMF (0.5ml) was added to the mixture and the reaction stirred under nitrogen for 15h. Further acetic hydrazide (25mg) was added

and the reaction stirred for a further 1.5h. The solvent was evaporated and the residue azeotroped with methanol. The crude material was purified by preparative HPLC and the product fractions evaporated. The solid was dissolved in methanol and loaded onto a pre-conditioned aminopropyl cartridge (5g). The compound was eluted with methanol and the solvent evaporated to give the title compound as a yellow solid (70mg). LC/MS; Rt 2.32min, MH^+ 380.

Example 188

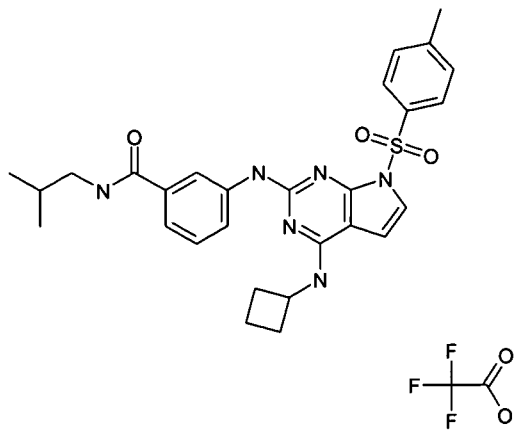
3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(2-methylpropyl)benzamide



A mixture of 3-({4-(cyclobutylamino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-(2-methylpropyl)benzamide trifluoroacetate (21mg) in sodium methoxide solution (0.5M, 0.5ml) was heated at 80°C for 2h. The solvent was evaporated and the residue dissolved in methanol. The solution was applied to a pre-conditioned SCX-2 SPE cartridge and the cartridge washed with methanol. The compound was eluted with 2N ammonia in methanol solution and the solvent evaporated. The crude material was purified by preparative HPLC to give the title compound (1.1mg). LC/MS; Rt 2.8min, MH^+ 379.

Intermediate 38

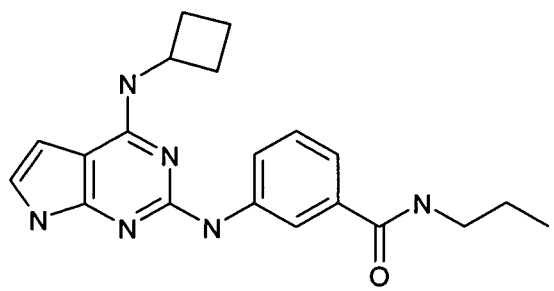
3-({4-(cyclobutylamino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-(2-methylpropyl)benzamide trifluoroacetate



A mixture of with *N*-cyclobutyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 3-amino-*N*-(2-methylpropyl)benzamide (47.2mg, AKos Consulting and Solutions GmbH) bis(dibenzylideneacetone) palladium (0) (6mg), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (4mg), cesium carbonate (80mg) in DMF (1.5ml) was heated in a sealed vial by microwave irradiation at 120°C for 30min. The reaction mixture was concentrated under vacuum and the residue suspended in methanol. The suspension was filtered through a silica cartridge (1g) and the filtrate reduced to dryness. The crude material was purified by preparative HPLC to give the title compound (21mg). LC/MS; Rt: 3.95min, MH^+ 533.

Example 189

3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-propylbenzamide

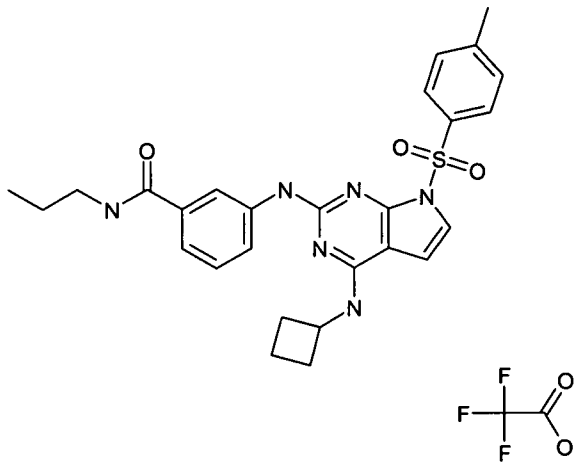


A mixture of 3-({4-(cyclobutylamino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-propylbenzamide trifluoroacetate (20mg) in sodium methoxide solution

(0.5M, 0.5ml) was heated at 80°C for 2h. The solvent was evaporated and the residue dissolved in methanol. The solution was applied to a pre-conditioned SCX-2 cartridge and washed with methanol. The compound was eluted with 2N ammonia in methanol solution and the solvent evaporated to leave the title compound (3.5mg). LC/MS; Rt 2.65min, MH^+ 365.

Intermediate 39

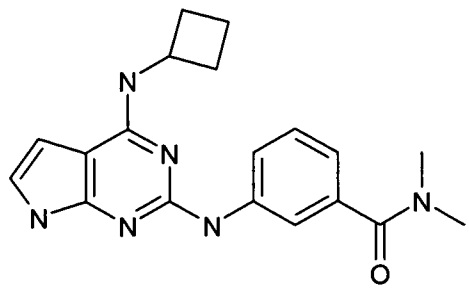
3-({4-(cyclobutylamino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-propylbenzamide trifluoroacetate



A mixture of with *N*-cyclobutyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), *N*-propyl-3-aminobenzamide (43.8mg, Journal of the American Chemical Society (1993), 115(9), 3548-57), bis(dibenzylideneacetone) palladium (0) (6mg), 2-dicyclohexylphosphino-2' -(*N,N*-dimethylamino) biphenyl (4mg), cesium carbonate (80mg) in DMF (1.5ml) was heated in a sealed vial by microwave irradiation at 120°C for 30min. The solvent was evaporated under vacuum and the residue suspended in methanol. The suspension was filtered through a silica cartridge (1g) and the solvent evaporated from the filtrate. The crude material was purified by preparative HPLC to give the title compound (20mg). LC/MS; Rt 3.85min, MH^+ 519.

Example 190

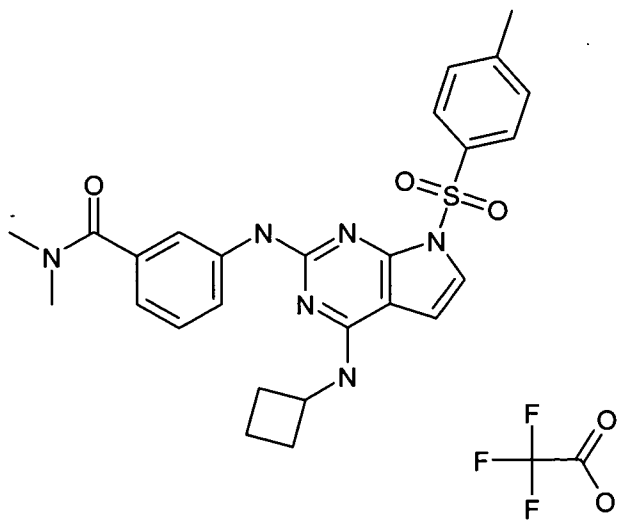
3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N,N*-dimethylbenzamide



A mixture of 3-({4-(cyclobutylamino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl} amino)-*N*,*N*-dimethylbenzamide trifluoroacetate (22mg) in sodium methoxide solution (0.5M, 0.5ml) was heated at 80°C for 2h. The solvent was evaporated and the residue dissolved in methanol. The solution was applied to a pre-conditioned SCX-2 SPE cartridge and the cartridge washed with methanol. The compound was eluted with 2N ammonia in methanol solution and the solvent evaporated to leave the title compound (5mg). LC/MS; Rt 2.49min, MH^+ 351.

Intermediate 40

3-({4-(cyclobutylamino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*,*N*-dimethylbenzamide trifluoroacetate

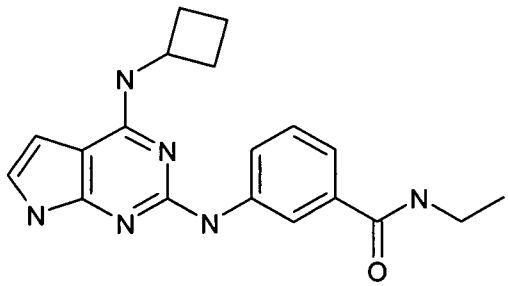


A mixture of *N*-cyclobutyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 3-amino-*N*,*N*-dimethyl-benzamide (40.4mg, Butt Park Ltd.),

bis(dibenzylideneacetone) palladium (0) (6mg), 2-dicyclohexylphosphino-2 ' -(*N,N*-dimethylamino) biphenyl (4mg), cesium carbonate (80mg) in DMF (1.5ml) in a sealed vessel, was heated by microwave irradiation at 120°C for 10min. The reaction mixture was reduced to dryness and the residue adsorbed onto Florisil. The crude material was purified by chromatography on a silica cartridge (50g) eluting with an ethyl acetate / cyclohexane gradient (0-100%). Further purification by preparative HPLC gave the title compound (22mg). LC/MS; Rt 3.6min, MH^+ 505.

Example 191

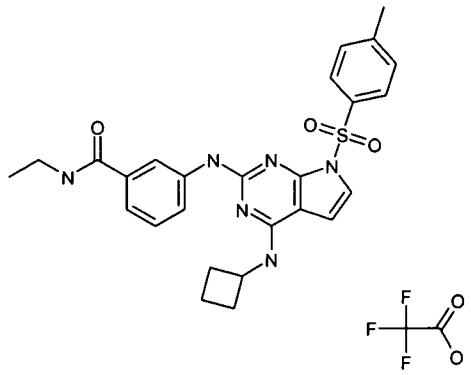
3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-ethylbenzamide



A mixture of 3-({4-(cyclobutylamino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl} amino)-*N*-ethylbenzamide trifluoroacetate (10mg) in sodium methoxide solution (0.5M, 0.5ml) was heated at 80°C for 2h. The solvent was evaporated and the residue dissolved in methanol. The solution was applied to a pre-conditioned SCX-2 SPE cartridge and the cartridge washed with methanol. The compound was eluted with 2N ammonia in methanol solution and the solvent evaporated to leave the title compound (2.5mg). LC/MS; Rt 2.59min, MH^+ 351.

Intermediate 41

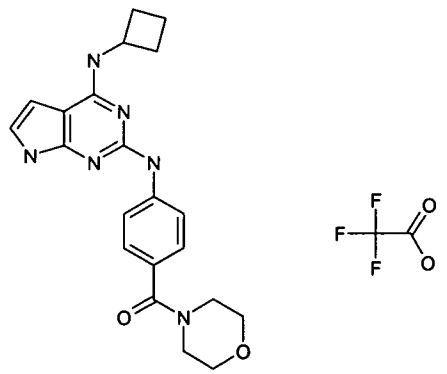
3-({4-(cyclobutylamino)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-ethylbenzamide trifluoroacetate



A mixture of *N*-cyclobutyl-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 3-amino-*N*-ethylbenzamide (40.4mg, Cell-Based Bio Inc.), bis(dibenzylideneacetone) palladium (0) (6mg), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (4mg) and cesium carbonate (80mg) in DMF (1.5ml) in a sealed vessel, was heated by microwave irradiation at 120°C for 10min. The reaction mixture was evaporated under vacuum and then adsorbed onto Florisil. The crude material was purified by chromatography on a silica cartridge (50g) eluting with an ethyl acetate / cyclohexane gradient (0-100%). Further purification by preparative HPLC gave the title compound (10mg). LC/MS; Rt 3.75min, MH^+ 505.

Example 192

N^4-cyclobutyl-N^2-[4-(4-morpholinylcarbonyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate

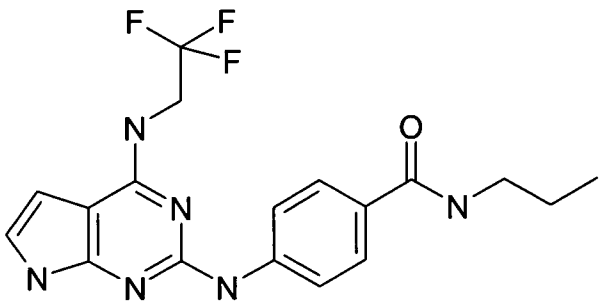


A mixture of 4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoic acid (64mg), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (83.6mg), DIPEA (0.104ml) in anhydrous DMF (0.5ml) was left to react over 10min. Half of the mixture was dispensed into a solution of morpholine

(0.013ml) in DMF (0.25ml) and the mixture left to react over the weekend. The solvent was evaporated (vacuum centrifuge) and the residue dissolved in chloroform (0.5ml). The solution was applied to a pre-conditioned aminopropyl cartridge (1g) and the cartridge washed with chloroform (3ml). The compound was eluted in ethyl acetate (3ml), and 20% methanol in ethyl acetate (3ml) washes. The product fractions were combined, the solvents evaporated and the residue purified by preparative HPLC to give the title compound as a yellow gum (24mg). LC/MS; Rt 2.47min, MH^+ 393.

Example 193

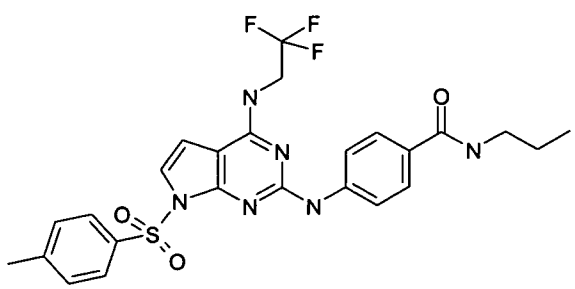
***N*-Propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**



4-({7-[(4-Methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-propylbenzamide (550mg) and potassium carbonate (414mg) in methanol / water (4:1, 12.5ml) was heated at reflux for 5h. The cooled reaction was diluted with water and the precipitate isolated by filtration. The solid was washed with ether to leave the title compound as a white solid (315mg). LC/MS; Rt 3.10min, MH^+ 393.

Intermediate 42

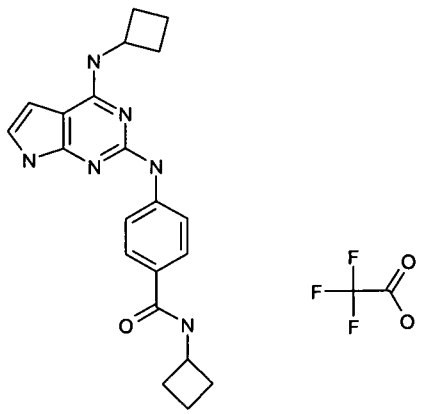
4-({7-[(4-Methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-propylbenzamide



A mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (500mg), 4-amino-*N*-propylbenzamide (267mg, Buttpark Screening Library), tris(dibenzylideneacetone)dipalladium (68mg), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (30mg) and potassium carbonate (222mg) in t-butanol (10ml) was heated at reflux under nitrogen overnight. The cooled reaction was partitioned between ethyl acetate and water and the organic phase washed with water and brine. The organic phase was dried (hydrophobic frit) and reduced to dryness *in vacuo*. The residue was purified by chromatography on a silica cartridge (50g) eluting with an ethyl acetate / cyclohexane gradient (1:15 to 7:1). The solvents were evaporated from the product fractions to leave the title compound (556mg). LC/MS; Rt 3.5min, MH^+ 547.

Example 194

***N*-cyclobutyl-4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide trifluoroacetate**



A mixture of 4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoic acid (64mg), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (83.6mg), DIPEA (0.104ml) in anhydrous DMF (0.5ml) was left to react over 10min. Half of the mixture was dispensed into a solution of cyclobutylamine (0.013ml) in DMF (0.25ml) and the mixture left to react over the weekend. The solvent was evaporated in a vacuum centrifuge and the residue dissolved in chloroform (0.5ml). The solution was applied to a pre-conditioned aminopropyl cartridge (1g) and the cartridge washed with chloroform (3ml). The compound was eluted with ethyl acetate (3ml), and 20% methanol in ethyl acetate (3ml). The product fractions were combined, the solvents evaporated and the residue purified by preparative HPLC to give the title compound as a white solid

(27mg). LC/MS; Rt 2.84min, MH^+ 377.

Method 8:

2-Chloro-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (22.2mg), amine (3eq), cesium carbonate (65mg), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (10mg) and tris(dibenzylideneacetone)dipalladium (0) (16mg) were mixed in DMF (1.3ml) and the mixture degassed. The vial was sealed and the reaction irradiated in a microwave at 150°C for 45min. The reaction was concentrated, the residue dissolved in water and the organics extracted with chloroform. The organic phase was separated, concentrated and the residue purified by MDAP. The fractions containing product were evaporated to dryness to give the desired product.

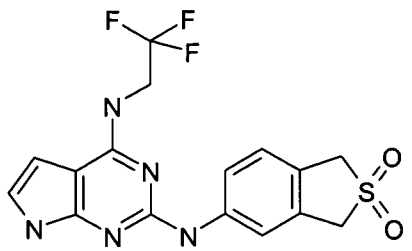
The following were prepared using method 8:

Example	Structure	Name	Amine Reagent/ Source	LC/MS Rt (min)	LC/MS MH^+
195		*N*-(5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-2-pyridinyl)acetamide trifluoroacetate	*N*-(5-amino-2-pyridinyl)acetamide / Apollo Chem	2.48	338
196		methyl (5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-2-pyridinyl)acetate trifluoroacetate	methyl (5-amino-2-pyridinyl)acetate	2.49	353
197		N^4-cyclobutyl-N^2-[3-(4-methyl-1,3-oxazol-5-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	3-(4-methyl-1,3-oxazol-5-yl)aniline / Syngene International	3.06	361

198		N^4-cyclobutyl-N^2-[6-(methyloxy)-3-pyridinyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	6-(methyloxy)-3-pyridinamine / Aldrich	2.7	311
199		N^4-cyclobutyl-N^2-5-pyrimidinyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	5-pyrimidinamine / Chemstep product list	2.47	282

Example 200

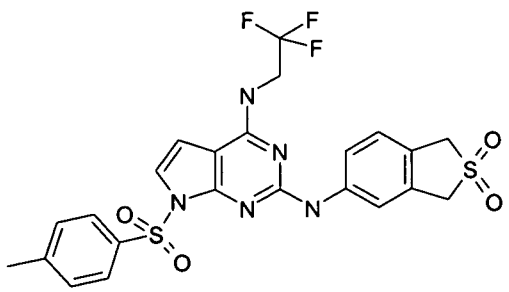
N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-7-[(4-methylphenyl)sulfonyl]-N^4-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (135mg) and sodium methoxide in methanol (0.5M, 5ml) were heated at 80°C for 1.5h. The reaction was left to cool, the methanol evaporated *in vacuo*, the residue triturated with water and filtered. The residual solid was washed with water, dissolved in acetone and reduced to dryness *in vacuo* and the residue triturated with ethyl acetate to give the title compound as a beige solid (70mg). LC/MS; Rt 2.77min, MH^+ 398.

Intermediate 43

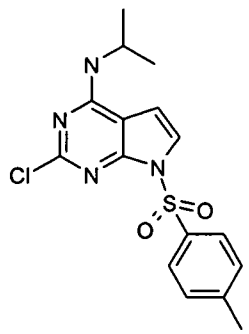
N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-7-[(4-methylphenyl)sulfonyl]-N^4-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



A mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (250mg), 2,2-dioxo-1,3-dihydrobenzo[c]thiophene-5-yl amine (136mg), tris(dibenzylideneacetone)dipalladium (0) (30mg), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (15mg) and potassium carbonate (125mg) in t-butanol (10ml) was heated by microwave irradiation in a sealed vial at 120°C for 50min. The cooled reaction was diluted with ethyl acetate, applied to a SCX-2 SPE (20g), the column washed with ethyl acetate and methanol and the product eluted with methanol / 0.880 ammonia. The solvents were evaporated from the basic fraction *in vacuo* and the residue dissolved in ethyl acetate, filtered through a silica cartridge (1g) washing with further ethyl acetate. The combined filtrate and washings were reduced to dryness *in vacuo* and the residue triturated with a little ethyl acetate to give the title compound as an off-white solid

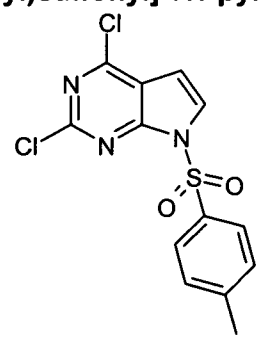
(138mg). LC/MS; Rt 3.61min, MH^+ 552.

Intermediate 44
2-chloro-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



To a suspension of 2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (70g) in 2-propanol (900ml) was added isopropylamine (70ml). The mixture was heated at 100°C for 30min then concentrated *in vacuo*. The residue was partitioned between water (1.5l) and ethyl acetate (300ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (2x 300ml). The combined organic extracts were dried over sodium sulphate and evaporated *in vacuo*. The residue was evaporated from ether to give the title compound as a gold coloured foam (72.2g). NMR [$CDCl_3$]; δH 8.10,(2H, d), 7.43,(1H, d), 7.33,(2H, d), 6.39,(1H, d), 4.97,(1H, br s), 4.37,(1H, br m), 2.41,(3H, s), 1.27,(6H, d). LC/MS; Rt 3.59min, MH^+ 365, 367.

Intermediate 45
2,4-Dichloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine

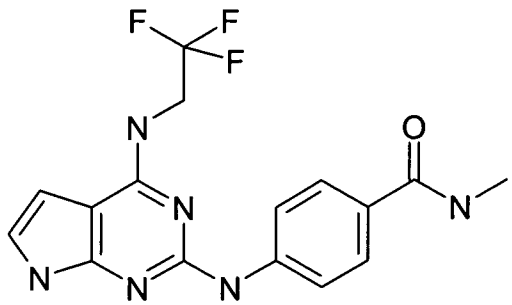


To a solution of 4-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (86.8g), chlorotrimethylsilane (570ml) and benzyl triethylammonium chloride (127.2g) in DCM (1.1l), under a nitrogen atmosphere, was added tert-butyl nitrite (52ml) dropwise over 20min. After stirring for 15min the mixture was cooled to ~20°C and treated cautiously with water (1.5l) whilst cooling the mixture in an ice bath. The layers were separated and the aqueous phase was further extracted with DCM (2x 500ml). The combined organic extracts were dried (sodium sulphate) and evaporated *in vacuo*. The residue was triturated with ether to give the title compound as a pale yellow solid (70.6g). NMR [$CDCl_3$]; δH 8.12,(2H, d), 7.76,(1H, d), 7.37,(2H, d), 6.68,(1H, d),

2.44,(3H, s). LC/MS; Rt 3.54min, MH^+ 342, 344, 346.

Example 201

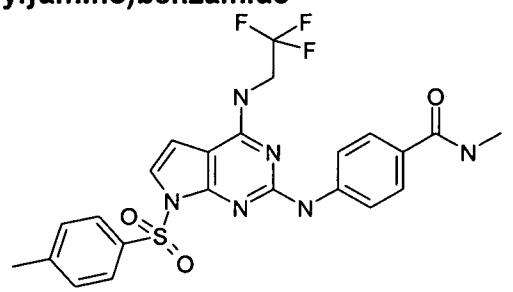
***N*-methyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**



N-Methyl-4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide (385mg) and sodium methoxide in methanol (0.5M, 5ml) were heated at 80°C for 1.5h. The reaction was left to cool to room temperature overnight, the methanol evaporated *in vacuo*, the residue triturated with water and filtered. The residual solid was adsorbed onto silica, applied to a silica cartridge (20g) and the cartridge eluted with an ethyl acetate / cyclohexane gradient (30-100%). The product fraction was reduced to dryness under vacuum, and the residue triturated with ether / ethyl acetate to give the title compound as a white solid (115mg). LC/MS; Rt 2.65min, MH^+ 365.

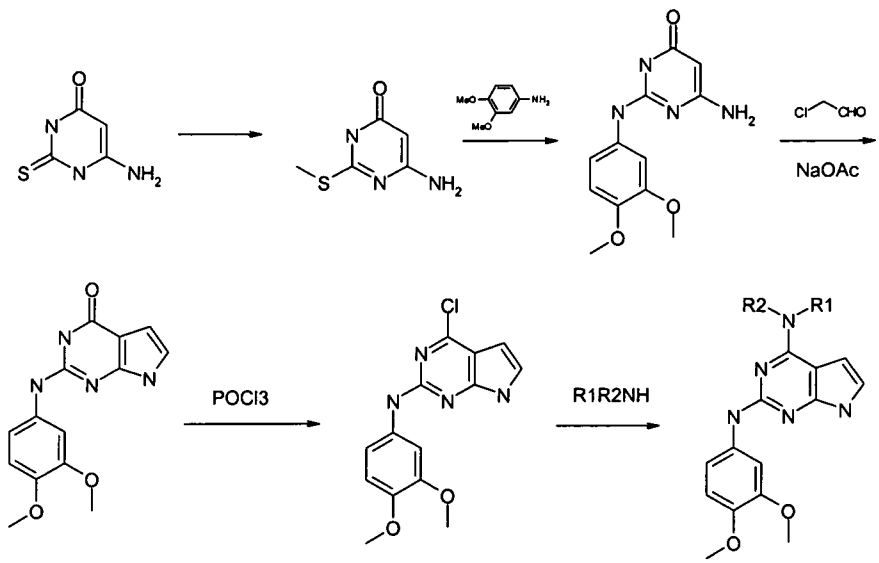
Intermediate 46

***N*-methyl-4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**

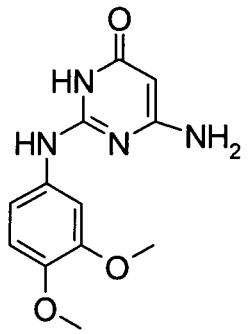


A mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (404mg), 4-amino-*N*-methylbenzamide (180mg), tris(dibenzylideneacetone)dipalladium (0) (91.6mg), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (47.3mg) and potassium carbonate (193mg) in t-butanol (18ml) was degassed and then heated at 80°C under nitrogen overnight. The cooled reaction was diluted with ethyl acetate, applied to a SCX-2 SPE (50g), the column washed with ethyl acetate and methanol and the product eluted with methanol / 0.880 ammonia. The solvents were evaporated to give the title compound as a beige foam (385mg). LC/MS; Rt 3.52min, MH^+ 519.

Scheme 1

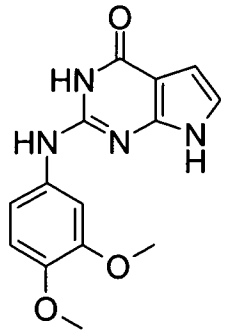


Intermediate 47
6-Amino-2-(3,4-dimethoxy-phenylamino)-3H-pyrimidin-4-one



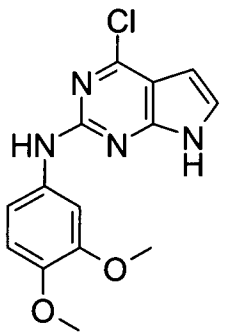
A mixture of 6-amino-2-(methylthio)-4(1*H*)-pyrimidinone (3.0g) and 3,4-dimethoxyaniline (3.4g) was heated with vigorous stirring at 19°C for 5h under argon. The cooled mixture was dissolved in chloroform and methanol (5:1, 80ml) and adsorbed onto silica (30g). The silica was placed into an injection column and eluted in a separation silica column (110g) with a methanol / DCM gradient (6-22%) to give, after evaporation of the solvents, a pale green solid (1.96g). NMR; [D_6-DMSO] δH 3.71,(s, 3H), 3.76,(s, 3H), 4.62,(s, 1H), 6.20,(s, 2H), 6.84,(d, 1H), 6.98,(dd, 1H), 7.35,(d, 1H), 8.38,(s, 1H), 9.57,(brs, 1H). LC/MS; MH^+ 263.

Intermediate 48
2-{[3,4-bis(methyloxy)phenyl]amino}-1,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one



A mixture of 6-amino-2-(3,4-dimethoxyphenylamino)-3H-pyrimidin-4-one (2.45g), chloroacetaldehyde (1.92g, 40% in water), sodium acetate (1.53g) in IPA (20ml) and water (5ml) was heated to 80°C. Stirring was continued for 10min at 80°C. After cooling, the solvent was removed by evaporation. The residue was dissolved in chloroform and methanol (5:1, 60ml) and adsorbed onto silica gel (25g), the silica was placed into an injection column and eluted in a separation silica column (110g) with a methanol / DCM gradient (5-20%) to give, after evaporation of the solvents, a pale purple solid (1.85g). NMR; [D_6-DMSO] δH 3.73,(s, 3H), 3.78,(s, 3H), 6.27,(dd, 1H), 6.73,(dd, 1H), 6.90,(d, 1Hz), 7.04,(dd, 1H), 7.36,(d, 1H), 8.35,(s, 1H), 10.10,(s, 1H), 11.31,(s, 1H). LC/MS; MH^+ 287.

Intermediate 49
***N*-[3,4-bis(methyloxy)phenyl]-4-chloro-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine**



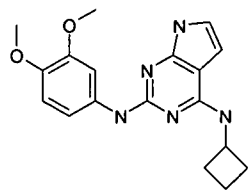
A mixture of
2-{[3,4-bis(methyloxy)phenyl]amino}-1,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (1.8g) and phosphorus oxychloride (24.5g) was heated at 105°C for 1h under argon. Excess phosphorus oxychloride was removed by evaporation and crushed ice was added to the residue. The formed solid was collected by filtration and dissolved in chloroform / methanol (5:1, 60ml) and adsorbed onto silica gel (25g). The silica was placed into an injection column and eluted in a separation silica column (110g) with a methanol / DCM gradient (5-20%) to give, after evaporation of the solvents, a pale purple solid (981mg). NMR; [D_6-DMSO] δH 3.72,(s, 3H), 3.77,(s, 3H), 6.37,(dd, 1H), 6.88,(d, 1H), 7.24,(dd, 1H), 7.27,(dd, 1H), 7.56,(d, 1H), 9.44,(s, 1H), 11.83,(s, 1H). LC/MS; MH^+ 305, 307.

Method 9:

A mixture of *N*-[3,4-bis(methyloxy)phenyl]-4-chloro-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (40mg) and amine (1.5-20 eq) in IPA (2.5ml) and *N*-methylpyrrolidone (0.2ml) in a sealed tube was stirred for 13h. The crude mixture was concentrated and purified by MDAP to provide the title compound.

Example 202

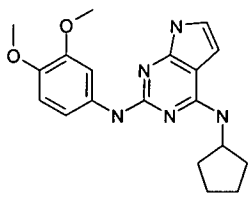
N^2-[3,4-bis(methyloxy)phenyl]-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



N^2-[3,4-bis(methyloxy)phenyl]-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine was prepared according to Method 9. NMR; [D_6-DMSO] δH 1.68,(m, 2H), 2.04,(m, 2H), 2.31,(m, 2H), 3.69,(s, 3H), 3.78,(s, 3H), 4.73,(m, 1H), 6.41,(dd, 1H), 6.75,(dd, 1H), 6.80,(d, 1H), 7.27,(dd, 1H), 7.36,(d, 1H), 7.68,(d, 1H), 8.37,(s, 1H), 10.89,(s, 1H). LC/MS; MH^+ 340.

Example 203

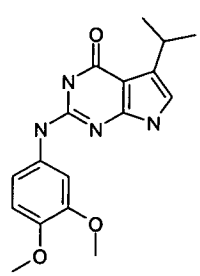
N^2-[3,4-bis(methyloxy)phenyl]-N^4-cyclopentyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



N^2-[3,4-bis(methyloxy)phenyl]-N^4-cyclopentyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine was prepared according to Method 9. NMR; [D_6-DMSO] δH 1.55,(m, 4H), 1.74,(m, 2H), 2.00,(m, 2H), 3.69,(s, 3H), 3.75,(s, 3H), 4.53,(m, 1H), 6.45,(dd, 1H), 6.73,(dd, 1H), 6.80,(d, 1H), 7.02,(d, 1H), 7.31,(dd, 1H), 7.64,(d, 1H), 8.34,(s, 1H), 10.86,(s, 1H). LC/MS; MH^+ 354.

Intermediate 50

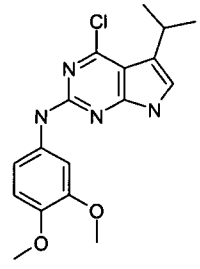
2-{[3,4-bis(methyloxy)phenyl]amino}-5-(1-methylethyl)-1,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one



To a solution of 3-methylbutyraldehyde (2.0g) in ether (30ml) was added 5,5-dibromo-pyrimidine-2,4,6-trione (3.4g, Aldrich) over a period of 30min and the reaction mixture was stirred for 2h at ambient temperature. The mixture was washed with saturated sodium bicarbonate and extracted with ether. The organic phase was collected and dried (sodium sulphate) and concentrated under reduced pressure to give the brominated aldehyde which was used for next reaction without any purification.

A mixture of bromomated aldehyde (1.3g), 6-amino-2-(3,4-dimethoxy-phenylamino)-3*H*-pyrimidin-4-one (1.5g) and sodium acetate (940mg) in water (15ml) and IPA (15ml) was gradually heated up to 80°C and stirred for 4h at 80°C. After evaporation of solvent, the residue was purified by chromatography on silica gel to afford 2-{[3,4-bis(methyloxy)phenyl]amino}-5-(1-methylethyl)-1,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (1.0g). NMR; [D_6-DMSO] δH 1.21,(d, 6H), 3.06,(m, 1H), 3.72,(s, 3H), 3.78,(s, 3H), 6.43,(d, 1H), 6.88,(d, 1H), 7.02,(dd, 1H), 7.35,(d, 1H), 8.30,(s, 1H), 9.98,(s, 1H), 10.94,(s, 1H). LC/MS; MH^+ 329.

Intermediate 51
***N*-[3,4-bis(methyloxy)phenyl]-4-chloro-5-(1-methylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine**

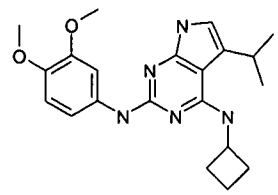


2-{[3,4-Bis(methyloxy)phenyl]amino}-5-(1-methylethyl)-1,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (575mg) was treated with phosphorous oxychloride at 110°C and after evaporation of excess phosphorous oxychloride, crushed ice was added to the residue, and the generated precipitate was collected by filtration (320mg).

Method 10:

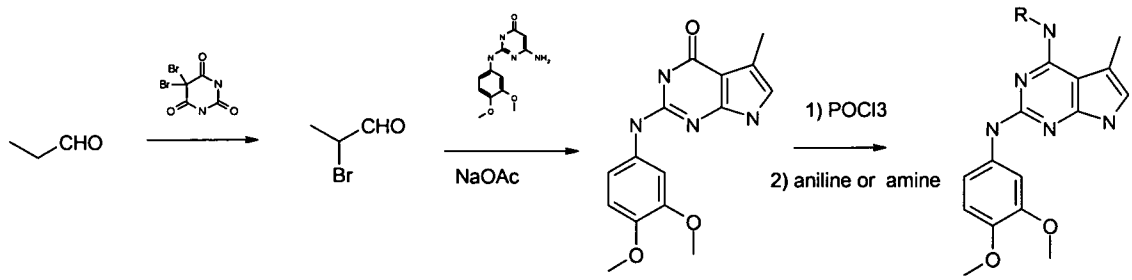
A mixture of *N*-[3,4-bis(methyloxy)phenyl]-4-chloro-5-(1-methylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine and amine (1.5-20eq) in IPA in a sealed tube was heated at 120°C for 13h. After removal of solvent, the residue was purified by MDAP.

Example 204
***N^2*-[3,4-bis(methyloxy)phenyl]-*N^4*-cyclobutyl-5-(1-methylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine**

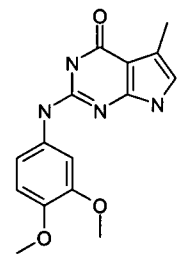


N^2-[3,4-bis(methyloxy)phenyl]-N^4-cyclobutyl-5-(1-methylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine was prepared according to Method 10. NMR; [D_6-DMSO] δH 1.21,(d, 6H), 1.57-1.75,(m, 2H), 2.05-2.18,(m, 2H), 2.25-2.37,(m, 2H), 3.69,(s, 3H), 3.78,(s, 3H), 4.81,(m, 1H), 5.92,(d, 1H), 6.51,(d, 1H), 6.81,(d, 1H), 7.26,(dd, 1H), 7.65,(d, 1H), 8.17,(s, 1H), 8.39,(s, 1H), 10.66,(s, 1H). LC/MS; MH^+ 382.

Scheme 2



Intermediate 52
2-{[3,4-bis(methyloxy)phenyl]amino}-5-methyl-1,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one

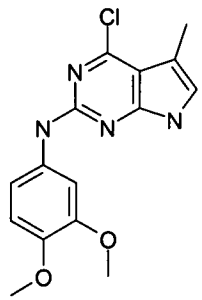


To the solution of propionaldehyde (2.0g) in ether (120ml) was added 5,5-dibromopyrimidine-2,4,6-trione (5.0g, Aldrich) over a period of 30min and the reaction mixture was stirred for 2h at ambient temperature. The mixture was washed with saturated sodium bicarbonate and extracted with ether. The organic phase was collected and dried (sodium sulphate) and concentrated under reduced pressure to give 2-bromopropionaldehyde, which was used without further purification.

The mixture of 2-bromopropionaldehyde (1.4g) and 6-amino-2-(3,4-dimethoxyphenylamino)-3H-pyrimidin-4-one (2.5g) and sodium acetate (1.6g) in water (15ml) and IPA (15ml) was gradually heated up to 80°C and stirred for 3h at 80°C. After evaporation of solvent, to the residue was added water and the generated precipitate was purified by chromatography on silica gel to afford 2-{[3,4-bis(methyloxy)phenyl]amino}-5-methyl-1,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-

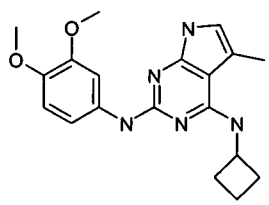
4-one (974mg). NMR; [D_6-DMSO] δH 2.20,(s, 3H), 3.72,(s, 3H), 3.77,(s, 3H), 6.45,(m, 1H), 6.89,(d, 1H), 7.02,(dd, 1H), 7.35,(d, 1H), 8.29,(s, 1H), 10.00,(s, 1H), 10.94,(s, 1H).

Intermediate 53
***N*-[3,4-bis(methyloxy)phenyl]-4-chloro-5-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine**



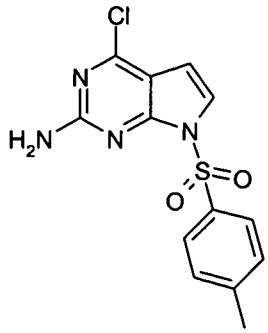
2-{[3,4-Bis(methyloxy)phenyl]amino}-5-methyl-1,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (141mg) was chlorinated with phosphorous oxychloride at 110°C and after evaporation of excess phosphorous oxychloride, crushed ice was added to the residue, the precipitate was collected and purified by chromatography on silica gel to afford
N-[3,4-bis(methyloxy)phenyl]-4-chloro-5-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (41mg). NMR; [D_6-DMSO] δH 2.31,(s, 3H), 3.71,(s, 3H), 3.76,(s, 3H), 6.87,(d, 1H), 6.99,(s, 1H), 7.25,(dd, 1H), 7.52,(d, 1H), 9.37,(s, 1H), 11.48,(s, 1H).

Example 205
***N*^{2}-[3,4-bis(methyloxy)phenyl]-*N*^{4}-cyclobutyl-5-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine**



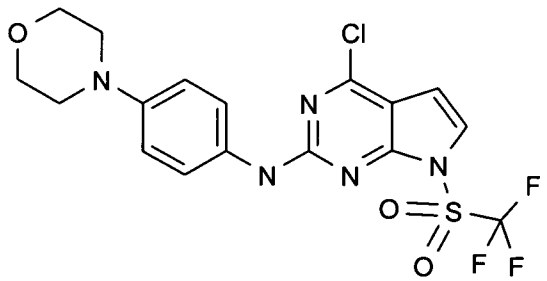
A mixture of *N*-[3,4-bis(methyloxy)phenyl]-4-chloro-5-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine and cyclobutylamine (5eq.) in IPA (0.04M) in a sealed tube was heated at 120°C for 13h. After removal of solvent, the residue was purified by MDAP. NMR; [D_6-DMSO] δH 1.57-1.76,(m, 2H), 2.09-2.19,(m, 2H), 2.25-2.34,(m, 2H), 2.33,(s, 3H), 3.69,(s, 3H), 3.78,(s, 3H), 4.68-4.82,(s, 1H), 6.05,(d, 1H), 6.49,(s, 1H), 6.81,(d, 1H), 7.27,(dd, 1H), 7.65,(d, 1H), 8.38,(s, 1H), 10.59,(s, 1H). LC/MS; MH^+ 354.

Intermediate 54
4-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine



Sodium hydride (60% dispersion in oil, 2.2g) was added to a stirred cooled (ice-bath) solution of 4-chloro-1H-pyrrolo[2,3-d]pyrimidin-2-amine (8.0g, WO2004024082) in DMF (120ml) under nitrogen. After 15min a solution of 4-toluenesulphonyl chloride (11g) in DMF (50ml) was added over 10min. The mixture was stirred for 25min and poured into a 10% ammonium chloride solution (800ml) and extracted into ethyl acetate (3x 200ml). The combined extracts were washed with water (3x 200ml), dried (sodium sulphate) and evaporated *in vacuo* to give the title compound as a yellow solid (15g). LC/MS; Rt 3.34min, MH^+ 325.

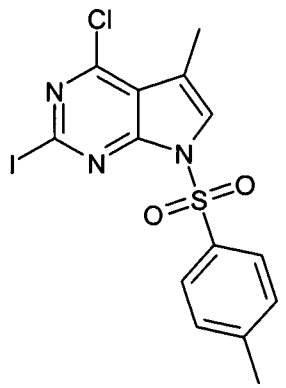
Intermediate 55
4-chloro-*N*-[4-(4-morpholinyl)phenyl]-7-[(trifluoromethyl)sulfonyl]-7*H*-pyrrolo[2, 3-*d*]pyrimidin-2-amine



4-Chloro-*N*-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (500mg) was suspended in DMF (10ml) and treated with *N*-phenyltrifluoromethanesulphonamide (651mg, Lancaster) and potassium carbonate (251mg). The reaction was stirred at 25°C for 30min. The reaction was treated with *N*-phenyltrifluoromethanesulphonamide (108mg, Lancaster) and potassium carbonate (42mg) and the reaction stirred at 25°C for 2h. The reaction was diluted with iced water (20ml) and the organics extracted with ethyl acetate (2x 20ml). The combined organics were dried (magnesium sulphate) and concentrated. The residue was purified by chromatography on a silica column (20g), eluting with an ethyl acetate / cyclohexane gradient (0-100%). The fractions containing product were evaporated to dryness and the residue dried at 100°C to give the title compound (466mg). LC/MS; Rt 3.75min, MH^+ 461.87.

Intermediate 56
4-chloro-2-iodo-5-methyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidi

ne



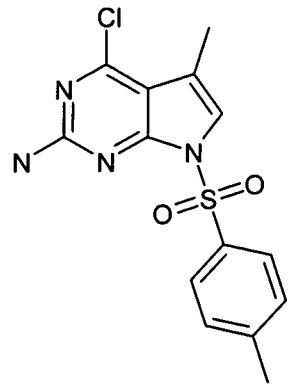
A mixture of 4-chloro-5-methyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (1.0g), diiodomethane (2.8ml), copper iodide (0.68g), and iodine (0.91g) in anhydrous THF (17ml) was treated with tert-butyl nitrite (1.48ml). The mixture was heated at 80°C for 45min and then left to cool to ambient temperature. The reaction mixture was poured into aqueous sodium sulphite (5%, 125ml).

A mixture of 4-chloro-5-methyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (7.4g), diiodomethane (20.4ml), copper iodide (5.02g) and iodine (6.69g) in anhydrous THF (120ml) was treated with tert-butyl nitrite (11ml). The mixture was heated to 80°C for 1h and then left to cool to ambient temperature. The reaction mixture was poured into aqueous sodium sulphite (5%, 500ml).

The two reaction mixtures were combined and extracted with ethyl acetate (3x 200ml). The combined organics were washed with aqueous sodium sulphite and water. The solvent was evaporated and the residue azeotroped with ether and toluene. The residue was triturated with ether, and the solid isolated by filtration. The solid was dried in an oven to give the title compound as a yellow solid (2.02g). LC/MS; Rt 3.86min, MH^+ 447.87 / 449.84.

The filtrate was evaporated and suspended in methanol. The solid was filtered, washed with methanol and dried in the vacuum oven to give the title compound as a white solid (2.2g). LC/MS; Rt 3.86min, MH^+ 447.87, 449.83.

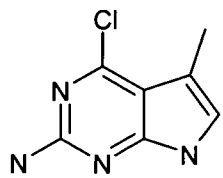
Intermediate 57
4-chloro-5-methyl-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine



A solution of 4-chloro-5-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (10.4g) in DMF (125ml) was stirred under nitrogen at 0°C. The solution was treated with sodium hydride (60% in mineral oil, 2.7g) added portionwise and stirred for 10min. A solution of p-toluenesulphonylchloride (13g) in DMF (50ml) was added dropwise over 10min. The reaction mixture was stirred at room temperature for 25min and then poured into saturated aqueous ammonium chloride (1l) and stirred. The mixture was extracted with ethyl acetate (3x 500ml) and concentrated. The residual solution was washed with water (500ml), dried (magnesium sulphate) and the solvent evaporated. The residual solid was suspended in DCM, stirred and filtered to obtain the title compound as a light brown solid (2.3g). LC/MS; Rt: 3.36min, MH^+ 337, 339.

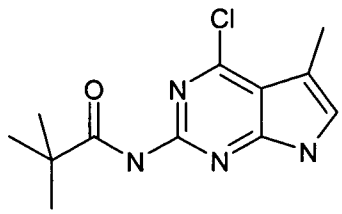
The solid which was suspended in the aqueous wash was isolated by filtration and dried in an oven overnight to give the title compound as a pale brown solid (8.3g). LC/MS; Rt: 3.46min, MH^+ 337, 339.

Intermediate 58
4-chloro-5-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine



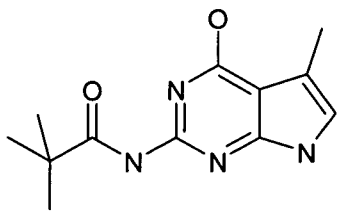
A mixture of *N*-(4-chloro-5-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2,2-dimethylpropanamide (18.4g) in aqueous sodium hydroxide (2N, 200ml) was stirred at 100°C for 2.5h. The mixture was cooled to ambient temperature and the precipitate isolated by filtration. The yellow solid was dried in an oven to give the title compound (10.4g). LC/MS; Rt 2.53min, MH^+ 183, 185.

Intermediate 59
***N*-(4-chloro-5-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-2,2-dimethylpropanamide**



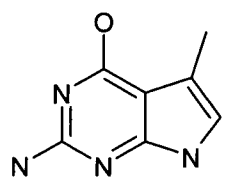
A stirred mixture of 2,2-dimethyl-*N*-(5-methyl-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)propanamide (19.8g) in phosphorus oxychloride (160ml) was heated at 110°C for 50min. The excess phosphorus oxychloride was evaporated under vacuum and the residue added to 0.880 ammonia solution (200ml) in ice (ca 300ml). The mixture was stirred vigorously for 45min and filtered. The precipitate was dried in an oven to give the title compound as a brown solid (18.4g, 86%). LC/MS; Rt 2.85min, MH^+ 267, 269.

Intermediate 60
2,2-dimethyl-*N*-(5-methyl-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)propanamide



A stirred mixture of 2-amino-5-methyl-1,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (16.6g) and 4-(dimethylamino)pyridine (0.62g) in trimethylacetic anhydride (90ml) was stirred at 120°C for 1.5h. The reaction mixture was left to cool to room temperature and then stood in an ice bath. Freezer cold ether (300ml) was added and the precipitate filtered to give the title compound (19.6g, 78%). LC/MS; Rt 2.5min, MH^+ 249.

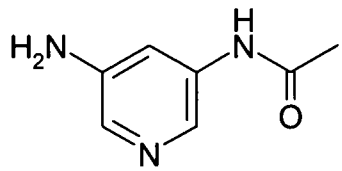
Intermediate 61
2-amino-5-methyl-1,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one



A mixture of 2-chloropropionaldehyde dimethyl acetal (11.9ml, Fluka) in hydrochloric acid (1N, 44ml) and ethanol (13.5ml) was stirred at 70°C for 2h and the reaction mixture removed from the heat source. A mixture of 2,4-diamino-6-hydroxypyrimidine (10g, Aldrich) and sodium bicarbonate (16.6g) in water (100ml) was stirred at 50°C for

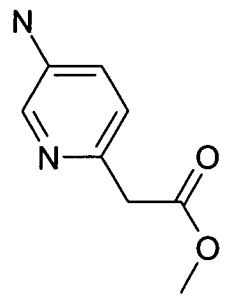
15min. The hydrolysed acetal mixture was added cautiously and stirred for 15min. The mixture was allowed to cool and then stood in an ice bath. Saturated aqueous ammonium chloride (50ml) was added, the precipitate isolated by filtration and washed with ice-cold water. The solid was dried in a vacuum oven overnight to give the title compound (11.2g, 86%). LC/MS; Rt 1.70min, MH^+ 165.

Intermediate 62
***N*-(5-amino-3-pyridinyl)acetamide**



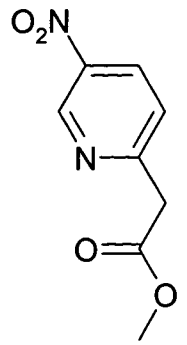
3,5-Diaminopyridine (0.20g, Synchem) was dissolved in dimethoxyethane (26.4ml) and stirred under nitrogen. Acetic anhydride (0.18g) was added and the reaction mixture was heated to reflux for 1h. More acetic anhydride (0.94g) was added and heating continued for 1h. The reaction mixture was evaporated to dryness under reduced pressure and the residue was triturated with ether, collected by filtration and dried under vacuum to give the title compound as a cream solid (0.25g) which was used without further purification. LC/MS; Rt 0.59min, MH^+ 152.

Intermediate 63
Methyl (5-amino-2-pyridinyl)acetate



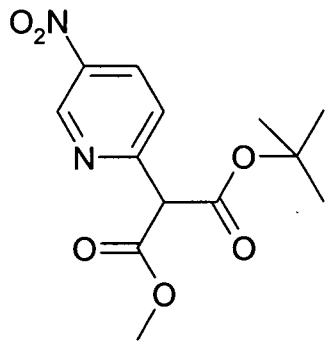
Methyl (5-nitro-2-pyridinyl)acetate (6.39g) was suspended in ethanol (30ml) and added to palladium on carbon (10%, 0.64g) dissolved in ethanol (20ml). Ammonium formate (10.28g) was added and the mixture refluxed under nitrogen for 1h. The reaction was filtered through Celite and concentrated. The residue was purified by chromatography eluting with DCM / methanol (19:1), the fractions containing product were evaporated to dryness to give the title compound (4.57g).

Intermediate 64
Methyl (5-nitro-2-pyridinyl)acetate



1,1-Dimethylethyl methyl (5-nitro-2-pyridinyl)propanedioate (10.26g) was suspended in dry DCM (50ml) and trifluoroacetic acid (8.01ml) added slowly. The reaction was stirred at 25°C under nitrogen for 18h. The reaction was diluted with DCM and washed with saturated sodium bicarbonate solution. The organics were extracted into DCM (x3), the combined extracts washed with brine, dried (magnesium sulphate) and reduced to dryness to leave the title compound (6.405g). Microanalysis; Predicted C 48.99%, H 4.08%, N 14.29%, Found C 49.13%, H 4.19%, N 14.01%.

Intermediate 65
1,1-dimethylethyl methyl (5-nitro-2-pyridinyl)propanedioate

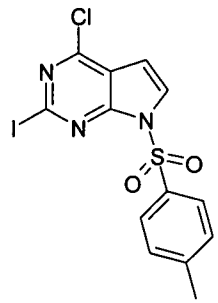


2-Chloro-5-nitropyridine (14.8g Aldrich) was suspended in dry DMF (150ml) and cooled to 0°C. Sodium hydride (60% in mineral oil, 7.46g) was added and the reaction stirred at room temperature for 10min. The reaction temperature was lowered to 0°C and tert-butyl methyl malonate (20.03ml) added dropwise keeping the reaction temperature below 5°C, the reaction was then stirred at room temperature for 2h. The reaction was poured into water (1200ml) and the organics extracted into ethyl acetate (x3). The combined organics were washed with brine, dried (magnesium sulphate) and concentrated. The residue was purified by chromatography, eluting with cyclohexane / ethyl acetate (5:1) and the fractions containing product were concentrated to give the title compound as a yellow gum (7.25g).

The water and DMF were evaporated from the aqueous phase, the residue suspended in ethyl acetate and poured into water. The organics were extracted into ethyl acetate (x3). The combined organics were dried (magnesium sulphate) and

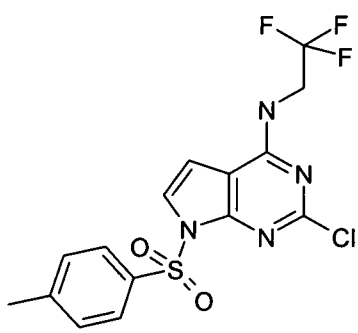
concentrated. The residue was combined with impure product from the previous column and purified by chromatography, eluting with cyclohexane / ethyl acetate (6:1). The fractions containing product were concentrated to leave the title compound which was combined with the previously isolated material to give the title compound (10.44g). Microanalysis; Predicted C 52.70%, H 5.41%, N 9.46%, Found C 52.73%, H 5.35%, N 9.20%.

Intermediate 66
4-chloro-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine



tert-Butyl nitrite (23ml) was added to a stirred mixture of 4-chloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (15g), cuprous iodide (10.6g), iodine (13.7g) and diiodomethane (44ml) in THF (250ml) at room temperature. The mixture was then heated to 80°C over 20min and kept at this temperature for 45min. The cooled reaction mixture was poured into an aqueous solution of sodium sulphite (1000ml) and extracted into ethyl acetate (3x 300ml). The combined extracts were washed with water (2x 300ml), dried (sodium sulphate) and the solvent evaporated. The residue was purified by flash chromatography on silica (800g) eluting with using cyclohexane / ether (3:1). The appropriate fractions were evaporated to give the title compound as an off-white solid (8.5g). LC/MS; Rt 3.74min, MH^+ 435.

Intermediate 67
2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

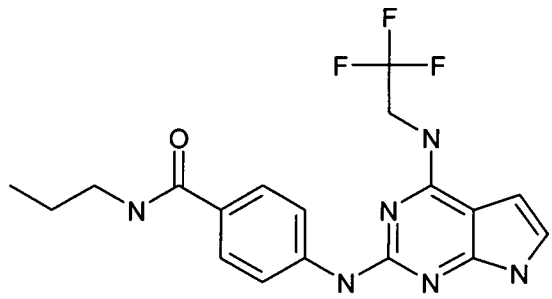


A mixture of 2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (4.0g), 2,2,2-trifluoroethylamine (1.49g, Aldrich), DIPEA (3.23ml) and ethanol (100ml)

was heated at 95°C under nitrogen overnight. The reaction mixture was concentrated, the residue dissolved in ethyl acetate (500ml) and washed with water (5x 300ml), and the organic phase concentrated. The residue was dissolved in ethanol (100ml), 2,2,2-trifluoroethylamine (1.49g, Aldrich), DIPEA (3.23ml) added and the mixture heated at 95°C under nitrogen overnight. The mixture was concentrated, the residue dissolved in ethyl acetate (450ml) and washed with water (5x 200ml). The organic phase was dried (hydrophobic frit) and concentrated to give the title compound (4.43g). LC/MS; Rt 3.64min, MH^+ 405.

Example 206

***N*-Propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**

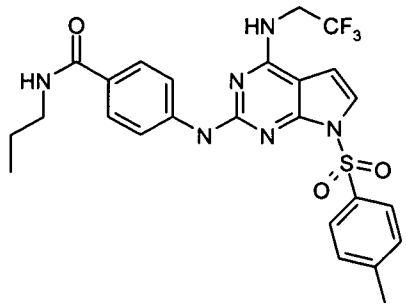


To

4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-propylbenzamide (101g) was added methanol (1500ml) followed by water (500ml) and solid potassium carbonate (76.5g). The initial solution rapidly became cloudy as it was heated to reflux. After 5h at reflux the reaction was cooled and filtered. The isolated white solid washed with water (~1.5l) and sucked dry on the filter. This solid was suspended in water containing 5% methanol by volume (500ml), another 500ml of methanol / water was added and the mixture stirred well for 1h, filtered under vacuum and washed with methanol / water (250ml). The solid was sucked dry and then further dried under high vacuum at 40°C, to give the desired product as a white solid (60.3g). LC/MS; Rt 2.90min, MH^+ 393. NMR; [D_6-DMSO] δH 11.22,(1H, s), 9.10,(1H, s), 8.19,(1H, t), 7.93-7.86,(3H, m), 7.73,(2H, d), 6.89,(1H, m), 6.51,(1H, m), 4.38,(2H, m), 3.20,(2H, q), 1.53,(2H, m), 0.89,(3H, t).

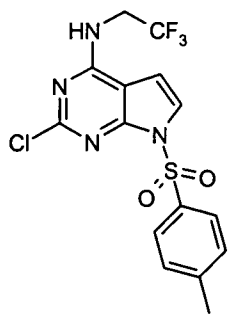
Intermediate 68

4-({7-[(4-Methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-propylbenzamide



To 4-amino-*N*-propylbenzamide (36.7g) was added 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (69.4g), solid potassium carbonate (34.4g) and nitrogen-purged tert-butanol (1700ml). This mixture was purged with nitrogen for 10min, tris(dibenzylideneacetone)dipalladium (0) (3.14g) and 2-dicyclohexylphosphino-2,4,6-triisopropyl biphenyl (3.28g) were added. The mixture was heated at 85°C overnight under nitrogen, excluding light. The reaction was cooled, partitioned between ethyl acetate and water, the organic phase washed with water, brine, dried and evaporated *in vacuo* to a dark red oil/foam. This crude product was dissolved in warm ethyl acetate (500ml) and cyclohexane (500ml) gradually added. The resulting solid was isolated by filtration under vacuum and the isolated beige solid washed with cyclohexane. The sticky solid was dissolved in ethyl acetate and evaporated to give a solid which was purified by chromatography on silica (1.5kg), eluting with an ethyl acetate / DCM gradient (0-50%). Evaporation of the solvents from the appropriate fractions gave the desired product as a white foam (70.76g). LC/MS; Rt 3.54min, MH^+ 547. NMR; [D_6-DMSO] δH 9.51,(1H, s), 8.34-8.29,(2H, m), 7.99-7.96,(4H, m), 7.84,(2H, d), 7.37-7.36,(3H, m), 6.85,(1H, d), 4.36,(2H, m), 3.23,(2H, q), 2.31,(3H, s), 1.55,(2H, m), 0.90,(3H, t) plus ethyl acetate.

Intermediate 69
2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

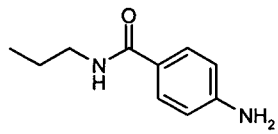


To 2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (140g) suspended in ethanol (1900ml) was added diisopropylethylamine (105.9g) followed by trifluoroethylamine (81.2g). The mixture was heated to reflux, using a dry-ice

condenser on top of the water condenser. After 4.5h trifluoroethylamine (40.6g) was added. The reaction was stirred at 75°C overnight. Trifluoroethylamine (40.6g) was added after slight cooling and heating continued. After 23.5h the reaction was cooled and the volatiles evaporated. The resulting oil was dissolved in ethyl acetate (1100ml), washed with water, brine, dried (magnesium sulphate) and evaporated to a brown oil that solidified overnight. This slightly waxy solid was crushed and stirred well in ether (350ml) for 15min. Hexane was added (300ml) and the slurry filtered under vacuum. The solid was washed with ether / hexane (1:1, 300ml) and sucked dry before being dried under high vacuum to give the desired product as a pale yellow-beige solid (111.4g). LC/MS; Rt 3.56min, MH^+ 405. NMR; [D_6-DMSO] δH 8.90,(1H, m), 7.96,(2H, d), 7.65,(1H, d), 7.46,(2H, d), 6.96,(1H, d), 4.30,(2H, m), 2.37,(3H, s).

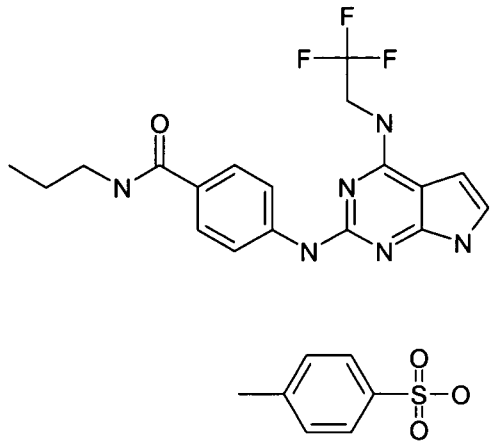
The filtrate from the first crop was evaporated and re-worked as above (x2) to give a second crop of product, (27.59g).

Intermediate 70
4-Amino-*N*-propylbenzamide



To palladium on carbon (10%, 50% wet, 4g) was added ethyl acetate (100ml) followed by the nitroamide (100g, Butt Park) in ethyl acetate (1600ml) and the mixture hydrogenated at room temperature and atmospheric pressure overnight. The reaction was filtered and the catalyst washed with ethyl acetate. The filtrate and washings were dried (magnesium sulphate), filtered and evaporated. To give the desired product as a pale gold oil which was further dried under vacuum for 1h (89.0g). LC/MS; Rt 1.85min, MH^+ 179. NMR; [D_6-DMSO] δH 7.96,(1H, t), 7.56,(2H, d), 6.52,(2H, d), 5.56,(2H, br s), 3.15,(2H, q), 1.49,(2H, m), 0.86,(3H, t).

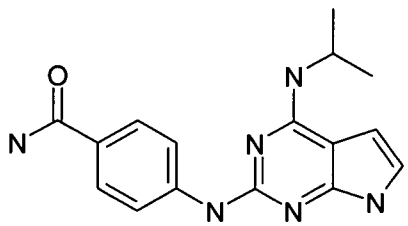
Example 207
***N*-Propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide 4-methylbenzenesulfonate**



N-Propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)ben zamide (61.5g) was suspended in dry THF (1050ml) and the mixture stirred at 40°C under nitrogen. A solution of p-toluene sulphonic acid monohydrate (29.8g, Aldrich) in dry THF (185ml) was added dropwise. After the first 50ml had been added the mixture was seeded with a little *N*-propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)ben zamide 4-methylbenzenesulfonate. The remainder of the p-toluene sulphonic acid was added dropwise over ~45min keeping the reaction temperature at ~40°C. After addition was complete the reaction mixture was stirred at 40°C for a further 1h, cooled to 0°C over 2h, held at 0°C for 0.5h, then warmed to ambient over 0.5h. The crystals were filtered off, washed with THF (500ml), and dried *in vacuo* at 40°C overnight. The crystals were ground and re-dried at 40°C for a further night to yield the desired product (87.5g). NMR; [D_6-DMSO] δH 11.71,(1H, s), 9.78,(1H, br s), 8.94,(1H, br s), 8.35,(1H, t), 7.83,(2H, d), 7.74,(2H, d), 7.51,(2H, d), 7.13,(2H, d), 7.02,(1H, s), 6.68,(1H, s), 4.41,(2H, m), 3.31,(2H, q), 2.29,(3H, s), 1.53,(2H, m), 0.89,(3H, t).

Example 208

4-({4-[(1-Methylethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

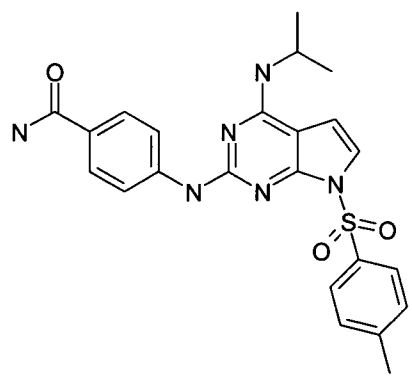


To 4-({4-[(1-methylethyl)amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2 -yl}amino)benzamide (50.52g) in methanol (1250ml) was added anhydrous potassium carbonate (45g) and water (250ml). The suspension was heated to reflux. After 4.75h the reaction was cooled, the methanol evaporated *in vacuo* and the aqueous residue extracted with ethyl acetate (1l, then 3x 100ml). The combined organics were washed with brine, dried (magnesium sulphate), filtered and the solvents evaporated to give a brown foam. This was purified by chromatography on silica

(1kg), eluting with ethyl acetate and then with increasing percentages of methanol (0-5%), to give, after evaporation of the solvents from the appropriate fractions, the desired product as a slightly green foam (32.3g). LC/MS; Rt 2.21min, MH^+ 311.

This material was dissolved with warming in acetone (400ml), water was added slowly until the mixture remained cloudy (total vol ~1.3l). Scratching initiated crystals, the mixture was left un-stoppered for 3 days, cooled in an ice-bath for ~2h and the crystals isolated by filtration. The solid was washed with a little water and then dried under high vacuum at 40°C overnight to give a pale yellowish solid (27.8g). LC/MS; Rt 2.25min, MH^+ 311. NMR; [D_6-DMSO] δH 11.03,(1H, s), 8.93,(1H, s), 7.91,(2H, d), 7.74,(2H, d), 7.72,(1H, br s), 7.04,(2H, br s), 6.80,(1H, s), 6.47,(1H, s), 4.44,(1H, m), 1.25,(6H, d) and acetone.

Intermediate 71
4-({4-[(1-Methylethyl)amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

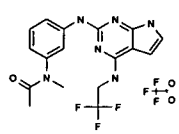
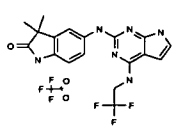


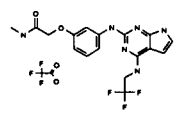
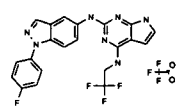
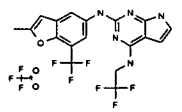
To
2-chloro-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (45g) was added 4-aminobenzamide (20.1g), nitrogen-purged tert-butanol (1125ml), anhydrous potassium carbonate (24.7g), 2-dicyclohexylphosphino-2,4,6-triisopropylbiphenyl (2.35g) and tris(dibenzylidene acetone)dipalladium (2.26g). The mixture was heated to reflux under nitrogen, excluding light. After 5.5h the mixture was cooled slightly and the solvent evaporated to leave red-brown oil/foam. This residue was diluted with water (1000ml) and extracted with ethyl acetate. The combined organics were washed with brine, dried (magnesium sulphate), filtered through celite and the solvent evaporated to leave a red-brown oil/foam. This material was purified by column chromatography on silica (1600g), eluting with DCM / ethyl acetate ((2:1 through to 1:1 and finally with 2:3). Evaporation of the solvents from the appropriate fractions gave the desired compound as a pale pink-beige solid (42.1g). LC/MS; Rt 3.32min, MH^+ 465. NMR; [D_6-DMSO] δH 9.31,(1H, s), 7.97,(4H, d), 7.83,(2H, d), 7.80,(1H, br s), 7.47, (1H, d), 7.38,(2H, d), 7.28,(1H, d), 7.11,(1H, br s), 6.80,(1H, d), 4.37,(1H, m), 2.31,(3H, s), 1.21,(6H, d) and ethyl acetate.

Method 11:

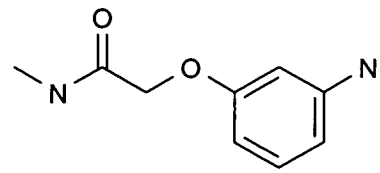
2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.6mmol) was suspended in t-butanol (6ml). One sixth of this mixture (~1ml) was treated with tris(dibenzylideneacetone)dipalladium (0) (5mol%, Aldrich), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (5mol%, Strem chemicals), potassium carbonate (0.14mmol) and an amine (0.15mmol). The reaction was allowed to heat at 80°C under reflux conditions overnight. The reaction was treated with tris(dibenzylideneacetone)dipalladium (0) (5mol%, Aldrich) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (5mol%) and potassium carbonate (0.14mmol) and stirred at 90°C for 16h. The reaction was diluted with ethyl acetate (1ml), filtered through Celite and concentrated under a stream of nitrogen. The reaction was redissolved in MeOH (1.5ml) and treated with sodium methoxide in methanol (0.5M, 500µl) and stirred at 80°C under reflux conditions for 2h. The reaction was concentrated under a stream of nitrogen, redissolved in ethyl acetate (2ml) and washed with water (2ml). The organic phase was separated (hydrophobic frit), concentrated and purified by MDAP.

The following examples were prepared using Method 11:

Example	Structure	Name	Amine Reagent/ Source	LC/MS Rt (min)	LC/MS MH^+
209		N-methyl-N-[3-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]acetamide trifluoroacetate	N-(3-aminophenyl)-N-methylacetamide / Merlin Synthesis	2.71	379
210		3,3-dimethyl-5-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-1,3-dihydro-2H-indol-2-one trifluoroacetate	5-amino-3,3-dimethyl-1,3-dihydro-2H-indol-2-one / Journal of the Chemical Society [Section] C: Organic	2.64	391

			(1971), (5), 952-5.		
211		N-methyl-2-{[3-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]oxy}acetamide trifluoroacetate	2-[(3-aminophenyl)oxy]-N-methylacetamide	2.71	395
212		N^2-[1-(4-fluorophenyl)-1*H*-indazol-5-yl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	1-(4-fluorophenyl)-1H-indazol-5-amine / Peakdale	3.52	442
213		N^2-[2-methyl-7-(trifluoromethyl)-1-benzofuran-5-yl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-methyl-7-(trifluoromethyl)-1-benzofuran-5-amine / N.D.Zelinsky Institute Building Blocks	3.69	430

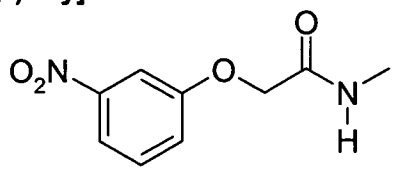
Intermediate 72



2-[(3-Aminophenyl)oxy]-*N*-methylacetamide

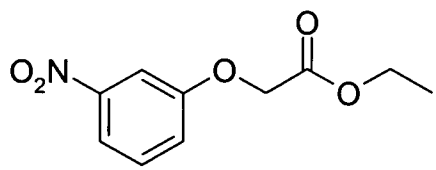
A stirred solution of *N*-methyl-2-[(3-nitrophenyl)oxy]acetamide (3.92g) in ethanol (100ml) was treated with palladium on carbon (5%wt, 700mg) and stirred under 1Atm. of hydrogen for 1.5h. The reaction was filtered through a pad of Celite and concentrated *in vacuo* to afford the title compound as a solid (3.12g, 93%). NMR; [D_6-DMSO] δH 7.92,(1H, bs), 6.90,(1H, t), 6.20-6.15,(2H, m), 6.08,(1H, dd), 5.10,(2H, s), 2.63,(3H, d).

Intermediate 73
***N*-Methyl-2-[(3-nitrophenyl)oxy]acetamide**



A solution of methylamine in methanol (2M, 80ml) was added dropwise to ethyl [(3-nitrophenyl)oxy]acetate and stirred for 30min. The resultant solid was collected by filtration and dried *in vacuo* to afford the title compound as a white crystalline solid (3.928g). The filtrate was concentrated *in vacuo* and trituration with ether afforded a second batch of the title compound as a very pale pink crystalline solid (900mg). NMR; [D_6-DMSO] δH 8.16,(1H, s), 7.83,(1H, dd), 7.77,(1H, t), 7.60,(1H, t), 7.44,(1H, dd), 4.64,(2H, s), 2.67,(3H, d).

Intermediate 74
Ethyl [(3-nitrophenyl)oxy]acetate

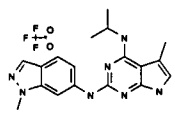
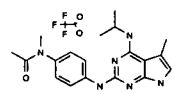


Ethyl bromoacetate (10.0ml) was added to a stirred suspension of potassium carbonate (20.76g, 0.15mol) and 3-nitrophenol (10.45g) in DMF (65ml) under nitrogen atmosphere. The reaction was heated to 70°C for 2h. The reaction was filtered and concentrated *in vacuo*. The residue was treated with water (200ml) and extracted with ethyl acetate (300ml). The combined extracts were dried (magnesium sulphate) and concentrated *in vacuo* to afford the title compound as an orange oil (16.78g). NMR; [$CDCl_3$] δH 7.89,(1H, dq), 7.73,(1H, t), 7.48,(1H, t), 7.28(1H, dq), 4.71(2H, s), 4.31,(q, 2H), 1.32,(3H, t).

Method 12:

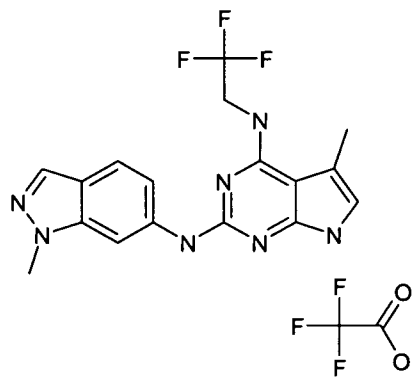
2-Iodo-5-methyl-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyri midin-4-amine (0.8mmol) was taken up in DMF (8ml). One eighth of this mixture (~1ml) was and treated with bis(dibenzylideneacetone) palladium (0) (10mol%, Aldrich), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (15mol%, strem chemicals), cesium carbonate (0.3mmol) and amine (0.2mmol) in DMF (1ml). The reaction was heated at 80°C for 2h. The reaction was filtered through Celite, concentrated (vacuum centrifuge) and the residue redissolved in methanol (1.5ml). This solution was treated with 0.5M sodium methoxide in methanol (500µl) and stirred at 80°C for 2h. The reaction was concentrated and purified using MDAP (3 runs).

The following examples were prepared using method 12:

Example	Structure	Name	Amine Reagent/ Source	LC/MS Rt (min)	LC/MS MH^+
214		5-methyl-N^4-(1-methylethyl)-N^2-(1-methyl-1H-indazol-6-yl)-1H-pyrrolo[2,3-d]pyrimidine-2,4-diamine trifluoroacetate	1-methyl-1H-indazol-6-amine / Pharm Lab Product List.	2.76	336
215		N-methyl-N-[4-({5-methyl-4-[(1-methylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]acetamide trifluoroacetate	N-(4-aminophenyl)-N-methylacetamide / Aldrich	2.51	353

Example 216

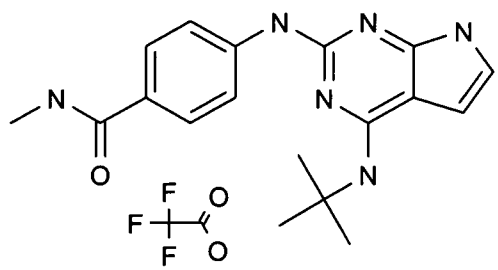
5-methyl-N^2-(1-methyl-1*H*-indazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate



2-Iodo-5-methyl-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.8mmol) was taken up in DMF (8ml). One eighth of this mixture (~1ml) was and treated with bis(dibenzylideneacetone) palladium (0) (10mol%, Aldrich), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (15mol%, strem chemicals), cesium carbonate (0.3mmol) and 1-methyl-1H-indazol-6-amine (0.2mmol, Pharm Lab Product List) in DMF (1ml). The reaction was heated at 80°C for 2h. The reaction was filtered through Celite, concentrated (vacuum centrifuge) and the residue redissolved in methanol (1.5ml). This solution was treated with 0.5M sodium methoxide in methanol (500µl) and stirred at 80°C for 2h. The reaction was concentrated and purified using MDAP (3 runs). LC/MS; MH^+ 376, Rt 3.05min.

Example 217

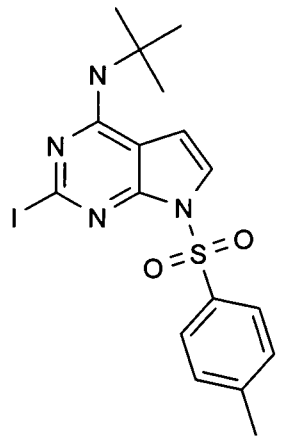
4-({4-[(1,1-dimethylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-methylbenzamide trifluoroacetate



N-(1,1-Dimethylethyl)-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.8mmol) was dissolved in DMF (16ml). Bis(dibenzylideneacetone) palladium (0) (10mol%, Aldrich), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (15mol%), cesium carbonate (0.3mmol) and 4-amino-*N*-methylbenzamide (0.15mmol) were combined with an aliquot of this solution (2ml). The reaction was heated at 80°C for 2h, allowed to cool, filtered through Celite and concentrated. The reaction was dissolved in methanol (1.5ml), treated with sodium methoxide in methanol (5M, 500µl), stirred at 70°C for 2h and left to stand at room temperature overnight. The reaction was heated for a further 5h, concentrated and purified using MDAP. The fractions containing product were evaporated to dryness to give title compound (3mg). LC/MS; Rt 2.58min, MH^+ 339.

Intermediate 75

***N*-(1,1-Dimethylethyl)-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine**



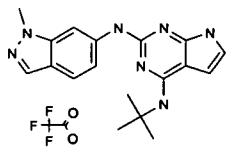
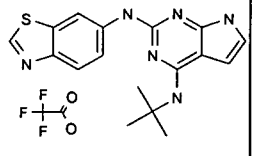
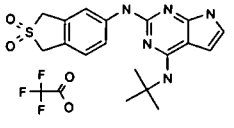
4-Chloro-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.15mmol) was suspended in ethanol (10ml) and treated with tert-butylamine (5.8mmol) and DIPEA (2.3mmol). The reaction was stirred at 80°C for 6.5h and then left to stand at room temperature over the weekend. The reaction was treated with tert-butylamine

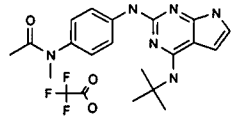
(100µl) and heated at 80°C for 2h. The reaction was concentrated and purified by chromatography on a silica cartridge (50g), eluting with an ethyl acetate / cyclohexane gradient (0-100%) over 30mins. The fractions containing product were combined and concentrated to give, after evaporation of the solvents, the title compound (0.4g). LC/MS; Rt 4.01min, MH^+ 471.

Method 13:

N-(1,1-Dimethylethyl)-2-iodo-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.8mmol) was taken up in DMF (16ml). One eighth of this mixture (~2ml) was treated with bis(dibenzylideneacetone) palladium (0) (10mol%, Aldrich), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl (15mol%, Strem chemicals), cesium carbonate (0.3mmol) and amine (0.15mmol). The reaction was heated at 80°C for 2h and allowed to cool before being filtered through Celite and concentrated. The reaction was taken up in MeOH (1.5ml) and treated with sodium methoxide in methanol (0.5M, 500µl) and allowed to stir at 70°C for 2h and left to stand at room temperature overnight. The reaction was then heated for a further 5h, concentrated and purified by MDAP (x2).

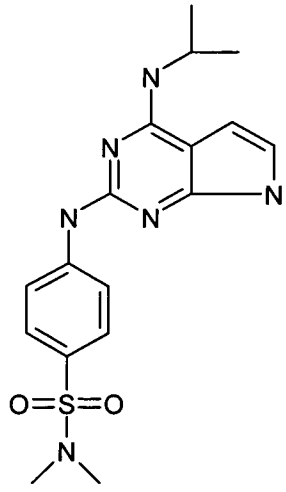
The following examples were prepared using Method 13:

Example	Structure	Name	Amine / Source	LC/MS Rt (min)	LC/MS MH^+
218		N^4-(1,1-dimethylethyl)-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	1-methyl-1*H*-indazol-6-amine / Pharm Lab Product List.	2.85	336
219		N^2-1,3-benzothiazol-6-yl-N^4-(1,1-dimethylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	1,3-benzothiazol-6-amine / Fluorochem	2.91	339
220		N^4-(1,1-dimethylethyl)-N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-1*H*-pyrrolo	1,3-dihydro-2-benzothiophen-5-amine	2.69	372

		[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2,2-dioxide / Maybridge		
221		*N*-[4-({4-[(1,1-dimethylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]-N-methylacetamide trifluoroacetate	*N*-(4-aminophenyl)-*N*-methylacetamide / Aldrich	2.63	353

Example 222

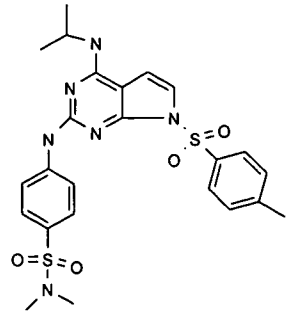
***N,N*-Dimethyl-4-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzenesulfonamide**



To a solution of *N,N*-dimethyl-4-({4-[(1-methylethyl)amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzenesulfonamide (77mg) in THF (3ml) was added tetrabutylammonium fluoride (1.0M solution in THF, 0.87ml). The resultant solution was stood at room temperature for 16h then heated in a sealed vial first at 80°C for 30min, then at 100°C for 30min by microwave irradiation. The reaction was concentrated *in vacuo* then partitioned between ethyl acetate (10ml) and saturated aqueous sodium carbonate (5ml). The organic layer was washed with saturated aqueous sodium carbonate (5ml), water (5ml) and concentrated *in vacuo*. The residual foam was purified by MDAP and the fractions containing the product combined and concentrated *in vacuo* to give the title compound as a cream solid (35mg). LC/MS; Rt 2.94min, MH^+ 375.

Intermediate 76

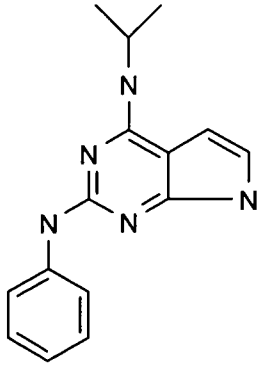
N,N-dimethyl-4-({4-[(1-methylethyl)amino]-7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzenesulfonamide



To a stirred mixture of 2-chloro-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (80mg), 4-amino-*N*,*N*-dimethylbenzenesulfonamide (52.7mg), potassium carbonate (42.4mg) and tris(dibenzylideneacetone)dipalladium (0) (20.1mg) in t-butanol (3ml) at room temperature under nitrogen, was added 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (15.6mg). The mixture was heated at 120°C in a sealed vessel by microwave irradiation for 40min. The resultant solution was partitioned between water (35ml) and ethyl acetate (15ml), the aqueous phase extracted with ethyl acetate (15ml). The combined organic phases were concentrated *in vacuo*. The residue was purified by chromatography on a silica cartridge (50g), eluting with ethyl acetate / cyclohexane (1:4 then 1:2). The appropriate fractions combined and concentrated *in vacuo* to give the title compound as a clear gum (80mg). LC/MS; Rt 3.84min, MH^+ 529.

Example 223

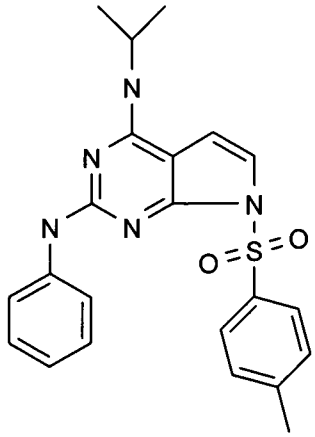
N^4-(1-methylethyl)-N^2-phenyl-1H-pyrrolo[2,3-d]pyrimidine-2,4-diamine



To a solution of N^4-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-N^2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (221mg) in THF (8ml) was added tetrabutylammonium fluoride (1.0M solution in THF, 3.15ml). The mixture was stirred under nitrogen at room temperature for 2h then heated 70°C for 17h. The reaction was concentrated *in vacuo* and the residue partitioned between ethyl acetate (20ml) and aqueous sodium bicarbonate (10ml). The organic layer was washed with aqueous sodium bicarbonate (10ml), water (10ml) and concentrated *in vacuo*. The residue was purified by chromatography

on a silica cartridge (20g), eluting with a gradient of methanol / DCM (0-15%) plus 1% triethylamine over 30min. The fractions containing the product were combined and concentrated *in vacuo* to give the title compound (100mg). LC/MS; Rt 2.91min, MH^+ 268.

Intermediate 77
N^4-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-N^2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



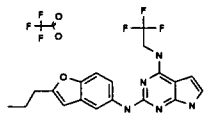
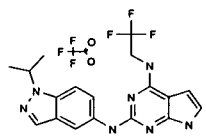
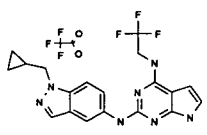
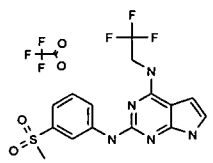
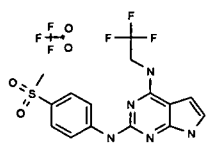
To a stirred mixture of 2-chloro-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (250mg), aniline (0.075ml), potassium carbonate (133mg) and tris(dibenzylideneacetone)dipalladium (0) (63mg) in t-butanol (10ml) at room temperature under nitrogen, was added 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (49mg). The mixture was heated at 120°C by microwave irradiation for 40min. The reaction was then treated with additional tris(dibenzylideneacetone)dipalladium (0) (10mg) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (10mg) and heated at 120°C by microwave irradiation for 15min. The reaction was concentrated *in vacuo*, the residue dissolved in methanol / DCM and adsorbed onto Florisil; before being purified by chromatography on a silica cartridge (50g), eluting with an ethyl acetate / cyclohexane gradient (0-50%) over 40min. The appropriate fractions were combined and concentrated *in vacuo* to give the title compound as a brown solid (223mg). LC/MS; Rt 3.84min, MH^+ 422.

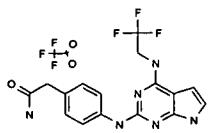
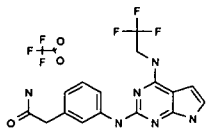
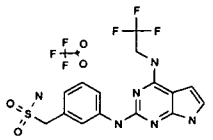
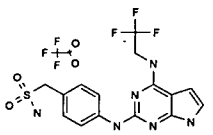
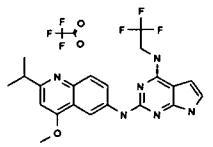
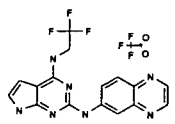
Method 14:

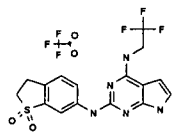
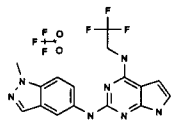
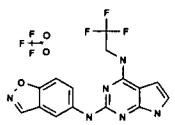
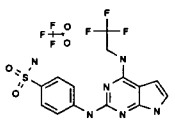
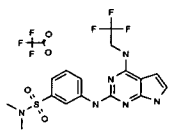
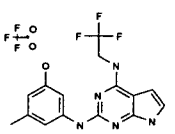
2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (2.4mmol) was taken up in t-butanol (48ml). One twenty-forth of this solution (~2ml) was treated with tris(dibenzylideneacetone)dipalladium (0) (0.01mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (0.01mmol), potassium carbonate (0.3mmol) and amine (0.2mmol). The reaction was heated at 90°C under reflux conditions for 16h. The reaction was diluted with ethyl acetate (1ml), filtered through Celite and concentrated under a stream of nitrogen. The residue was suspended in methanol (1.5ml) and treated with sodium methoxide in methanol (0.5M,

500µl) and stirred at 80°C under reflux conditions for 2h. The reaction was concentrated, the residue redissolved in ethyl acetate (1ml) and washed with water (1ml). The organic phase was concentrated and purified by MDAP.

The following samples were prepared using Method 14:

Example	Structure	Name	Amine Reagent/ Source	LC/MS Rt (min)	LC/MS MH^+
224		N^2-(2-propyl-1-benzofuran-5-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	(2-propyl-1-benzofuran-5-yl)amine / Key Organics Ltd	3.43	390
225		N^2-[1-(1-methylethyl)-1*H*-indazol-5-yl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	1-(1-methylethyl)-1H-indazol-5-amine / Zannan Pharma	2.86	390
226		N^2-[1-(cyclopropylmethyl)-1*H*-indazol-5-yl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	1-(cyclopropylmethyl)-1H-indazol-5-amine / Zannan Pharma	2.90	402
227		N^2-[3-(methylsulfonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	[3-(methylsulfonyl)phenyl]amine hydrochloride / Acros	2.80	386
228		N^2-[4-(methylsulfonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	4-(methylsulfonyl)aniline / Peakdale	2.83	386

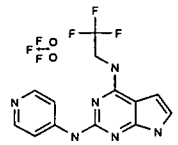
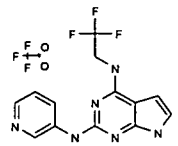
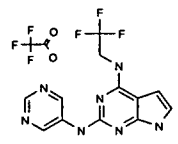
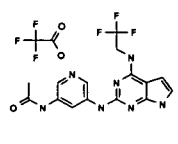
229		2-[4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]acetamide trifluoroacetate	2-(4-aminophenyl)acetamide / Peakdale	2.31	365
230		2-[3-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]acetamide trifluoroacetate	2-(3-aminophenyl)acetamide / Chemstep	2.35	365
231		1-[3-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]methanesulfonamide trifluoroacetate	1-(3-aminophenyl)methanesulfonamide / Peakdale	2.48	401
232		1-[4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]methanesulfonamide trifluoroacetate	1-(4-aminophenyl)methanesulfonamide / Peakdale	2.47	401
233		N^2-[2-(1-methylethyl)-4-(methyloxy)-6-quinolinyl]-N^4-(2,2,2-trifluoroethyl)-1H-pyrrolo[2,3-d]pyrimidine-2,4-diamine trifluoroacetate	2-(1-methylethyl)-4-(methyloxy)-6-quinolinamine	2.63	431
234		*N*^{2}-6-quinoxalinyl-*N*^{4}-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	6-quinoxalinamine / Maybridge	2.86	360

235		N^2-(1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)-N^4-(2,2,2-trifluoroethyl)-1H-pyrrolo[2,3-d]pyrimidine-2,4-diamine trifluoroacetate	2,3-dihydro-1-benzothiophen-6-amine 1,1-dioxide/Park Research	2.74	398
236		*N*^{2}-(1-methyl-1*H*-indazol-5-yl)-*N*^{4}-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	1-methyl-1H-indazol-5-amine / Bionet BB	2.59	362
237		*N*^{2}-1,2-benzisoxazol-5-yl-*N*^{4}-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	1,2-benzisoxazol-5-amine / Key Organics Ltd	2.70	349
238		4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzenesulfonamide trifluoroacetate	4-aminobenzenesulfonamide / Sigma	2.66	387
239		N,N-dimethyl-3-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzenesulfonamide trifluoroacetate	3-amino-N,N-dimethylbenzenesulfonamide / Asinex	3.05	415
240		3-methyl-5-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenol trifluoroacetate (salt)	3-amino-5-methylphenol / WO 2005115145	2.76	338

Method 15:

2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.1mmol) was suspended in t-butanol (2ml), and treated with tris(dibenzylideneacetone)dipalladium (0) (0.01mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (0.01mmol), potassium carbonate (0.3mmol) and amine (0.15mmol). The reaction was heated at 90°C over night, allowed to cool and then taken up in ethyl acetate and filtered through Celite. The filtrate was concentrated, the residue suspended in methanol (1.5ml) and treated with sodium methoxide in methanol (0.5M, 500µl) and heated at 70°C for 1.5h. The reactions were concentrated and purified by MDAP.

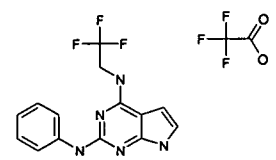
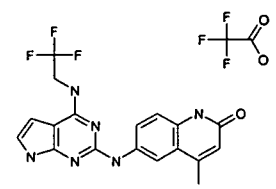
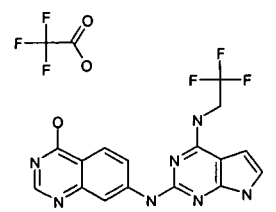
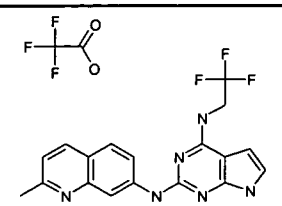
The following examples were prepared using Method 15:

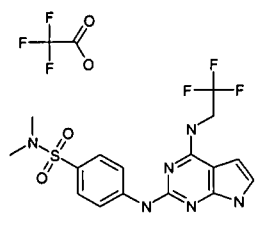
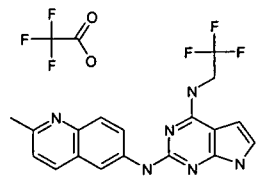
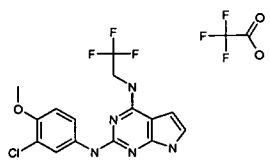
Example	Structure	Name	Amine Reagent/ Source	LC/MS Rt (min)	LC/MS MH^+
241		N^2-4-pyridinyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	4-pyridinamine / Aldrich	2.16	309
242		N^2-3-pyridinyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	3-pyridinamine / Aldrich	2.20	309
243)		N^2-5-pyrimidinyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	5-pyrimidinamine / Chemstep	2.55	310
244		N-[5-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-3-pyridinyl] acetamide trifluoroacetate	N-(5-amino-3-pyridinyl)acetamide	2.34	366

Method 16:

A mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (40.5mg), the aniline (0.15mM), potassium carbonate (41.5mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (4.8mg) and tris(dibenzylideneacetone)dipalladium (0) (9.2mg) in t-butanol (2.0ml) was stirred at 80°C under nitrogen overnight. The reaction was left to cool to room temperature under nitrogen. The reaction was diluted with ethyl acetate (2ml) and filtered through a Celite cartridge. The filtrate was evaporated and the residue treated with sodium methoxide in methanol (0.5M, 2ml). The reaction was stirred at 80°C under nitrogen for 2.25h. The solvent was evaporated and the residue purified by MDAP. The appropriate fractions were combined and reduced to dryness to leave the desired product.

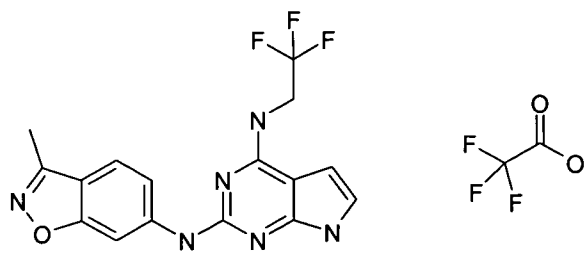
The following examples were prepared using Method 16:

Example	Structure	Name	Aniline / Source	LC/MS MH^+	LC/MS Rt (min)
245		N^2-phenyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	Aniline / Aldrich	308	2.92
246		4-methyl-6-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-2(1H)-quinolinone trifluoroacetate	6-Amino-4-methyl-2(1H)-quinolinone / Fluorochem	289	2.65
247		7-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-4(1H)-quinazolinone trifluoroacetate	7-amino-4(1*H*)-quinazolinone / Specs	376	2.64
248		N^2-(2-methyl-7-quinolinyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2	2-Methyl-7-quinolinamine / Journal of Medicinal	373	2.44

		,4-diamine trifluoroacetate	Chemistry, 20(11), 1528-31; 1977		
249		N,N-dimethyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzenesulfonamide trifluoroacetate	4-Amino-*N*,*N*-dimethylbenzenesulfonamide / MicroChemistry Ltd.	415	3.06
250		N^2-(2-methyl-6-quinolinyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	6-Amino-2-methylquinoline / Avocado	373	2.41
251		N^2-[3-chloro-4-(methyloxy)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	3-Chloro-4-(methyloxy)aniline / Aldrich	372	3.18

Example 252

N2-(3-Methyl-1,2-benzisoxazol-6-yl)-N4-(2,2,2-trifluoroethyl)-1H-pyrrolo[2,3-d]pyrimidine-2,4-diamine trifluoroacetate

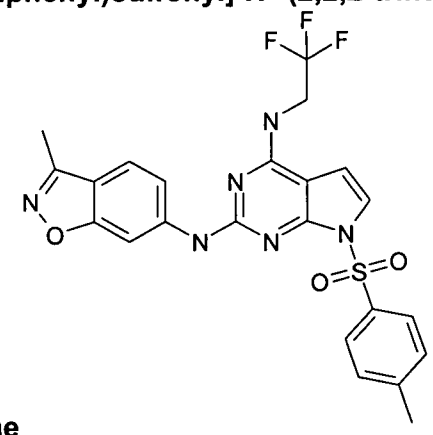


N^2-(3-methyl-1,2-benzisoxazol-6-yl)-7-[(4-methylphenyl)sulfonyl]-N^4-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (33mg) was dissolved in methanol (2ml) and sodium methoxide in methanol (0.5M, 2ml) added. The mixture was heated at 80°C under nitrogen for 90min. The reaction mixture was allowed to cool to room

temperature and hydrochloric acid (2M, 650µl) added. The solvent was evaporated under vacuum, the residue was dissolved in methanol and filtered through an aminopropyl SPE cartridge (1g). The column was washed with methanol (30ml) and the solvent evaporated under a stream of nitrogen. The residue was dissolved in DMSO (2ml), filtered and the filtrate purified by MDAP. Evaporation of the solvent from appropriate fractions left the title compound (12.2mg). LC/MS; Rt 3.19min, MH^+ 363.

Intermediate 78

N^2-(3-methyl-1,2-benzisoxazol-6-yl)-7-[(4-methylphenyl)sulfonyl]-N^4-(2,2,2-trifluo

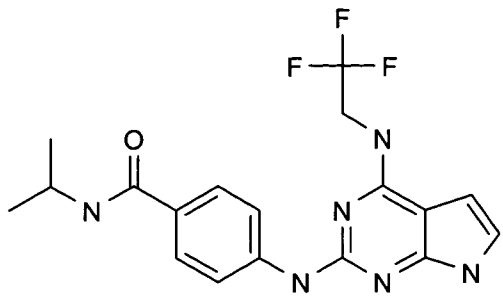


roethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

A mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-N-(2,2,2-trifluoroethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (310mg), 3-methyl-1,2-benzisoxazol-6-amine (148mg, Chemstep Product List), tris(dibenzylideneacetone)dipalladium (0) (281mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (219mg) and potassium carbonate (68mg) in t-butanol (11ml) was heated at 150°C in a sealed vial by microwave irradiation for 2h. The solvent was removed under vacuum, the residue dissolved in methanol and filtered through an SCX-2 SPE cartridge (20g). The column was washed with methanol and the product eluted with 2M ammonia in methanol. The basic fractions were concentrated *in vacuo* and the residue dried *in vacuo* overnight. The residue was adsorbed onto Florisil and purified by chromatography on a silica column (20g), eluting with an ethyl acetate / cyclohexane gradient (0-100%) over 30min. After evaporation of the solvents *in vacuo*, the residual oil was dissolved in methanol and eluted through an aminopropyl SPE (1g). The column was washed with methanol and the solvent was evaporated under vacuum to yield the desired product (33mg, purity 66%). LC/MS; Rt 3.79min, MH^+ 517.

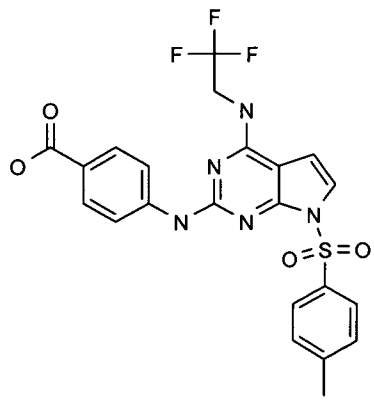
Example 253

***N*-(1-methylethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**



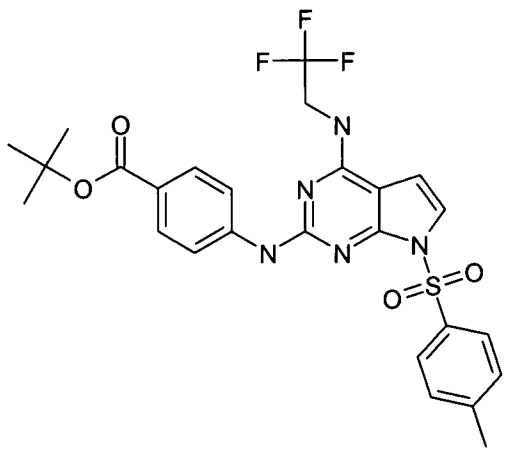
The 4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid (60mg), TBTU (42mg) and DIPEA (0.062ml) in DMF (0.75ml) were stirred at room temperature in a stoppered flask. After 30min isopropylamine (0.101ml) was added and the reaction stirred for 1h. The reaction was reduced to dryness *in vacuo* and the residue azeotroped with methanol. The residue, dissolved in methanol, was applied to a pre-conditioned SCX-2 cartridge (5g), which was washed with methanol and the product eluted with 2N ammonia in methanol. The basic fraction was reduced to dryness, the residue dissolved in water (0.5ml) and methanol (1.5ml) and potassium carbonate (41mg) added. The mixture was stirred at 85°C for 6h. Potassium carbonate (30mg) was added and the reaction stirred at 85°C for a further 15h. The reaction was filtered, the solid washed with water and ether and dried *in vacuo*, to give the title compound as an off-white solid (17mg). LC/MS; MH^+ 393, Rt 3.03min.

Intermediate 79
4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid



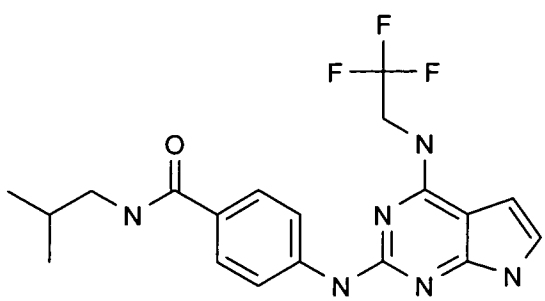
The 1,1-dimethylethyl 4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoate (150mg), in DCM (6ml) was treated with TFA (1ml) and stirred at room temperature for 1.75h. The volatiles were evaporated under vacuum and the residual solid dissolved in ethyl acetate (25ml). The solution was washed with water (2x 25ml) and dried (hydrophobic frit). Evaporation of the solvent left the title compound as a green solid (130mg). LC/MS; MH^+ 506, Rt 3.72min.

Intermediate 80
1,1-dimethylethyl
4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoate



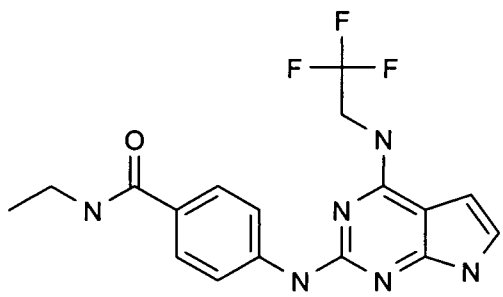
A mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (200mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (11.8mg), tris(dibenzylideneacetone)dipalladium (0) (45.2mg), potassium carbonate (95.6mg) and tert-butyl 4-aminobenzoate (114.5mg, Fluka) in t-butanol (5ml) was degassed. The vessel was sealed and irradiated at 120°C for 3h in a microwave. The reaction mixture was reduced to dryness and the residue suspended in ethyl acetate. The suspension was applied to a SCX-2 cartridge (10g, pre-conditioned with methanol followed by ethyl acetate) and eluted with ethyl acetate, methanol and 2N ammonia in methanol. The ammonia fraction was concentrated, redissolved in methanol and adsorbed onto Florisil. This was purified by chromatography on a silica cartridge (100g), eluting with an ethyl acetate / cyclohexane gradient (0-50%). The appropriate fractions were combined, reduced to dryness and azeotroped with ether to give the title compound as a yellow solid (150mg). LC/MS; MH^+ 562, Rt 4.00min.

Example 254
***N*-(2-methylpropyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**



The 4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid (60mg), TBTU (42mg) and DIPEA (0.062ml) in DMF (0.75ml) were stirred at room temperature in a stoppered flask. After 30min isobutylamine (0.117ml) was added and the mixture stirred for 1h. The solvent was evaporated under vacuum and the residue azeotroped with methanol. The residue in methanol was applied to a pre-conditioned SCX-2 cartridge (5g), the cartridge washed with methanol and the product eluted with 2N ammonia in methanol. The basic fraction was reduced to dryness and the residue dissolved in water (0.5ml) and methanol (1.5ml). Potassium carbonate (69mg) was added and the mixture stirred at 85°C for 7h. The mixture was filtered and the solid washed with water and ether. The washes were repeated and the ether fractions were combined with the solid and reduced to dryness. The residual solid was dissolved in warm methanol and applied to a SCX-2 cartridge (5g, pre-conditioned with methanol). The cartridge was washed with methanol and the product eluted with 2N ammonia in methanol solution. The ammonia fraction was reduced to dryness to leave the title compound as a white solid (23.2mg). LC/MS; MH^+ 407, Rt 3.09min.

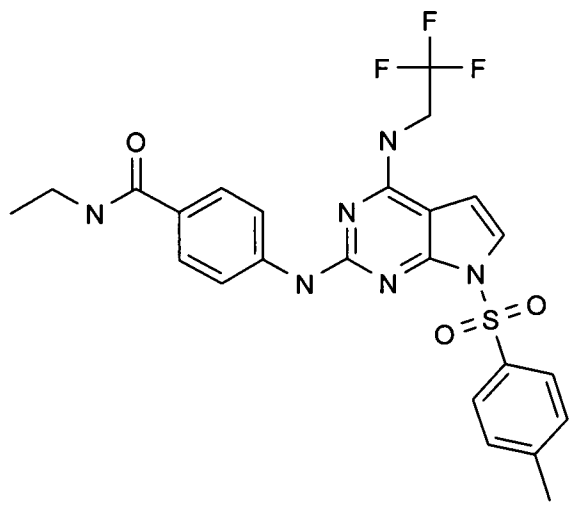
Example 255
***N*-ethyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**



N-Ethyl-4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide (306mg) and potassium carbonate (794mg) in methanol (10ml) and water (5ml) were stirred at 85°C for 2.5h. The reaction was allowed to cool to ambient temperature and the solvents evaporated under vacuum. The solid was suspended in methanol, filtered and the filtrate applied to an SCX-2 cartridge (20g, pre-conditioned with methanol). The cartridge was washed with methanol the product eluted with 2N ammonia in methanol. The ammonia fractions were combined and reduced to dryness. The residual solid was dissolved in methanol and adsorbed onto Florisil. This material was purified by chromatography on a silica cartridge (50g), eluting with a DCM / methanol gradient (0-25%) over 30min. A precipitate formed in one of the eluted fractions, this was isolated by filtration and washed with DCM. After drying *in vacuo,* this yielded the title compound as a white /

pink solid (12mg). LC/MS; MH^+ 379, Rt 2.81min.

Intermediate 81
***N*-Ethyl-4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**

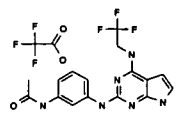
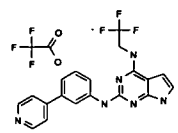


The
2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (350mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (21mg), tris(dibenzylideneacetone)dipalladium (0) (48mg), potassium carbonate (167mg) and 4-(ethylcarbamyl)aniline (170mg) in t-butanol (12ml) were heated at 80°C under nitrogen for ~18h. The reaction was removed from the heat source and the contents transferred to a microwave vessel. The mixture was degassed with nitrogen and further tris(dibenzylideneacetone)dipalladium (0) (48mg) was added. The mixture was heated in a sealed vessel by microwave irradiation at 105°C for 2h. The reaction mixture was degassed with nitrogen and heated in the microwave again at 105°C for 1.5h. The reaction mixture was evaporated under vacuum and the residue suspended in ethyl acetate. The suspension was filtered through Celite, the filtrate was adsorbed onto Florisil and purified by chromatography on a silica cartridge (100g), eluting with an ethyl acetate / cyclohexane gradient (0-100%) over 60min. The appropriate fractions were combined and the solvents removed by evaporation to give the title compound as a yellow oil (306mg). LC/MS; MH^+ 533, Rt 3.61min

Method 17:
2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (995mg) was suspended in t-butanol (48ml). An aliquot (2ml) of this mixture was treated with tris(dibenzylideneacetone)dipalladium (0) (0.01mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (0.01mmol), potassium carbonate (0.3mmol) and an amine (0.2mmol). The reaction was heated at 90°C over the weekend, allowed to cool and the solvent evaporated under a stream of nitrogen. Then residue was suspended in ethyl acetate (2ml) and filtered through Celite. The filtrate was concentrated, suspended in methanol (1.5ml) and treated with sodium

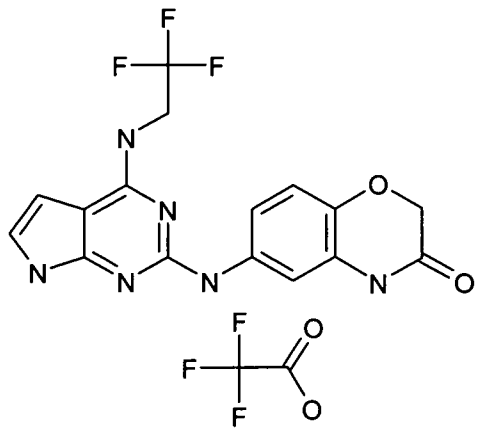
methoxide in methanol (0.5M, 500µl) and heated at 70°C for 2.5h. The reaction was concentrated and purified using MDAP.

The following examples were prepared using Method 17:

Example	Structure	Name	Amine / Source	LC/MS Rt (min)	LC/MS MH^+
256		N-[3-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]acetamide trifluoroacetate	N-(3-aminophenyl)acetamide hydrochloride / Acros	2.52	365
257		N^2-[3-(4-pyridinyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	3-(4-pyridinyl)aniline / Maybridge	2.62	385

Example 258

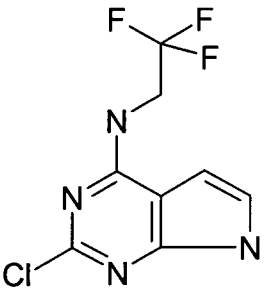
6-({4-[(2,2,2-Trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-2*H*-1,4-benzoxazin-3(4*H*)-one trifluoroacetate



6-Amino-2*H*-1,4-benzoxazin-3(4*H*)-one (32.8mg, ABCR) was added to a mixture of 2-chloro-*N*-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (25mg),

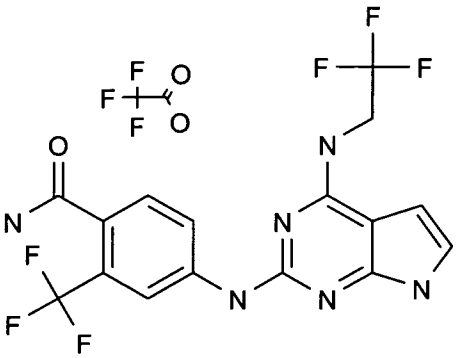
tris(dibenzylideneacetone)dipalladium (0) (9.2mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (7.1mg), potassium carbonate (27.6mg), in t-butanol (1.5ml). The reaction was heated by microwave irradiation at 120°C for 40min in a sealed vial. The reaction mixture was diluted with ethanol and filtered through a plug of Celite. The solvent was evaporated under a stream of nitrogen and the residue was purified by MDAP, to give after evaporation of the solvents, the title compound (10.0mg). LC/MS ; Rt 2.73min, MH^+ 379.

Intermediate 82
2-chloro-*N*-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (6.1g) was treated with aqueous sodium hydroxide (2N, 80ml) and t-butanol (80ml) and the suspension stirred at 50°C for 4h. The reaction was allowed to cool to room temperature overnight before heating at 60°C for 6h. The reaction was concentrated *in vacuo* to ~80ml, neutralized with hydrochloric acid (2N) and extracted with ethyl acetate (2x 80ml). The combined organic extracts were dried (hydrophobic frit) and reduced to dryness *in vacuo*, to give the title compound as a cream solid (3.76g). LC/MS; Rt 2.89min, MH^+ 251.

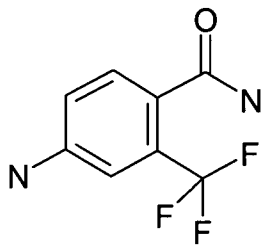
Example 259
4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-2-(trifluoromethyl)benzamide trifluoroacetate



2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (2.4mmol) was taken up in t-butanol (48ml). An aliquot (2ml) of this mixture was treated with tris(dibenzylideneacetone)dipalladium (0) (0.01mmol),

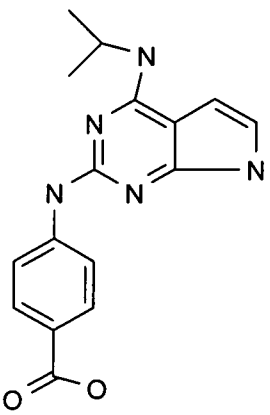
2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (0.01mmol), potassium carbonate (0.3mmol) and 4-amino-2-(trifluoromethyl)benzamide (0.2mmol) and allowed to stir at 90°C overnight. The reaction was diluted with ethyl acetate (2ml) and filtered through Celite. The filtrate was concentrated and the residue treated with methanol (1.5ml) and sodium methoxide in methanol (0.5M, 500µl) and heated at 70°C for 2h. The reaction was diluted with water (1.5ml), a precipitate formed which was isolated by filtration and purified using MDAP. The fractions containing product were concentrated to give title compound (0.0115g). LC/MS; Rt 2.85min, MH^+ 418.94.

Intermediate 83
4-amino-2-(trifluoromethyl)benzamide



4-Amino-2-(trifluoromethyl)benzoic acid (825mg, Matrix Scientific) in DMF (8.0ml) was treated with HATU (1.68g) and DIPEA (2.10ml) and the mixture stirred under nitrogen for 15min. Aqueous ammonia solution (16ml) was added and the reaction stirred at room temperature overnight. The volatiles were evaporated *in vacuo* and the residue azeotroped with DCM. The residue was dissolved in methanol, adsorbed onto Florisil and applied to a silica cartridge (100g). The cartridge was eluted with a methanol / DCM (0-30%) + 1% triethylamine gradient. Appropriate fractions were combined and reduced to dryness. The resulting solid was washed with DCM and the solid isolated by filtration to give the tile compound as a white solid (611mg). LC/MS; MH^+ 205, Rt 0.96min.

Example 260
4-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic

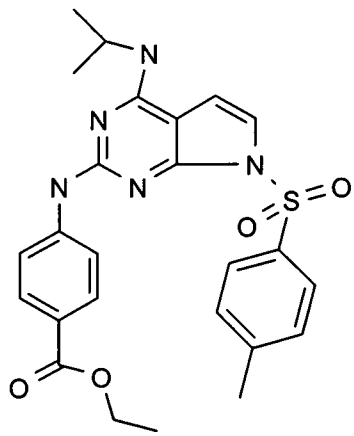


acid

Ethyl 4-({4-[(1-methylethyl)amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoate (130mg) was dissolved in a solution of sodium methoxide in

methanol (0.5M, 5ml) and the reaction heated at 80°C under nitrogen for ~2h. The reaction was allowed to cool to room temperature, aqueous sodium hydroxide solution (2N, 2ml) added and the reaction stirred at ambient temperature for ~3h. The reaction was left in a freezer overnight and then stirred for a further ~4h at room temperature. The reaction was diluted with water (total volume ~20ml), and neutralised with glacial acetic acid. The resulting precipitate was isolated by filtration, washed with water and sucked dry on the sinter. The solid was dissolved in acetone, the solution filtered and the product precipitated by addition of water. The precipitate was filtered off, washed with water and sucked dry on the sinter to give the desired product as a yellow solid (42mg). LC/MS; MH^+ 311.97, Rt 2.57min.

Intermediate 84
Ethyl
4-({4-[(1-methylethyl)amino]-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoate

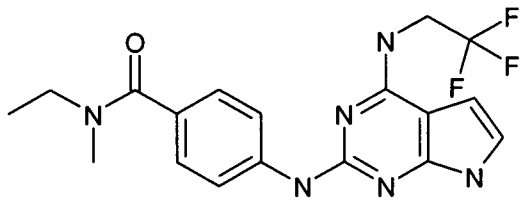


2-Chloro-*N*-(1-methylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (182mg), ethyl 4-aminobenzoate (99mg), tris(dibenzylideneacetone)dipalladium (0) (23mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (11.8mg) and potassium carbonate (103.7mg) were mixed in t-butanol (8ml), the mixture degassed and then heated at 90°C under nitrogen for ~20h. The reaction was allowed to cool, diluted with ethyl acetate and adsorbed onto silica. The silica was applied to a silica cartridge (10g) and the cartridge eluted with an ethyl acetate / cyclohexane gradient (0-100%). The product fractions were reduced to dryness, adsorbed onto silica and applied to a silica cartridge (10g). The cartridge was eluted with an ethyl acetate / cyclohexane gradient (0-40%). The appropriate fractions were reduced to dryness *in vacuo*, the residue dissolved in methanol and filtered through an SCX-2 SPE (1g) washing the cartridge with further methanol. The combined filtrate and washings were concentrated *in vacuo* to give the title compound as a yellow glassy solid. NMR; [D_6-DMSO] δH 9.52,(1H, s), 8.03,(2H, d), 7.97,(2H, d), 7.87,(2H, d), 7.53,(1H, d), 7.38,(2H, d), 7.30,(1H, m), 6.82,(1H, m), 4.40-4.34,(1H, m), 4.28,(2H, q), 2.32,(3H,

s), 1.32,(3H, t), 1.21,(6H, d).

Example 261

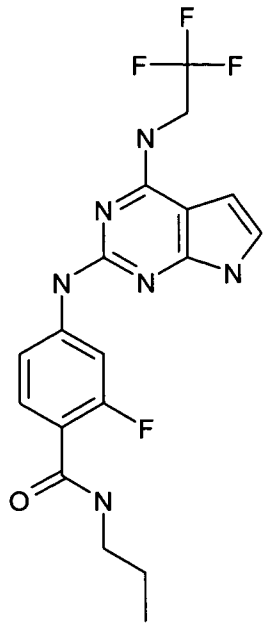
***N*-ethyl-*N*-methyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**



A mixture of 4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid (35.1mg) and TBTU (35.3mg) in DMF (0.5ml) was treated with DIPEA (0.053ml) and the mixture was stirred vigorously at room temperature for 30min. *N*-Ethylmethylamine (0.086ml) was added and the mixture stirred for 1.25h. DIPEA (0.026ml) and TBTU (15.0mg) were added and the mixture was stirred for 30min. *N*-Ethylmethylamine (0.042ml) was then added and the mixture stirred for a further 1.25h. The solvent was evaporated under vacuum, the residue dissolved in a small amount of methanol and applied to an SCX-2 cartridge (1g, pre-conditioned with methanol). The cartridge was eluted with methanol, then with 2M ammonia in methanol. The appropriate fractions were collected and the solvent evaporated under vacuum. The residue was further purified by MDAP to give, after the appropriate fractions were combined and the solvent evaporated under vacuum, the title compound (12mg). LC/MS; Rt 2.76min, MH^+ 393.

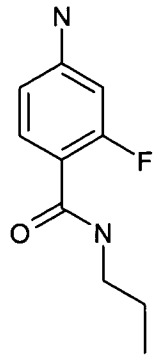
Example 262

2-fluoro-*N*-propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide



A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-amino-2-fluoro-*N*-propylbenzamide (58mg) and potassium carbonate (48.4mg) in t-butanol (4.5ml) under nitrogen, was treated with 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (17.9mg) and tris(dibenzylideneacetone)dipalladium (0) (22.9mg) were added and the stirred mixture was heated in a sealed tube in a microwave at 120°C for 1h. The mixture was cooled to room temperature and was partitioned between water (30ml) and ethyl acetate (30ml). The aqueous phase was extracted with ethyl acetate (30ml) and the solvent was evaporated from the combined organics *in vacuo*. The residue was treated with a solution of sodium methoxide in methanol (0.5M, 5ml) and the mixture heated at 80°C under nitrogen for 30min. The mixture was cooled to room temperature and the methanol was evaporated *in vacuo*. Water (30ml) was added and the mixture was extracted with ethyl acetate (2x 25ml). The combined organic phases were reduced to dryness *in vacuo*. The residue was purified by MDAP, the appropriate fractions were combined and the solvent evaporated *in vacuo* to leave the title compound as a white solid (58mg). LC/MS; Rt 3.13min, MH^+ 411.

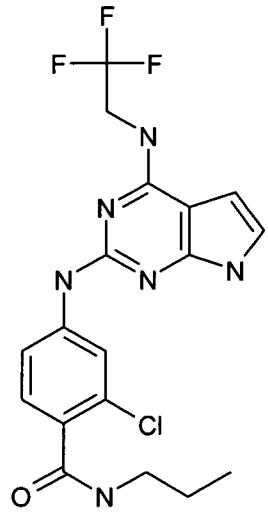
Intermediate 85
4-amino-2-fluoro-*N*-propylbenzamide



4-Amino-2-fluorobenzoic acid (300mg, Apin Chemicals Ltd.) was added to a stirred solution of PyBOP (1.08g), propylamine (561mg) and DIPEA (3.24ml) in DMF (15ml) at room temperature under nitrogen and the mixture was stirred overnight. The solvent was evaporated *in vacuo*, the residual gum was dissolved in the minimum amount of chloroform / methanol (4:1) and filtered through to an aminopropyl cartridge (50g). The cartridge was washed with chloroform / methanol (4:1) and the solvent evaporated from the combined filtrate and washings. The residue was dissolved in the minimum quantity of DCM, absorbed onto a silica cartridge and purified by chromatography, eluting with an ethyl acetate / cyclohexane gradient (0-100%) over 1h. Combination of the appropriate fractions and evaporation of the solvent *in vacuo* gave the title compound (296mg). LC/MS; Rt 2.22min, MH^+ 197.

Example 263

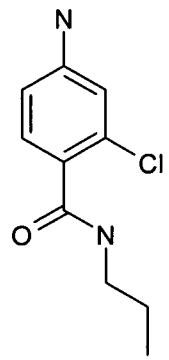
2-Chloro-*N*-propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide



A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-amino-2-chloro-*N*-propylbenzamide (65mg) and potassium carbonate (48.4mg) in t-butanol (4.5ml) under nitrogen, was treated with 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (17.9mg) and tris(dibenzylideneacetone)dipalladium (0) (22.9mg) were added and the stirred

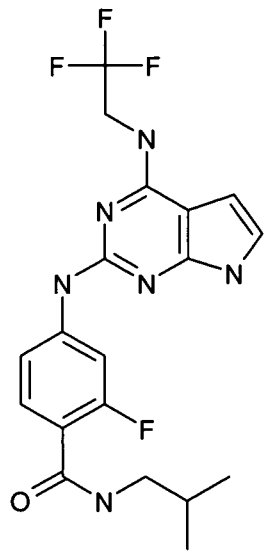
mixture was heated in a sealed tube in a microwave at 120°C for 1h. The mixture was cooled to room temperature and was partitioned between water (30ml) and ethyl acetate (30ml). The aqueous phase was extracted with ethyl acetate (30ml) and the solvent was evaporated from the combined organics *in vacuo*. The residue was purified by chromatography on a silica cartridge (50g) eluting with an ethyl acetate / cyclohexane gradient (0-100%) over 1h. After combination of the appropriate fractions and evaporation of the solvent *in vacuo*, the residue was treated with a solution of sodium methoxide in methanol (0.5M, 5ml) and the mixture heated at 80°C under nitrogen for 30min. The mixture was cooled to room temperature and the methanol was evaporated *in vacuo*. Water (30ml) was added and the mixture was extracted with ethyl acetate (2x 25ml). The combined organic phases were reduced to dryness *in vacuo*. The residue was purified by MDAP, the appropriate fractions combined and the solvent evaporated *in vacuo* to leave the title compound as a white solid (6mg). LC/MS Rt 3.04min, MH^+ 426.8.

Intermediate 86
4-Amino-2-chloro-*N*-propylbenzamide



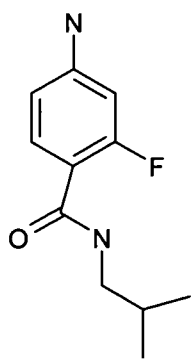
4-Amino-2-chlorobenzoic acid (300mg, Aldrich) was added to a stirred solution of PyBOP (1.0g), propylamine (517mg) and DIPEA (3.0ml) in DMF (15ml) at room temperature under nitrogen and the mixture was stirred overnight. The solvent was evaporated *in vacuo*, the residual gum was dissolved in the minimum amount of chloroform / methanol (4:1) and filtered through to an aminopropyl cartridge (50g). The cartridge was washed with chloroform / methanol (4:1) and the solvent evaporated from the combined filtrate and washings. The residue was dissolved in the minimum quantity of DCM, absorbed onto a silica cartridge and purified by chromatography, eluting with an ethyl acetate / cyclohexane gradient (0-100%) over 1h. Combination of the appropriate fractions and evaporation of the solvent *in vacuo* gave the title compound (356mg). LC/MS: Rt 2.19min, MH^+ 213.

Example 264
2-Fluoro-*N*-(2-methylpropyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*] pyrimidin-2-yl}amino)benzamide



A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-amino-2-fluoro-*N*-(2-methylpropyl)benzamide (63mg) and potassium carbonate (48mg) in t-butanol (4.5ml) was treated with 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (18mg) and tris(dibenzylideneacetone)dipalladium (0) (23mg) and the stirred mixture was heated in a sealed tube in a microwave at 120°C for 1h. The mixture was cooled to room temperature and was partitioned between water (30ml) and ethyl acetate (30ml). The aqueous phase was extracted with ethyl acetate (30ml) and the solvent was evaporated from the combined organics *in vacuo*. The residue was treated with a solution of sodium methoxide in methanol (0.5M, 5ml) and the mixture heated at 80°C under nitrogen for 30min. The mixture was cooled to room temperature and the methanol was evaporated *in vacuo*. Water (30ml) was added and the mixture was extracted with ethyl acetate (2x 25ml). The combined organic phases were reduced to dryness *in vacuo*. The residue was purified by MDAP, the appropriate fractions combined and the solvent evaporated *in vacuo* to leave the title compound as a white solid (60mg). LC/MS; Rt 3.27min, MH^+ 424.9.

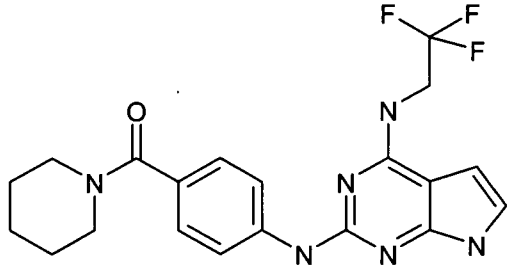
Intermediate 87
4-Amino-2-fluoro-*N*-(2-methylpropyl)benzamide



4-Amino-2-fluorobenzoic acid (300mg, Apin) was added to a stirred solution of PyBOP (1.11g), isobutylamine (707mg) and DIPEA (3.3ml) in DMF (15ml) at room temperature under nitrogen and the mixture was stirred overnight. The solvent was evaporated *in vacuo*, the resulting gum was dissolved in the minimum amount of DCM and absorbed onto an aminopropyl SPE (50g). The cartridge was eluted with an ethyl acetate / cyclohexane gradient (0-100%) over 30min, combination of the appropriate fractions and evaporation of the solvent left the title compound (353mg). LC/MS; Rt 2.50min, MH^+ 210.9.

Example 265

N^2-[4-(1-Piperidinylcarbonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

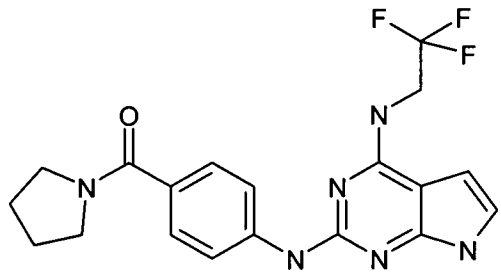


A mixture of 4-(1-piperidinylcarbonyl)aniline (100mg, Fluorochem), 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (165mg), potassium carbonate (79mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (9.8mg) and tris(dibenzylideneacetone)dipalladium (0) (22.5mg) in t-butanol (2.5ml) was heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature and the solvent was evaporated under vacuum. The residue was dissolved in a small amount of methanol and applied to an SCX-2 cartridge (5g, pre-conditioned with methanol). The cartridge was washed with methanol and the product eluted with 2M ammonia in methanol. The appropriate fractions were collected and the solvent evaporated under vacuum. The residue was dissolved in a small amount of methanol, adsorbed onto Florisil and purified by chromatography on a silica cartridge (70g) eluting with an ethyl acetate / cyclohexane gradient (0-100%) over 60min. After combination of the appropriate fractions and evaporation of the solvent under vacuum, the residue was dissolved in a small amount of ether and the solvent was evaporated under vacuum to leave a white solid (194mg).

The solid was treated with potassium carbonate (340mg), methanol (2ml) and water (1ml) and the mixture was heated at 80°C overnight. Aqueous sodium hydroxide solution (2M, 1ml) was added and heating to 80°C continued for a further 4.5h. The mixture was cooled to room temperature and was partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate (3x 20ml). The organic phases were combined and the solvent evaporated under vacuum. Sodium methoxide in methanol (0.5M, 3ml) was added to the residue and this stirred mixture was heated at 80°C for 3h. The solvent was evaporated under vacuum, the residue

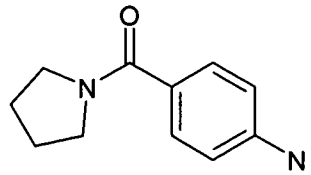
dissolved in the minimum amount of methanol and the solution applied to an SCX-2 cartridge (10g, pre-conditioned with methanol). The cartridge was washed with methanol and the product eluted with 2M ammonia in methanol. The appropriate fractions were combined and the solvent was evaporated under vacuum. The residue was purified by MDAP to give, after the appropriate fractions were combined and the solvent evaporated under vacuum, the title compound (14mg). LC/MS; Rt 2.96min, MH^+ 419.

Example 266
N^2-[4-(1-pyrrolidinylcarbonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



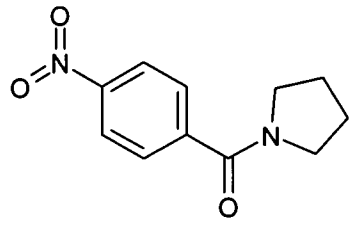
A stirred mixture of 4-(1-pyrrolidinylcarbonyl)aniline (56.4mg), 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), potassium carbonate (48mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (6mg) and tris(dibenzylideneacetone)dipalladium (0) (14mg) in t-butanol (2.5ml) was heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature and potassium carbonate (24mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (3mg) and tris(dibenzylideneacetone)dipalladium (0) (7mg) were added. The stirred mixture was then heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature and applied to an SCX-2 cartridge (20g). The cartridge was washed with ethyl acetate, and the product eluted with 2M ammonia in methanol. The appropriate fractions were combined and the solvent evaporated under vacuum. The residue was suspended with IPA (3ml), treated with aqueous sodium hydroxide solution (2M, 3ml) and the mixture was heated at 60°C overnight. The solvent was evaporated under vacuum, the residue dissolved in ethyl acetate and washed twice with hydrochloric acid. The organic phase was reduced to dryness *in vacuo*. The residue was purified by MDAP, the appropriate fractions combined and the solvent evaporated under vacuum, to give the title compound (17mg). LC/MS; Rt 2.83min, MH^+ 405.

Intermediate 88
4-(1-pyrrolidinylcarbonyl)aniline



A solution of 1-[(4-nitrophenyl)carbonyl]pyrrolidine (500mg) in ethanol (30ml) was hydrogenated (1Atm.) over palladium on carbon (5%, 50mg) overnight. The mixture was filtered through Celite, and the catalyst washed twice with ethanol. The solvent was evaporated under vacuum to give the title compound as a white solid (402mg). LC/MS; Rt 1.86min, MH^+ 191.

Intermediate 89

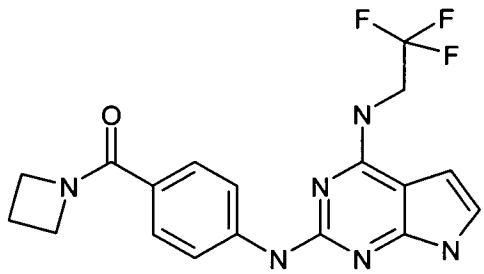


1-[(4-nitrophenyl)carbonyl]pyrrolidine

A mixture of 4-nitrobenzoyl chloride (750mg) in DCM (50ml) was treated with pyrrolidine (1.66ml) and the mixture was stirred at room temperature under nitrogen for 5h. Hydrochloric acid (1M, 50ml) was added and the mixture was stirred vigorously for 20min. The layers were separated and the organic phase washed with sodium hydrogen carbonate solution (50ml), then water and reduced to dryness under vacuum to give the title compound (500mg). LC/MS; Rt 2.54min, MH^+ 221.

Example 267

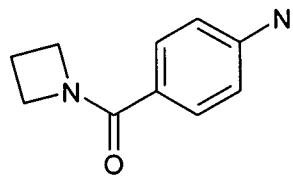
N^2-[4-(1-azetidinylcarbonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



A stirred mixture of 4-(1-azetidinylcarbonyl)aniline (52.2mg), 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), potassium carbonate (47.8mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (6mg) and tris(dibenzylideneacetone)dipalladium (0) (13.6mg) in in t-butanol (2.5ml) was heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature and applied to an SCX-2 SPE cartridge (20g). The cartridge was washed with methanol, ethyl acetate, and the product eluted with 2M ammonia in methanol. The basic fractions were collected and the solvent evaporated under

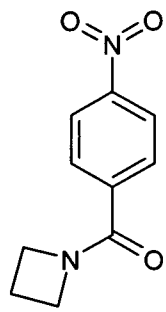
vacuum. The residue was suspended in IPA (3ml) and treated with aqueous sodium hydroxide solution (2M, 3ml) and the mixture was heated at 60°C overnight. The solvent was evaporated under reduced pressure. DCM was added to the residue and the insoluble material was isolated by filtration. The solid was dissolved in methanol (30ml) and the solvent was evaporated under vacuum. The residue was dissolved in chloroform, the solution applied to an aminopropyl SPE (10g) and eluted with chloroform, ethyl acetate and methanol. The chloroform fractions were combined and the solvent evaporated under vacuum. The residue was purified by MDAP to give, after the appropriate fractions were combined and the solvent evaporated under vacuum, the title compound (6mg). LC/MS; Rt 2.73min, MH^+ 391.

Intermediate 90
4-(1-Azetidinylcarbonyl)aniline



A solution of 1-[(4-nitrophenyl)carbonyl]azetidine (463mg) in ethanol (30ml) was hydrogenated over palladium on carbon (46.3mg) overnight. The mixture was filtered through a Celite pad which was washed twice with ethanol. The solvent was evaporated under vacuum to give the title compound as a yellow solid. (340mg). LC/MS; Rt 1.72min, MH^+ 177.

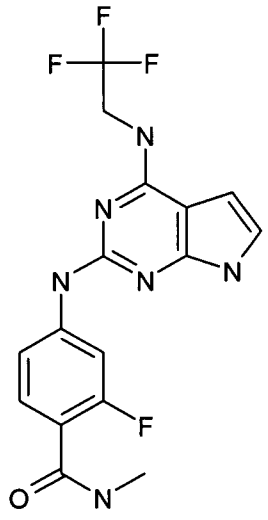
Intermediate 91
1-[(4-Nitrophenyl)carbonyl]azetidine



A mixture of 4-nitrobenzoyl chloride (750mg) and potassium carbonate (607mg) in DCM (50ml) was treated with azetidine (0.408ml) and the mixture was stirred at room temperature under nitrogen for 4h 20min. Potassium carbonate (606mg) and azetidine (0.408ml) were added and the mixture was stirred at room temperature for a further 40min. Water (50ml) was added and the mixture was stirred vigorously for 15min. The layers were allowed to separate and the organic phase was isolated (hydrophobic frit). The solvent was evaporated under vacuum to give the title compound as a yellow solid (463mg). LC/MS; Rt 2.41min, MH^+ 207.

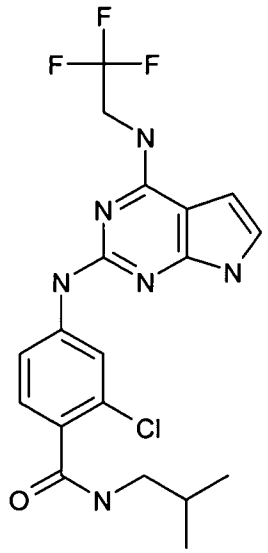
Example 268

2-Fluoro-*N*-methyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide



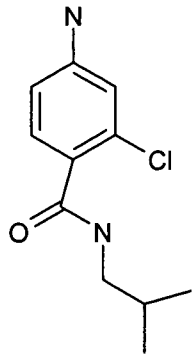
4-Amino-2-fluorobenzoic acid (600mg, Apin) was added to a stirred solution of PyBOP (2.21g), methylamine hydrochloride (1.306g) and DIPEA (10.11ml) in DMF (30ml) at room temperature under nitrogen and the mixture was stirred overnight. The solvent was evaporated *in vacuo* to leave a gum, which was triturated with DCM (15ml) and filtered. The filtrate was applied to an aminopropyl SPE cartridge (70g) and the material was purified by chromatography. Elution with an ethyl acetate / cyclohexane gradient (0-100%) over 30min gave, after combination of the appropriate fractions and evaporation of the solvent *in vacuo*, two batches of material: batch 1 as an oily yellow solid (756mg) and batch 2 as an oily white solid (262mg). The latter was triturated with diethyl ether (5ml) and filtered under reduced pressure to give a white solid (145mg). A portion of this solid (140mg) was mixed with 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), potassium carbonate (48mg) and t-butanol (4.5ml) and degassed with nitrogen for 10min. 2-Dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (18mg) and tris(dibenzylideneacetone)dipalladium (0) (23mg) were added and the stirred mixture was heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature and was partitioned between phosphate buffer solution (pH6.5, 15ml) and ethyl acetate (15ml). The aqueous phase was extracted with ethyl acetate (15ml), the combined organic phases were dried (sodium sulphate) and the solvent was removed by evaporation *in vacuo* to give a brown oil (ca. 300mg). This oil was treated with sodium methoxide solution in methanol (0.5M, 5.0ml) and the mixture was stirred under nitrogen and heated to 50°C for 1.5h. The mixture was cooled to room temperature and the solvent was removed by evaporation *in vacuo*. The residue was triturated with water (20ml) and filtered. The solid was purified by MDAP, appropriate fractions combined and the solvent removed by evaporation *in vacuo* to give the title compound as a white solid (35mg). LC/MS; Rt 2.83min, MH^+ 383.

Example 269
2-chloro-*N*-(2-methylpropyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*] pyrimidin-2-yl}amino)benzamide



A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-amino-2-chloro-*N*-(2-methylpropyl)benzamide (68mg) and potassium carbonate (48.4mg) in t-butanol (4.5ml) was treated with 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (17.9mg) and tris(dibenzylideneacetone)dipalladium (0) (22.9mg) and the stirred mixture was heated in a sealed vial in a microwave at 120°C for 1h. The mixture was cooled to room temperature and was partitioned between water (30ml) and ethyl acetate (30ml). The aqueous phase was extracted with ethyl acetate (30ml) and the solvent was evaporated from the combined organics *in vacuo*. The residue was purified by MDAP, the appropriate fractions combined and reduced to dryness. The residue was treated with a solution of sodium methoxide in methanol (0.5M) and the mixture heated at 80°C under nitrogen for 2h. The mixture was cooled and the methanol was evaporated *in vacuo*. Water (30ml) was added and the mixture was extracted with ethyl acetate (2x 25ml). The combined organic phases were reduced to dryness *in vacuo*. The residue was purified by chromatography on a silica cartridge eluting with a gradient of (50% Methanol in DCM + 1% triethylamine) / cyclohexane (0-100%). After evaporation of the solvent from appropriate fractions, the residue was further purified by MDAP. Appropriate fractions combined and the solvent evaporated to leave the title compound as a white solid. LC/MS; Rt 3.20min, MH^+ 441.

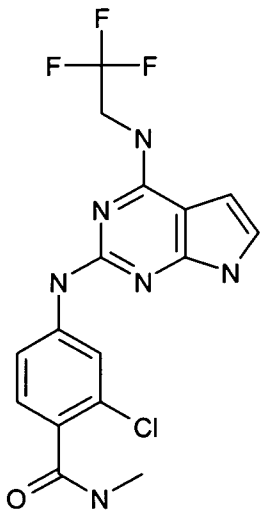
Intermediate 92
4-Amino-2-chloro-*N*-(2-methylpropyl)benzamide



4-Amino-2-fluorobenzoic acid (300mg, Apin) was added to a stirred solution of PyBOP (1.0g), isobutylamine (639mg) and DIPEA (2.26g) in DMF (15ml) at room temperature under nitrogen and the mixture was stirred overnight. The solvent was evaporated *in vacuo*, the resulting gum was dissolved in the minimum amount of DCM and absorbed onto an aminopropyl SPE (50g). The cartridge was eluted with an ethyl acetate / cyclohexane gradient (0-100%) over 30min, combination of the appropriate fractions and evaporation of the solvent left the title compound (357mg). LC/MS; Rt 2.48min, MH^+ 227.

Example 270

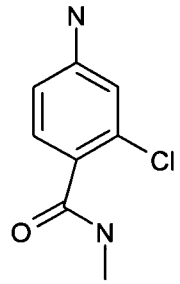
2-chloro-*N*-methyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide



A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-amino-2-chloro-*N*-methylbenzamide (92mg) and potassium carbonate (48.4mg) in t-butanol (4.5ml) was treated with 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (17.9mg) and tris(dibenzylideneacetone)dipalladium (0) (22.9mg) and the stirred mixture was heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature and partitioned between water (30ml) and ethyl acetate (30ml). The aqueous phase was extracted with ethyl acetate (30ml), and the solvent was evaporated from the combined organic phases *in vacuo*. The residue was treated

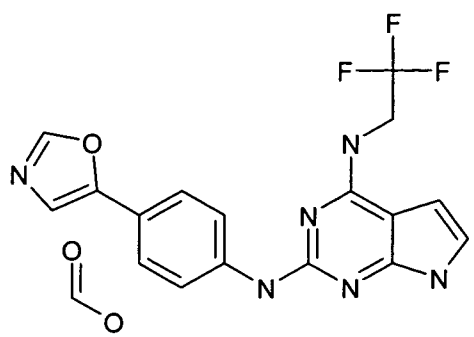
with a solution of sodium methoxide in methanol (0.5M, 5ml) and the mixture heated at 80°C under nitrogen for 30min. The mixture was cooled to room temperature and the methanol was evaporated *in vacuo*. Water (30ml) was added and the mixture was extracted with ethyl acetate (2x 25ml). The solvent was removed from the combined organic phases by evaporation *in vacuo*. The residue was purified by MDAP, appropriate fractions were combined and the solvent removed by evaporation *in vacuo* to give the title compound as a white solid (11mg). LC/MS; Rt 2.79min, MH^+ 399.

Intermediate 93
4-amino-2-chloro-*N*-methylbenzamide



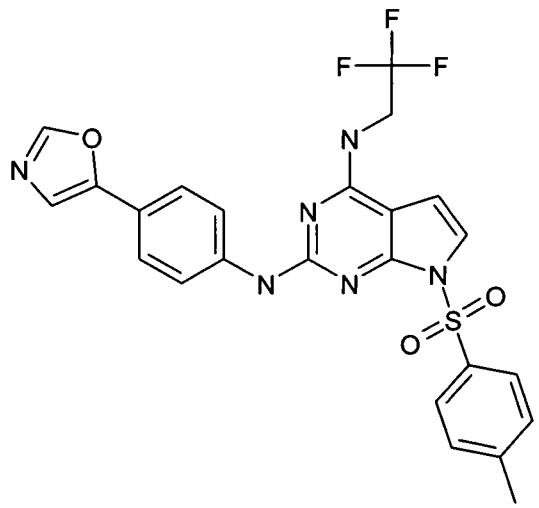
4-Amino-2-chlorobenzoic acid (300mg, Aldrich) was added to a stirred solution of PyBOP (1.0g), methylamine hydrochloride (590mg) and DIPEA (3.0ml) in DMF (15ml) at room temperature and the mixture was stirred overnight. The solvent was evaporated *in vacuo*, the resulting gum was dissolved in the minimum amount of chloroform / methanol (4:1), filtered through an aminopropyl cartridge (50g) and the cartridge eluted with DCM / methanol (4:1). Combination of the appropriate fractions and evaporation of the solvent *in vacuo* gave a residue which was further purified by chromatography on silica (50g), eluting with ethyl acetate / cyclohexane gradient (0-100%) over 1h. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, left the title compound (269mg). LC/MS; Rt 1.40min, MH^+ 185.

Example 271
Formic
acid-N^2-[4-(1,3-oxazol-5-yl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (1:1)



A solution of 7-[(4-methylphenyl)sulfonyl]-N^2-[4-(1,3-oxazol-5-yl)phenyl]-N^4-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (35mg) in THF (5ml) under nitrogen was treated with potassium trimethylsilanolate (34mg) and the mixture was stirred at 20°C for 2h. The mixture was then heated at 70°C (oil bath temperature) for 2h, cooled to room temperature and partitioned between ethyl acetate (10ml) and phosphate buffer solution (pH6.5, 10ml). The organic phase was dried (sodium sulphate) and the solvent evaporated *in vacuo*. The brown residue was purified by MDAP, the appropriate fractions were combined and the solvent removed by evaporation *in vacuo* to give the title compound as a straw coloured solid (7mg). LC/MS; Rt 2.96min, MH^+ 375.

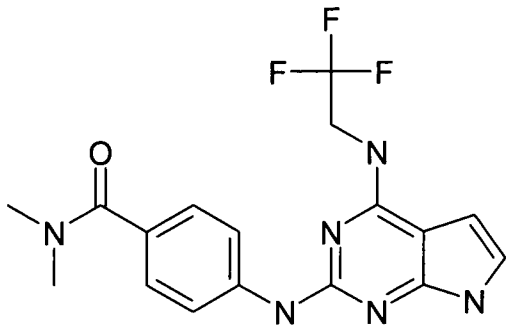
Intermediate 94
7-[(4-Methylphenyl)sulfonyl]-N^2-[4-(1,3-oxazol-5-yl)phenyl]-N^4-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-(1,3-oxazol-5-yl)aniline (47.5mg, Maybridge) and potassium carbonate (48mg) in t-butanol (4.5ml) and degassed with nitrogen for 10min. 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (18mg) and tris(dibenzylideneacetone)dipalladium (0) (23mg) were added and the stirred mixture was heated in a sealed vial by a microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature and was partitioned between water (20ml) and ethyl acetate (20ml). The organic phase was dried (sodium sulphate) and the solvent was removed by evaporation *in vacuo*. The residue was purified by chromatography on a silica cartridge (20g) eluting with a gradient of (50% methanol in DCM + 1% triethylamine) / cyclohexane (0-100%). The solvent was evaporated from appropriate fractions and the residue further purified by MDAP. The appropriate fractions were combined and the solvent removed by evaporation *in vacuo* to give the title compound as a straw coloured solid (35mg). LC/MS; Rt 3.66min, MH^+ 529.

Example 272

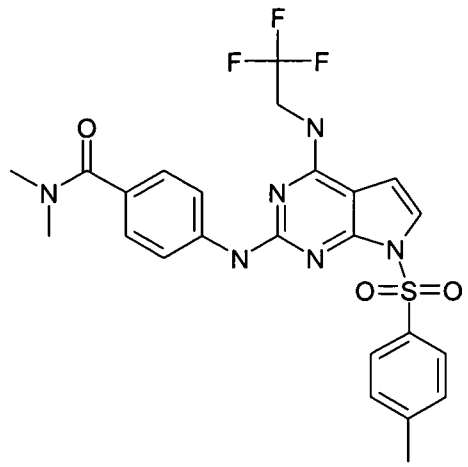
***N,N*-Dimethyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl} amino)benzamide**



The *N,N*-dimethyl-4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide (114mg) in IPA (3ml) was treated with aqueous sodium hydroxide (2N, 0.64ml) and heated at 80°C for 6h. The temperature was lowered to 70°C and the reaction stirred overnight. The reaction mixture was cooled to room temperature after 22h of heating and the solvents evaporated under vacuum. The residue was suspended in ethyl acetate and applied to an SCX-2 cartridge (5g, pre-conditioned with methanol and ethyl acetate). The cartridge was washed with ethyl acetate, methanol and the product eluted with 2N ammonia in methanol. The solvent was evaporated from the ammonia fraction, and the residual oil was dissolved in methanol and adsorbed onto Florisil. This material was purified by chromatography on a silica cartridge (20g), eluting with a gradient of ethyl acetate / methanol (1:1) in cyclohexane (10-100%). The appropriate fractions were combined and the solvents evaporated to leave a brown solid. Trituration with ether and drying under nitrogen gave the title compound as a yellow/brown solid (37.2mg). LC/MS; MH^+ 379, Rt 2.64min.

Intermediate 95

***N,N*-dimethyl-4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**



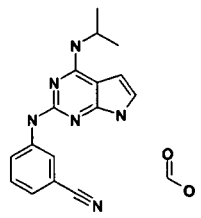
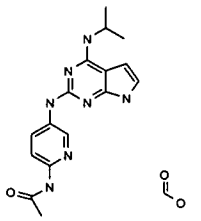
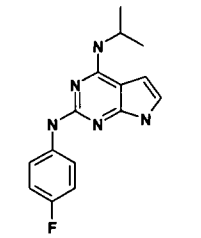
2-Chloro-7-[(4-methylphenyl)sulfonyl]-N-(2,2,2-trifluoroethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (117mg), 4-(N,N-dimethylcarbamoyl)aniline (57mg, Apollo Scientific Ltd), tris(dibenzylideneacetone)dipalladium (0) (16mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (6.9mg) and potassium carbonate (55.9mg) in t-butanol (2ml) was irradiated at 120°C in a sealed vessel by microwave for 1h. The reaction mixture was diluted with ethyl acetate and filtered through a pad of Celite. The filtrate was applied to an SCX-2 cartridge (5g, pre-conditioned with methanol and ethyl acetate. The cartridge was washed with ethyl acetate, methanol and the product eluted with 2N ammonia in methanol solution. The ammonia fraction was reduced to dryness under vacuum and adsorbed onto Florisil from methanol. This was purified by chromatography on a silica cartridge (20g), eluting with an ethyl acetate / cyclohexane gradient (25-100%). Appropriate fractions were combined, the solvents evaporated and azeotroped with ether to obtain the title compound as a glassy solid (114mg). LC/MS; MH^+ 533, Rt 3.41min.

Method 18:

A stirred mixture of 2-chloro-*N*-(1-methylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (21mg), potassium carbonate (19mg), tris(dibenzylideneacetone)dipalladium (0) (9mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (7mg) and the amine (1.2 eq) in t-butanol (2ml) was heated at 90°C for 16h. The reaction was diluted with ethanol and filtered through a pad of Celite. The Celite was washed with ethanol and the solvent was evaporated from combined washings. The residue was purified by MDAP and the solvents evaporated from the appropriate fractions to give the desired compound.

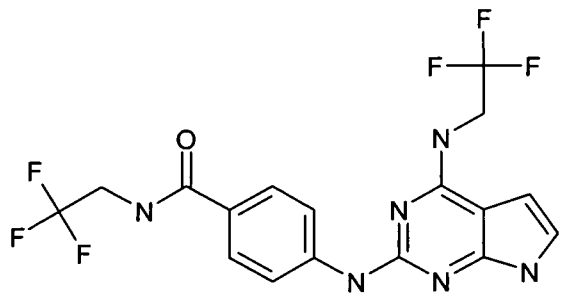
The following compounds were prepared using Method 18:

Example	Structure	Name	Amine / Source	LC/MS Rt (min)	LC/MS MH^+

273		formic acid - 3-({4-[(1-methylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzonitrile (1:1)	3-Aminobenzonitrile / Avocado	2.90	293
274		formic acid - N-[5-({4-[(1-methylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-2-pyridinyl]acetamide (1:1)	N-(5-Amino-2-pyridinyl)acetamide / Aldrich	2.30	326
275		N^2-(4-fluorophenyl)-N^4-(1-methylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine	4-Fluoroaniline / Acros	2.80	286

Example 276

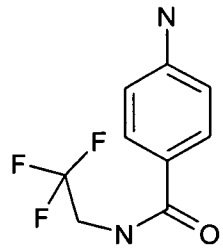
***N*-(2,2,2-trifluoroethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**



A stirred mixture of 4-amino-*N*-(2,2,2-trifluoroethyl)benzamide (64.7mg), 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), potassium carbonate (47.8mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (5.9mg) and tris(dibenzylideneacetone)dipalladium (0) (13.6mg) in in t-butanol (2.5ml) was heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature and applied to an SCX-2 SPE cartridge (20g). The cartridge was washed with methanol and the product eluted with 2M ammonia in methanol. The

ammoniacal fractions were collected and the solvent evaporated under vacuum. The residue was treated with IPA (3ml) and aqueous sodium hydroxide solution (2M, 3ml) and the mixture was heated at 60°C overnight. The solvent was evaporated under reduced pressure, the residue was dissolved in methanol and the solution was applied to an SCX-2 cartridge (20g). The cartridge was washed with methanol and the product eluted with a solution of 2M ammonia in methanol. The basic fractions were combined and the solvent evaporated under vacuum. The residue was purified by MDAP to give, after the appropriate fractions were combined and the solvent evaporated under vacuum, the title compound (60mg). LC/MS; Rt 2.99min, MH^+ 432.86.

Intermediate 96

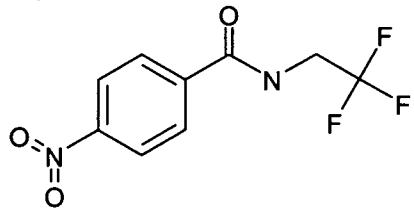


4-Amino-*N*-(2,2,2-trifluoroethyl)benzamide

A solution of 4-nitro-*N*-(2,2,2-trifluoroethyl)benzamide (550mg) in ethanol (30ml) was hydrogenated (1Atm.) over palladium on carbon (10%, 55mg) overnight. The mixture was filtered through a Celite pad and the residue washed with ethanol. The filtrate was refiltered through Celite and the Celite washed with ethanol. The solvent was evaporated from the combined filtrate and washings under vacuum to give the title compound as a white solid (290mg). LC/MS; Rt 1.91min, MH^+ 219.

Intermediate 97

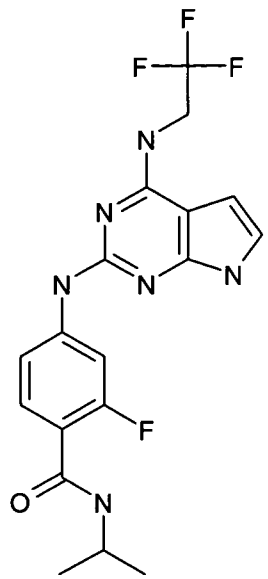
4-Nitro-*N*-(2,2,2-trifluoroethyl)benzamide



A mixture of 4-nitrobenzoyl chloride (750mg) and potassium carbonate (606.6mg) in DCM (40ml) was treated with 2,2,2-trifluoroethylamine (0.482ml) and the mixture was stirred at room temperature under nitrogen for 2h 40min. Potassium carbonate (606mg) and 2,2,2-trifluoroethylamine (0.482ml) were added and the mixture was stirred at room temperature for a further 1.5h. Water (40ml) was added and the mixture was stirred vigorously for 15min. The layers were allowed to separate, the organic phase isolated (hydrophobic frit) and the solvent evaporated under vacuum to give the title compound as a white solid (550mg). LC/MS: Rt 2.63min, $[M-H]^-$ 247.

Example 277

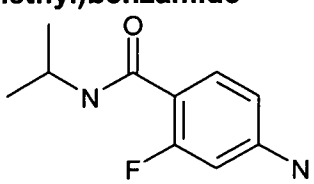
2-Fluoro-*N*-(1-methylethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide



A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-amino-2-fluoro-*N*-(1-methylethyl)benzamide (58.9mg) and potassium carbonate (48mg) in t-butanol (4.5ml) under nitrogen was treated with 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (17.9mg) and tris(dibenzylideneacetone)dipalladium (0) (22.9mg) were added and the stirred mixture was heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature, partitioned between water (30ml) and ethyl acetate (30ml) and the aqueous phase further extracted with ethyl acetate (30ml). The solvent was removed from the combined organic phases by evaporation *in vacuo*. The residue was treated with a solution of sodium methoxide in methanol (0.5M, 5ml) and the mixture heated at 80°C under nitrogen for 1h. The mixture was cooled to room temperature and the methanol was evaporated. Water (30ml) was added to the residue and the mixture was extracted with ethyl acetate (2x 25ml). The solvent was evaporated from the combined organic phases *in vacuo*. The residue was purified by MDAP, the appropriate fractions were combined and the solvent removed by evaporation *in vacuo* to give the title compound (62mg). LC/MS; Rt 3.13min, MH^+ 411.

Intermediate 98

4-Amino-2-fluoro-*N*-(1-methylethyl)benzamide

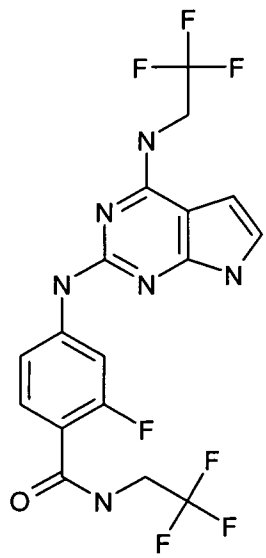


4-Amino-2-fluorobenzoic acid (300mg, Apin), PyBOP (1.1g), isopropylamine

(0.822ml) and DIPEA (2.497g) were mixed in DMF (15ml) at room temperature under nitrogen and the mixture stirred overnight. The solvent was evaporated *in vacuo*, the residual gum was dissolved in the minimum amount of DCM and was absorbed onto an aminopropyl cartridge (50g) and the material was purified by chromatography, eluting with ethyl acetate / cyclohexane (0-100%) over 30min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound (345mg). LC/MS; Rt 2.22min, MH^+ 197.

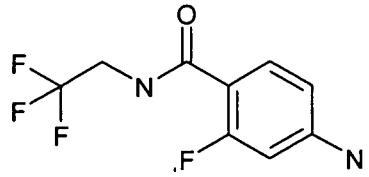
Example 278

2-fluoro-*N*-(2,2,2-trifluoroethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide



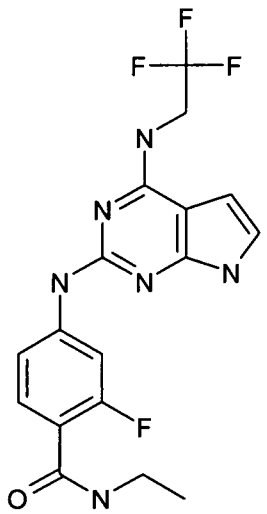
A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-amino-2-fluoro-*N*-(2,2,2-trifluoroethyl)benzamide (70.9mg) and potassium carbonate (48mg) in t-butanol (4.5ml) under nitrogen was treated with 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (17.9mg) and tris(dibenzylideneacetone)dipalladium (0) (22.9mg) and the stirred mixture was heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature, partitioned between water (30ml) and ethyl acetate (30ml) and the aqueous phase further extracted with ethyl acetate (30ml). The solvent was removed from the combined organic phases by evaporation *in vacuo*. The residue was treated with a solution of sodium methoxide in methanol (0.5M, 5ml) and the mixture heated at 80°C under nitrogen for 1h. The mixture was cooled to room temperature and the methanol was evaporated. Water (30ml) was added to the residue and the mixture was extracted with ethyl acetate (2x 25ml). The solvent was evaporated from the combined organic phases *in vacuo*. The residue was purified by MDAP, the appropriate fractions were combined and the solvent removed by evaporation *in vacuo* to give the title compound (45mg). LC/MS; Rt 3.21min, MH^+ 451.

Intermediate 99
4-Amino-2-fluoro-*N*-(2,2,2-trifluoroethyl)benzamide



4-Amino-2-fluorobenzoic acid (300mg) (Apin), PyBOP (1.1g), trifluoroethylamine (0.768ml) and DIPEA (2.497g) were mixed in DMF (15ml) at room temperature under nitrogen and the mixture was stirred overnight. The solvent was evaporated *in vacuo*, the residual gum was dissolved in the minimum amount of DCM and was absorbed onto an aminopropyl cartridge (50g) and the material was purified by chromatography, eluting with ethyl acetate / cyclohexane (0-100%) over 30min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound (423mg). LC/MS; Rt 2.32min, MH^+ 237.

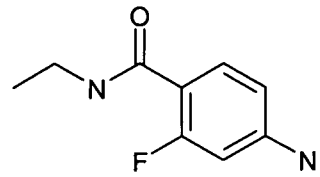
Example 279
***N*-Ethyl-2-fluoro-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**



A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-amino-*N*-ethyl-2-fluorobenzamide (54.7mg) and potassium carbonate (48mg) in t-butanol (4.5ml) under nitrogen was treated with 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (17.9mg) and tris(dibenzylideneacetone)dipalladium (0) (22.9mg) were added and the stirred mixture was heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature, partitioned between water (30ml) and ethyl acetate (30ml) and the aqueous phase further extracted with ethyl acetate (30ml). The solvent was removed from the combined organic phases by evaporation *in vacuo*.

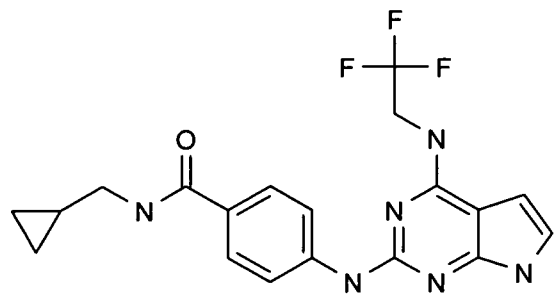
The residue was treated with a solution of sodium methoxide in methanol (0.5M, 5ml) and the mixture heated at 80°C under nitrogen for 1h. The mixture was cooled to room temperature and the methanol was evaporated. Water (30ml) was added to the residue and the mixture was extracted with ethyl acetate (2x 25ml). The solvent was evaporated from the combined organic phases *in vacuo*. The residue was purified by MDAP, the appropriate fractions were combined and the solvent removed by evaporation *in vacuo* to give the title compound (62mg). LC/MS; Rt 2.99min, MH^+ 397.

Intermediate 100
4-amino-*N*-ethyl-2-fluorobenzamide



4-Amino-2-fluorobenzoic acid (300mg, Apin), PyBOP (1.1g), ethylamine hydrochloride (787mg) and DIPEA (3.746g) were mixed in DMF (15ml) at room temperature under nitrogen and the mixture was stirred overnight. The solvent was evaporated *in vacuo*, the residual gum was dissolved in the minimum amount of DCM and was absorbed onto an aminopropyl cartridge (50g) and the material was purified by chromatography, eluting with ethyl acetate / cyclohexane (0-100%) over 30min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound (267mg). LC/MS; Rt 1.92min, MH^+ 183.

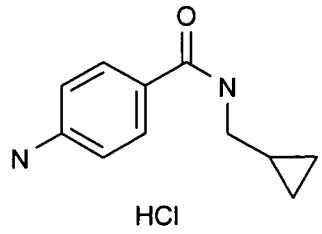
Example 280
***N*-(cyclopropylmethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**



2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-amino-*N*-(cyclopropylmethyl)benzamide hydrochloride (62.8mg) tris(dibenzylideneacetone)dipalladium (0) (13.6mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (5.9mg) and potassium carbonate (91.8mg) in t-butanol (1.5ml) was stirred and irradiated at 120°C in a sealed vessel in a microwave for 1h. The mixture was heated for a further 1h at 150°C. Tris(dibenzylideneacetone)dipalladium (0) (7mg) and potassium carbonate (17mg)

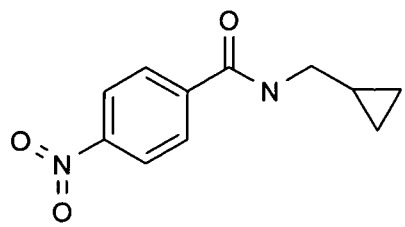
were added to the reaction. The vessel was sealed and the mixture heated at 150°C for 45min in the microwave. The reaction mixture was diluted with ethyl acetate (2ml) and filtered through Celite. The filtrate was applied to an SCX-2 cartridge (5g, pre-conditioned with methanol and ethyl acetate). The cartridge was washed with ethyl acetate, methanol and the product eluted with 2N ammonia in methanol solution. The ammonia fraction was reduced to dryness under reduced pressure and the residue dissolved in IPA (1.5ml). The solution was treated with aqueous sodium hydroxide (2N, 1ml) and the mixture stirred at 80°C for 16h. The solvents were evaporated under a stream of nitrogen and the residue suspended in methanol. The suspension was applied to an SCX-2 cartridge (2g, pre-conditioned with methanol). The solid retained on top of the cartridge was dried under nitrogen to obtain the title compound as an off-white solid (33mg). LC/MS; MH^+ 405, Rt 2.89min.

Intermediate 101
4-amino-*N*-(cyclopropylmethyl)benzamide hydrochloride



N-(Cyclopropylmethyl)-4-nitrobenzamide (23.8g) was dissolved in ethanol and hydrogenated over palladium on carbon (10%, 1.8g). The reaction was filtered, the ethanol evaporated *in vacuo* and the residual gum partitioned between ethyl acetate and sodium bicarbonate solution. The organic phase was reduced to dryness *in vacuo* and hydrochloric acid in dioxane (4N) added. The white solid was isolated by filtration, washed with ether and dried *in vacuo* to obtain the title compound (15.5g).
NMR; [D_6-DMSO] δH 9-8,(3H, bm), 7.81,(2H, d), 7.11,(2H, d), 3.12,(2H, m), 1.01,(1H, m), 0.42,(2H, m), 0.22 (2H, m).

Intermediate 102
***N*-(cyclopropylmethyl)-4-nitrobenzamide**

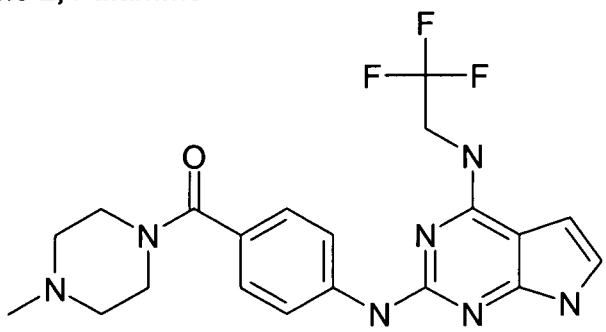


4-Nitrobenzoyl chloride (20g, Aldrich) was dissolved in DCM (500ml) and triethylamine (16.5ml) added. Cyclopropanemethylamine (21ml, Aldrich) was added (exothermic) and the reaction stirred at room temperature under nitrogen overnight. The volatiles were evaporated and the residue dried *in vacuo* to give the title

compound. LC/MS; MH^+ 221, Rt 2.70min.

Example 281

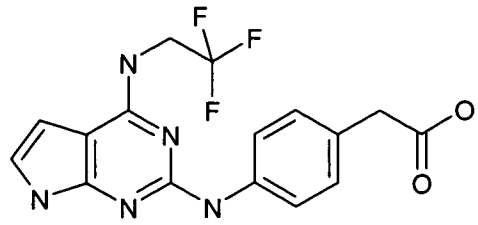
N^2-{4-[(4-Methyl-1-piperazinyl)carbonyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 1-(4-aminobenzoyl)-4-methylpiperazine (65.1mg, Butt Park Ltd), tris(dibenzylideneacetone)dipalladium (0) (13.6mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (5.9mg) and potassium carbonate (47.8mg) in t-butanol (1.5ml) was stirred and irradiated at 120°C in a sealed vessel by microwave for 1h. The mixture was heated for a further 30min at 150°C. The reaction mixture was diluted with ethyl acetate (2ml) and filtered through Celite. The filtrate was applied to an SCX-2 cartridge (5g, pre-conditioned with methanol and ethyl acetate). The cartridge was washed with ethyl acetate, methanol and the product eluted with 2N ammonia in methanol solution. The ammonia fraction was reduced to dryness *in vacuo* and the residue dissolved in IPA (1.5ml). The solution was treated with aqueous sodium hydroxide (2N, 1ml) and stirred at 80°C for 16h. The solvents were evaporated under a stream of nitrogen and the residue suspended in methanol. The suspension was applied to an SCX-2 cartridge (2g, pre-conditioned with methanol). The product was eluted in the methanol wash which was concentrated under vacuum. The residue was purified on MDAP and the appropriate fractions combined and evaporated. The sample was adsorbed from methanol onto Florisil and applied to a silica cartridge (20g). This was eluted with a gradient of ethyl acetate / methanol (1:1) in cyclohexane (10-100%). Appropriate fractions were combined, the solvents evaporated to obtain the title compound. LC/MS; MH^+ 434, Rt 2.03min.

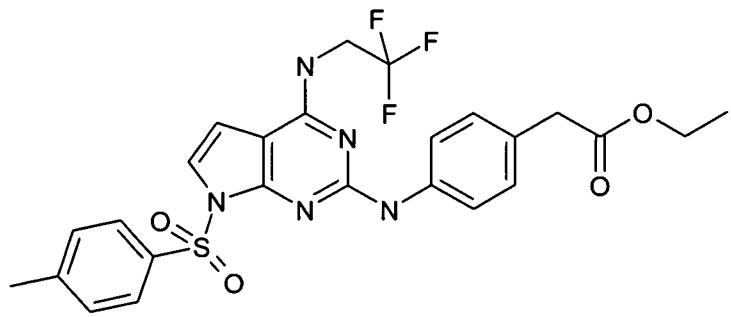
Example 282

[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetic acid



Ethyl
[4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetate (~200mg) was suspended in ethanol (2.5ml) and aqueous sodium hydroxide (2N, 2.5ml) added to the mixture. The reaction was heated at 80°C for ~1h, the solution allowed to cool, acidified to pH5 with glacial acetic acid and diluted with water. The resulting precipitate was isolated by filtration, washed with water, ether (<5ml) and ethyl acetate (<5ml) to leave the residual khaki solid as the desired product (120mg). LC/MS; MH^+ 366, Rt 2.56min.

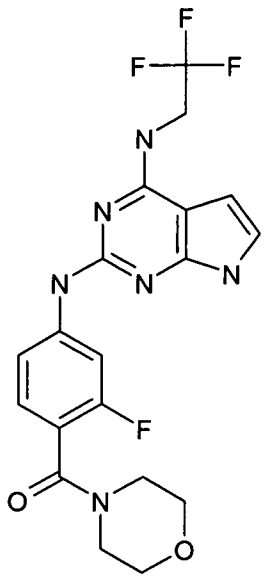
Intermediate 103
Ethyl
[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetate



2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (202mg), ethyl (4-aminophenyl)acetate (108mg, Avocado), tris(dibenzylideneacetone)dipalladium (28mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (12mg) and potassium carbonate (90mg) were mixed in t-butanol (5ml), the mixture degassed and heated at 100°C under nitrogen overnight. The cooled reaction was diluted with ethyl acetate and applied to an SCX-2 SPE (10g). The cartridge was washed with ethyl acetate and methanol and the product eluted with 0.880 ammonia / methanol. The combined ethyl acetate and methanol washes were filtered through to a second SCX-2 SPE (10g) and product eluted with 0.880 ammonia / methanol. The basic fractions from both columns were reduced to dryness *in vacuo*, the residue was dissolved in ethyl acetate and filtered through a silica cartridge (1g). The eluent was reduced to dryness *in vacuo* and the residue triturated with ethyl acetate / 40-60 petrol / ether to leave after filtration the desired product as a cream solid (~200mg). LC/MS; MH^+ 548, Rt 3.72min.

Example 283

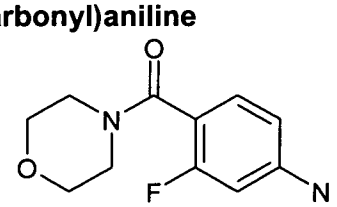
N^2-[3-fluoro-4-(4-morpholinylcarbonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 3-fluoro-4-(4-morpholinylcarbonyl)aniline (67.2mg) and potassium carbonate (48mg) in t-butanol (5ml), under nitrogen, was treated with 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (18mg) and tris(dibenzylideneacetone)dipalladium (0) (23mg) and the stirred mixture heated in a sealed vial by microwave irradiation at 120°C for 1h. The cooled reaction mixture was partitioned between water (20ml) and ethyl acetate (20ml). The aqueous phase was extracted with ethyl acetate (20ml) and the solvent from the combined organic phases evaporated *in vacuo*. The residue was treated with a solution of sodium methoxide in methanol (0.5M, 6ml) and the mixture heated at 80°C under nitrogen for 1h. The methanol was evaporated from the cooled mixture *in vacuo* and water (30ml) added to the residue. The mixture was extracted with ethyl acetate (2x 30ml), the solvent from the combined organic phases was removed by evaporation *in vacuo*. The residue was purified by MDAP, appropriate fractions were combined and the solvent removed by evaporation to give the title compound (52mg). LC/MS; Rt 2.80min, MH^+ 439.

Intermediate 104

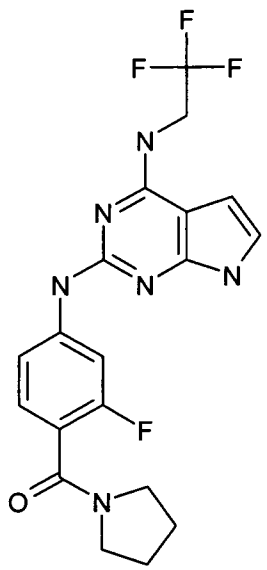
3-fluoro-4-(4-morpholinylcarbonyl)aniline



4-Amino-2-fluorobenzoic acid (300mg, Apin), PyBOP (1.1g), morpholine (0.85ml) and DIPEA (3.37ml) were mixed in DMF (15ml) and stirred at room temperature under nitrogen. The solvent was evaporated *in vacuo*, the residual gum was dissolved in the minimum amount of DCM and was absorbed onto an aminopropyl cartridge (50g) and the material was purified by chromatography, eluting with ethyl acetate / cyclohexane (0-100%) over 30min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound (403mg). LC/MS; Rt 1.79min, MH^+ 225.

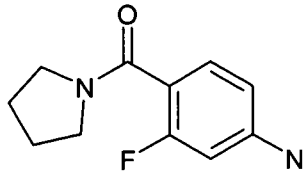
Example 284

N^2-[3-Fluoro-4-(1-pyrrolidinylcarbonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



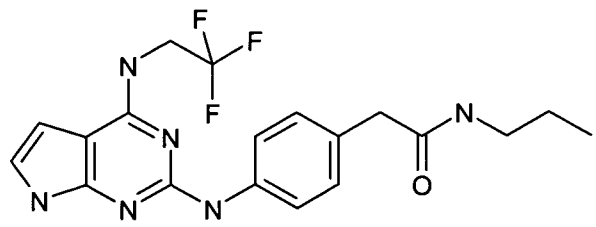
A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 3-fluoro-4-(1-pyrrolidinylcarbonyl)aniline (62.5mg) and potassium carbonate (48mg) in t-butanol (5ml), under nitrogen, was treated with 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (18mg) and tris(dibenzylideneacetone)dipalladium (0) (23mg) and the stirred mixture heated in a sealed vial by microwave irradiation at 120°C for 1h. The cooled reaction mixture was partitioned between water (20ml) and ethyl acetate (20ml). The aqueous phase was extracted with ethyl acetate (20ml) and the solvent from the combined organic phases evaporated *in vacuo*. The residue was treated with a solution of sodium methoxide in methanol (0.5M, 6ml) and the mixture heated at 80°C under nitrogen for 1h. The methanol was evaporated from the cooled mixture *in vacuo* and water (30ml) added to the residue. The mixture was extracted with ethyl acetate (2x 30ml), the solvent from the combined organic phases was removed by evaporation *in vacuo*. The residue was purified by MDAP, appropriate fractions were combined and the solvent removed by evaporation to give the title compound as a white solid (62.9mg). LC/MS; Rt 2.95min, MH^+ 423.

Intermediate 105
3-fluoro-4-(1-pyrrolidinylcarbonyl)aniline



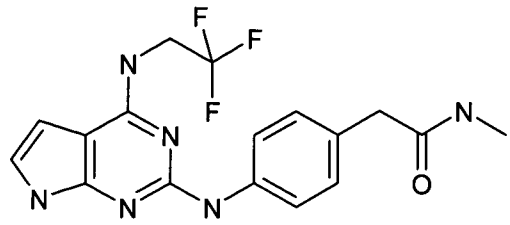
4-Amino-2-fluorobenzoic acid (300mg, Apin) was added to a stirred solution of PyBOP (1.1g), pyrrolidine (0.81ml) and DIPEA (3.37ml) were mixed in DMF (15ml) and stirred at room temperature under nitrogen. The solvent was evaporated *in vacuo*, the residual gum was dissolved in the minimum amount of DCM and was absorbed onto an aminopropyl cartridge (50g) and the material was purified by chromatography, eluting with ethyl acetate / cyclohexane (0-100%) over 30min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound (379mg). LC/MS; Rt 2.10min, MH^+ 209.

Example 285
***N*-propyl-2-[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetamide**



Diethylisopropylamine (52µl) was added to a solution of [4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetic acid (37mg) and TBTU (36mg) in DMF. The reaction was stirred at room temperature for ~5min, propylamine (9µl) was added and stirring continued for ~2.5h. The reaction was diluted with methanol (~2ml) and applied to an SCX-2 SPE (5g). The cartridge was washed with methanol and the product eluted with 0.880 ammonia / methanol. The basic fraction was reduced to dryness *in vacuo*, the residue dissolved in ethyl acetate and filtered through a silica cartridge (1g) washing with further ethyl acetate. The filtrate / washings were reduced to dryness *in vacuo* and the residue triturated with ethyl acetate (~0.5ml) and the solid isolated by filtration to give the desired product as a white solid (14.6mg). LC/MS; MH^+ 407, Rt 2.66min.

Example 286
***N*-methyl-2-[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetamide**

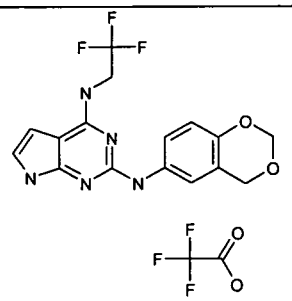
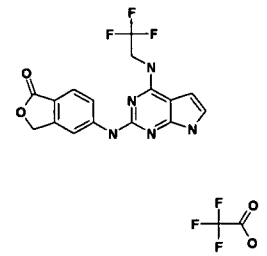
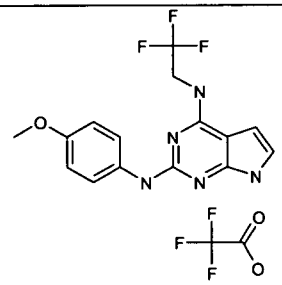
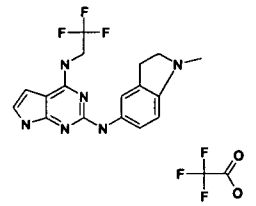
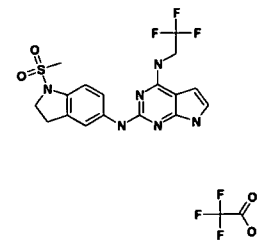


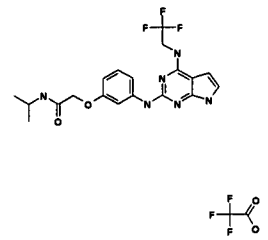
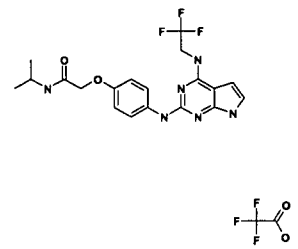
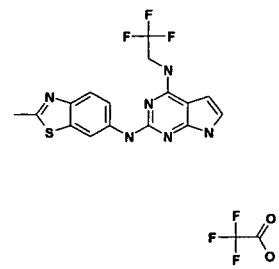
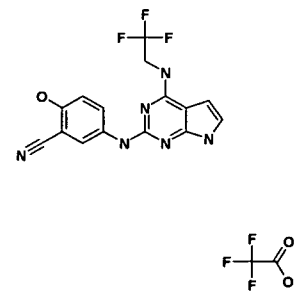
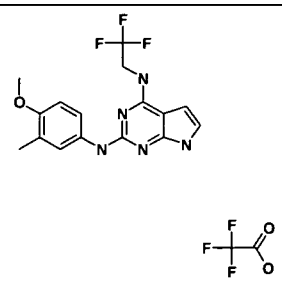
Diethylisopropylamine (70µl) was added to a solution of [4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetic acid (37mg) and TBTU (36mg) in DMF. The reaction was stirred at room temperature for ~5min, methylamine hydrochloride (7.4mg) was added and stirring continued for ~2.5h. The reaction was diluted with methanol (~2ml) and applied to an SCX-2 SPE (5g). The cartridge was washed with methanol and the product eluted with 0.880 ammonia / methanol. The basic fraction was reduced to dryness *in vacuo*, the residue dissolved in ethyl acetate and filtered through a silica cartridge (1g) washing with further ethyl acetate. The filtrate / washings were reduced to dryness *in vacuo* and the residue triturated with ethyl acetate (~0.5ml) and the solid isolated by filtration to give the desired product as a white solid (14.7mg). LC/MS; MH^+ 379, Rt 2.42min.

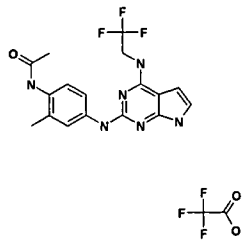
Method 19:

Potassium carbonate (475mg), tris(dibenzylideneacetone)dipalladium (0) (225mg) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (175mg) were stirred together for 20min to give a homogeneous solid. A portion of this solid (~35mg) was combined with 2-chloro-*N*-(1-methylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (25mg), the amine (2 eq) and t-butanol (1ml). The resultant mixture was heated at 90°C overnight. The reaction mixture was diluted with ethanol and filtered through Celite. The Celite was washed with ethanol and the combined filtrate and washings were evaporated under a stream of nitrogen. The residue was purified by MDAP, which gave, after evaporation of the solvents, the desired product.

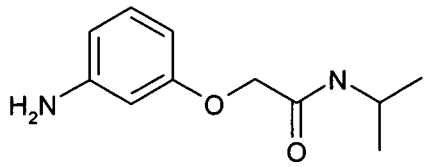
The following examples were prepared using Method 19:

Example	Structure	Name	Amine / Source	LC/MS Rt (min)	LC/MS MH^+
287		N^2-4*H*-1,3-benzodioxin-6-yl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	4H-1,3-Benzodioxin-6-amine / Maybridge	2.74	366
288		5-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-2-benzofuran-1(3*H*)-one trifluoroacetate	5-Amino-2-benzofuran-1(3H)-one / Apin	2.94	364
289		N^2-[4-(methyloxy)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	[4-(Methyloxy)phenyl]amine/ Aldrich	2.72	338
290		N^2-(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	1-Methyl-2,3-dihydro-1H-indol-5-amine/ Zhurnal Obshchei Khimii, 29, 317-23; 1959	2.52	363
291		N^2-[1-(methylsulfonyl)-2,3-dihydro-1*H*-indol-5-yl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine	1-(Methylsulfonyl)-2,3-dihydro-1H-indol-5-amine / Apollo Scientific	2.77	427

		trifluoroacetate			
292		*N*-(1-methylethyl)-2-{[3-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]oxy}acetamide trifluoroacetate	2-[(3-Aminophenyl)oxy]-N-(1-methylethyl)acetamide	2.90	423
293		*N*-(1-methylethyl)-2-{[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]oxy}acetamide trifluoroacetate	2-[(4-Aminophenyl)oxy]-N-(1-methylethyl)acetamide / J Chem Res, Synopses (1996), (9), 424-425	2.65	423
294		N^2-(2-methyl-1,3-benzothiazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-Methyl-1,3-benzothiazol-6-amine / Alfa	2.99	379
295		2-hydroxy-5-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzonitrile trifluoroacetate (salt)	5-Amino-2-hydroxybenzonitrile / Bioorganic & Med Chem Letters (2003) 13 (6) 1147-1150	2.69	349
296		N^2-[3-methyl-4-(methyloxy)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine	[3-Methyl-4-(methyloxy)phenyl]amine / Synthesis (1995) 397-408	2.90	352

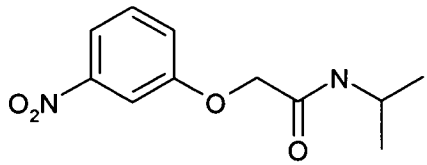
		trifluoroacetate			
297		*N*-[2-methyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetamide trifluoroacetate	N-(4-Amino-2-methylphenyl)acetamide / ABCR	2.43	379

Intermediate 106
2-[(3-aminophenyl)oxy]-N-(1-methylethyl)acetamide



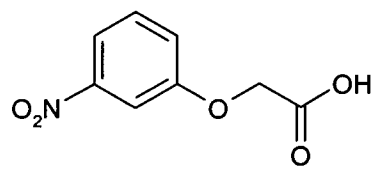
A stirred solution of *N*-(1-methylethyl)-2-[(3-nitrophenyl)oxy]acetamide (210mg) in ethanol (10ml) was treated with palladium on carbon (5%wt, 35mg) and stirred under an atmosphere of hydrogen for 16h. The reaction was filtered through a pad of Celite and the filtrate concentrated *in vacuo* to afford the title compound as a beige solid (141mg). NMR; [D_6-DMSO] δH 7.72,(1H, d), 6.90,(1H, t), 6.10,(3H, m), 5.06,(2H, s), 4.29,(2H, s), 3.91,(1H, m), 1.08,(6H, d).

Intermediate 107
***N*-(1-Methylethyl)-2-[(3-nitrophenyl)oxy]acetamide**



1-Hydroxybenzotriazole hydrate (369mg) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (532mg) were added to a stirred solution of [(3-nitrophenyl)oxy]acetic acid (490mg) in acetonitrile (10ml). Isopropylamine (0.254ml) was added and the reaction was stirred at 20°C for 2h. The reaction was treated with water (25ml) and extracted with ethyl acetate (50ml). The extract was washed sequentially with hydrochloric acid (2M, 50ml), sodium hydroxide (2M, 50ml), brine (50ml), then dried (magnesium sulphate) and concentrated *in vacuo*. The residual oil was purified by chromatography on a silica cartridge (10g), eluting with an ethyl acetate / cyclohexane gradient. Evaporation of the solvents from the appropriate fractions afforded the title compound as a beige solid (216mg). NMR; [D_6-DMSO] δH 8.02,(1H, bd), 7.84,(1H, dd), 7.77 (1H, t), 7.59,(1H, t), 7.42,(1H, dd), 4.60,(2H, s), 3.95,(1H, m), 1.09 (6H, d).

Intermediate 108
[(3-nitrophenyl)oxy]acetic acid

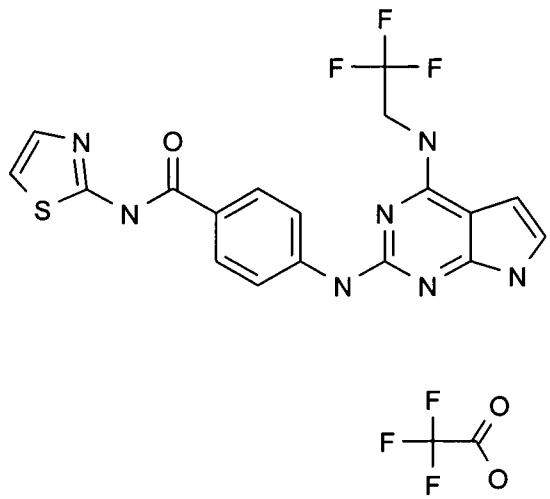


Aqueous sodium hydroxide (2M, 45ml) was added to stirred solution of ethyl [(3-nitrophenyl)oxy]acetate (2.0g) in ethanol (150ml). The reaction was heated at reflux for 16h. The reaction was concentrated *in vacuo*, the residue acidified to pH <1

with hydrochloric acid (2M) and extracted with ethyl acetate (600ml). The combined organic extracts were washed with brine (500ml), dried (magnesium sulphate) and concentrated *in vacuo.* The residual brown solid was purified by chromatography on a silica cartridge (100g), eluting with a DCM / methanol (0–49.5%) + 1% triethylamine) gradient. Combination of appropriate fractions and evaporation of the solvents afforded the title compound as a solid (338mg). NMR; [D_6-DMSO] δH 7.76,(1H, dd), 7.59,(1H, m), 7.52,(1H, t), 7.31,(1H, dd), 4.50,(2H, s).

Example 298

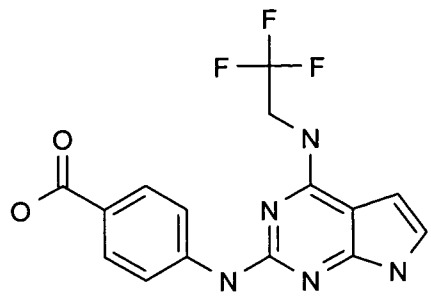
***N*-1,3-thiazol-2-yl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide trifluoroacetate**



A mixture of 4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid (105mg), TBTU (106mg) and DIPEA (0.156ml) in anhydrous DMF (0.75ml) was left at room temperature for 25min. A solution of 2-aminothiazole (11mg) in anhydrous DMF (0.25ml) was treated with a third (~0.25ml) of the activated ester mixture and left stirring at room temperature for 22h. TBTU (11mg) and DIPEA (0.012ml) was added and after 25min further 2-aminothiazole (22mg) added. The reaction was left stirring at ambient temperature for 23h. The reaction mixture was then heated at 80°C in a greenhouse under nitrogen for 7h. The reaction was removed from the heat source and the solvent evaporated (vacuum centrifuge). The sample was dissolved in methanol and loaded onto a pre-conditioned SCX-2 cartridge. The cartridge was eluted with methanol followed by 2N ammonia in methanol. Both elutions were combined and evaporated. The resulting brown residue was purified by MDAP to give the title compound as a yellow powder (18.9mg). LC/MS; MH^+ 434, Rt 3.12min

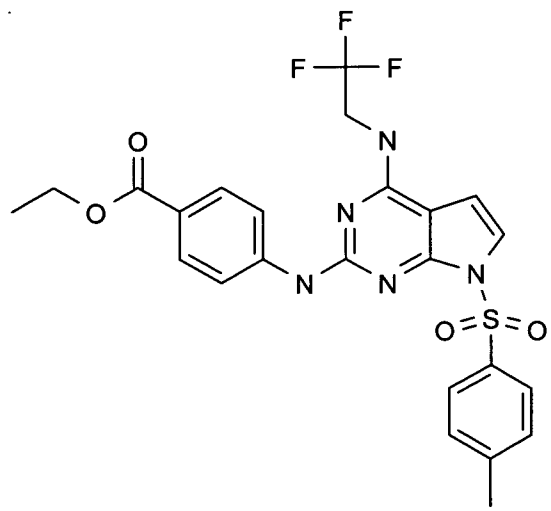
Example 299

4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid



Ethyl
4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoate (2.5g) was suspended in ethanol (60ml) and treated with aqueous sodium hydroxide (2N, 14.1ml). The mixture was stirred at 80°C for 3h and allowed to cool to ambient temperature. The reaction mixture was acidified with glacial acetic acid while stirring in an ice bath. The precipitate was isolated by filtration, dissolved in acetone, filtered and the acetone evaporated. The residue was recrystallised from ethyl acetate plus drops of acetone and water. The precipitated solid was isolated by filtration to give the title compound (1.0g). LC/MS; MH^+ 351.98, Rt 2.87min.

Intermediate 109
Ethyl
4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoate

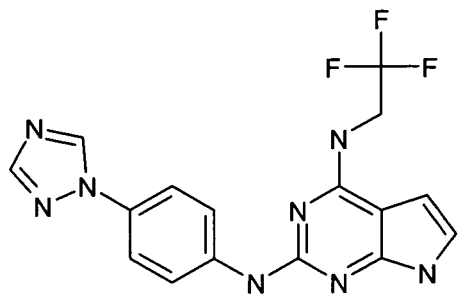


2-Chloro-7-[(4-methylphenyl)sulfonyl]-N-(2,2,2-trifluoroethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (7.5g), ethyl-4-aminobenzoate (3.37g), tris(dibenzylideneacetone)dipalladium (0) (510mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (142mg) and potassium carbonate (3.59g) in t-butanol (40ml) was heated at 110°C under nitrogen overnight. The solvent was evaporated *in vacuo* and the residue dissolved in ethyl acetate. The solution was filtered through Celite and the filtrate reduced to dryness. The residue

was crystallised from ethanol and the crystals isolated by filtration. These were dissolved in boiling ethanol, the solution allowed to cool initially to room temperature and then at ~4°C for 5h. The ethanol was drained from the resulting crystals, which were then further dried on a sinter to give the title compound (4.7g). LC/MS: MH^+ 533.98, Rt 3.84min.

Example 300

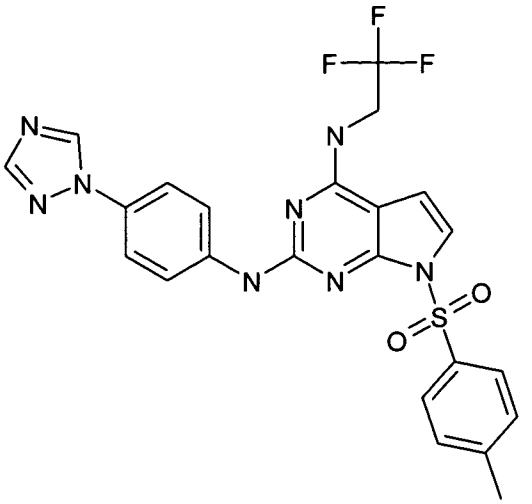
N^2-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



A solution of 7-[(4-methylphenyl)sulfonyl]-N^2-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]-N^4-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (112mg) in THF (10ml) under nitrogen was treated with potassium trimethylsilanolate (109mg) and the stirred mixture was heated at 70°C for 1.5h. The mixture was cooled to room temperature and phosphate buffer solution (pH6.5, 25ml) was added and the mixture extracted with ethyl acetate (25ml). The organic phase was dried (sodium sulphate) and the solvent evaporated *in vacuo*. The residue was purified by chromatography on a silica cartridge (10g), eluting with an ethyl acetate / cyclohexane gradient (0-100%) over 20min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound as a pale yellow solid (55mg). LC/MS; Rt 2.71min, MH^+ 375.

Intermediate 110

7-[(4-methylphenyl)sulfonyl]-N^2-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]-N^4-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

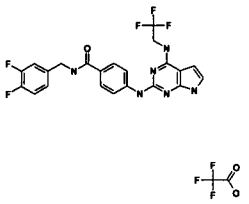
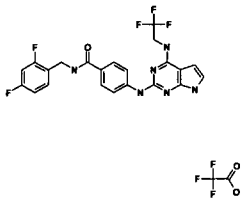
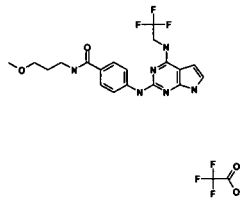
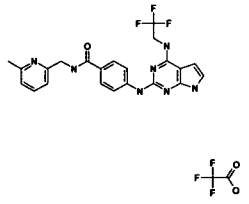


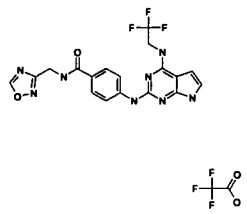
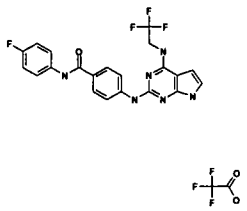
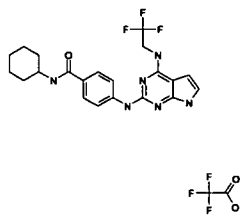
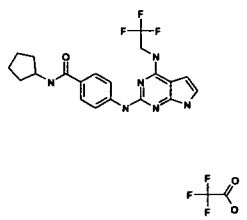
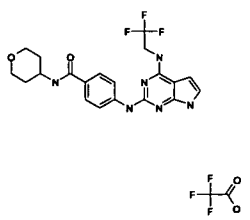
A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-(1*H*-1,2,4-triazol-1-yl)aniline (47mg, Acros) and potassium carbonate (48mg) in t-butanol (4.5ml) and degassed with nitrogen for 10min. 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (18mg) and tris(dibenzylideneacetone)dipalladium (0) (23mg) were added and the stirred mixture was heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature and was partitioned between phosphate buffer solution (pH6.5, 20ml) and ethyl acetate (20ml). The organic phase was dried (sodium sulphate) and the solvent was evaporated *in vacuo* at 30°C. The residue was purified by chromatography on a silica cartridge (10g) eluting with DCM, methanol / DCM (0.2:10) then (0.5:10) gave, after the appropriate fractions were combined and the solvent removed by evaporation *in vacuo*, the title compound as a straw coloured glass (115mg). LC/MS; Rt 3.46min, MH^+ 529.

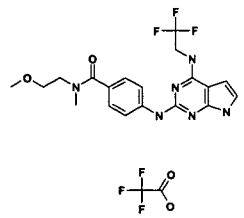
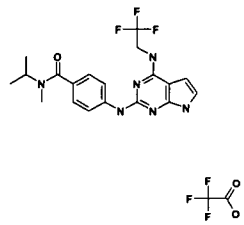
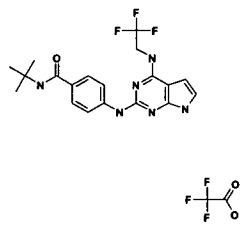
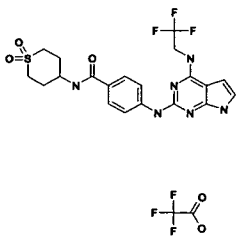
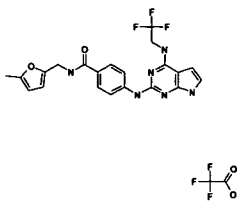
Method 20:

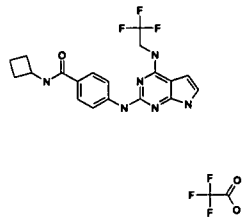
The 4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid (527mg) in anhydrous DMF (3.75ml) was treated with DIPEA (0.78ml) and TBTU (530mg) and left at room temperature for ~30min. The amine was dissolved in anhydrous DMF (0.25ml) (Amine salts were treated with DIPEA (0.035ml) to obtain the free base). A portion of the activated ester mixture (0.302ml) was dispensed into the amine solution. The reaction mixtures were left at room temperature under nitrogen overnight. The volatiles were evaporated (vacuum centrifuge) and the residue purified by MDAP. The appropriate fractions were combined and the solvents evaporated by vacuum centrifuge to give the desired product.

The following compounds were prepared using Method 20:

Example	Structure	Name	Starting Material	LC/MS MH^+	LC/MS Rt (min)
301		N-[(3,4-difluorophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	3,4-Difluorobenzlamine / Apollo	476.99	3.24
302		N-[(2,4-difluorophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	2,4-Difluorobenzylamine / Aldrich	476.99	3.22
303		N-[3-(methyloxy)propyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	3-Methoxypropylamine oxalate (1:1) / free base Aldrich	423	2.71
304		N-[(6-methyl-2-pyridinyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	[(6-Methyl-2-pyridinyl)methyl]amine hydroiodide / Aldrich	455.98	2.41

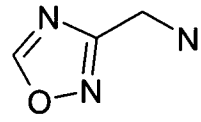
305		N-(1,2,4-oxadiazol-3-ylmethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	1,2,4-Oxadiazol-3-ylmethylamine hydrochloride	432.95	2.62
306		N-(4-fluorophenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	4-Fluoroaniline / Aldrich	444.99	3.31
307		N-cyclohexyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	Cyclohexylamine / Aldrich	433	3.20
308		N-cyclopentyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	Cyclopentylamine / Aldrich	419	3.07
309		N-(tetrahydro-2H-pyran-4-yl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	4-Aminotetrahydropyran / Peakdale	434.98	2.66

310		N-methyl-N-[2-(methyloxy)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	N-(2-Methoxyethyl)methylamine / Fluorochem	423	2.62
311		N-methyl-N-(1-methylethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	Methylisopropylamine / Aldrich	407	2.84
312		N-(1,1-dimethylethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	tert-Butylamine / Aldrich	407	3.06
313		N-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)amine hydrochloride	483	2.61
314		N-[(5-methyl-2-furanyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	[(5-methyl-2-furanyl)methyl]amine / Aldrich	445	3.08

		trifluoroacetate			
315		N-cyclobutyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	Cyclobutylamine / Aldrich	405	2.96

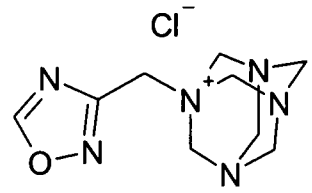
Intermediate 111
(1,2,4-oxadiazol-3-ylmethyl)amine hydrochloride

HCl



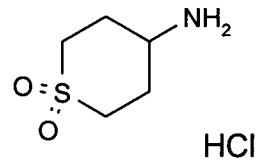
Concentrated hydrochloric acid (7.4ml) was dissolved in IMS (30ml) and the solution warmed to 50°C when 1-(1,2,4-oxadiazol-3-ylmethyl)-3,5,7-triaza-1-azoniatricyclo[3.3.1.1^{3,7}]decane chloride (7g) was added in one portion. The solid went into solution and shortly after a precipitate formed. The reaction mixture was then stirred with occasional warming for 2.5h and then stirred at room temperature overnight. The reaction mixture was quickly brought to reflux and was filtered hot. The filtrate was concentrated by half, cooled in an ice bath and ammonium chloride collected by filtration. The filtrate was concentrated by half, cooled in an ice bath and ammonium chloride collected by filtration. The filtrate was reduced to dryness and the solid washed with boiling IMS again and filtered one cool. Isolated solid is the desired product (79% purity, 0.6g). The filtrate was concentrated, the residue washed with cold IMS and the solid isolated by filtration to give a second batch of the title compound (0.8g, 80% purity).

Intermediate 112
1-(1,2,4-oxadiazol-3-ylmethyl)-3,5,7-triaza-1-azoniatricyclo[3.3.1.1^{3,7}]decane chloride



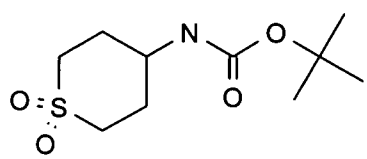
Hexamethylenetetramine (11.8g) was dissolved in hot DCM (100ml) and to this solution was added 3-(chloromethyl)-1,2,4-oxadiazole (10g, Apollo). The resulting mixture was stirred at reflux overnight. A white precipitate formed in the reaction mixture and was isolated by filteration and washed with DCM to obtain the title compound (13g).

Intermediate 113
(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)amine hydrochloride



1,1-Dimethylethyl(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)carbamate (9.9g) was dissolved in dioxane (210ml) and the solution stirred under nitrogen. Hydrochloric acid (5M, 105ml) was added dropwise to the solution with cooling in a water bath to which ice was added to keep the temperature below 25°C. The mixture was stirred at ambient temperature overnight and the solvent removed under vacuum. The residue was evaporated again from dioxane and the residual white powder dried on high vacuum and then in a vacuum oven at 40°C to obtain the title compound (7.2g). MS; MH^+ 150.

Intermediate 114
1,1-dimethylethyl (1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)carbamate

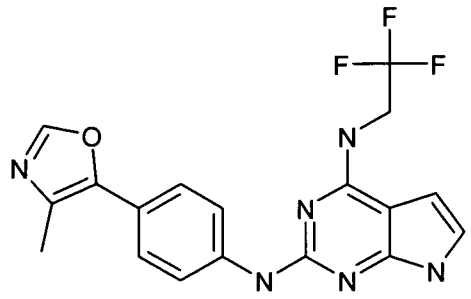


A solution of 1,1-dimethylethyl tetrahydro-2*H*-thiopyran-4-ylcarbamate (9.5g, Chemstep) in methanol (300ml) was stirred at 0-5°C in an ice / IMS bath. A solution of oxone (43.6g) in water (300ml) was added dropwise over a couple of hours keeping the temperature below 10°C. After the addition, water was added to the ice bath and the mixture stirred overnight whilst warming slowly to ambient temperature. The

mixture was poured with stirring into stirred aqueous potassium carbonate (10% w/v, 650ml). Further water was added (~200ml) and the mixture extracted with ethyl acetate (3x 500ml). The combined organics were washed with water (500ml), and brine (300ml), dried (magnesium sulphate), filtered and the solvent evaporated. The resulting white solid was dried on a high vacuum line to give the title compound (9.9g). LC/MS; $[MNH_4]^+$ 267.

Example 316

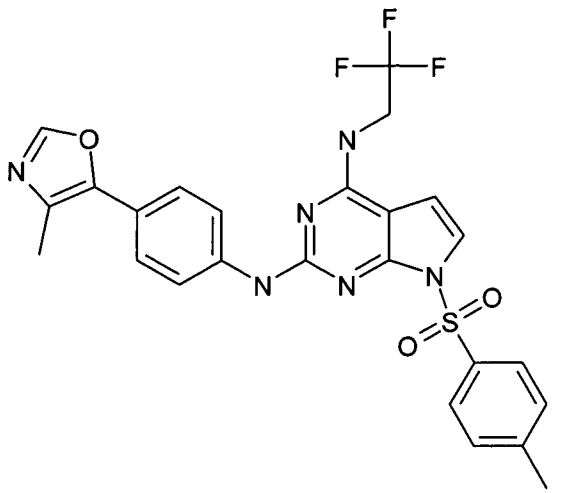
N^2-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*] pyrimidine-2,4-diamine



A solution of N^2-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]-7-[(4-methylphenyl)sulfonyl]-N^4-(2,2,2-trifluor oethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (126mg) in THF (10ml) under nitrogen was treated with potassium trimethylsilanolate (119mg) and the stirred mixture was heated at 70°C for 1.5h. The mixture was cooled to room temperature and phosphate buffer solution (pH6.5, 25ml) was added and the mixture extracted with ethyl acetate (25ml). The organic phase was dried (sodium sulphate), the solvent was evaporated *in vacuo* and the residue was purified by chromatography on a silica cartridge (10g), eluting with an ethyl acetate / cyclohexane gradient (0-100%) over 20min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave a residue (47mg) which was further purified by preparative tlc (20x20cm plate, 1mm thick layer of silica, Whatman PK6F). Elution with ethyl acetate gave, after the appropriate band was extracted with methanol / DCM and the solvent evaporated *in vacuo*, the title compound as a pale yellow solid (29mg). LC/MS; Rt 3.02min, MH^+ 389.

Intermediate 115

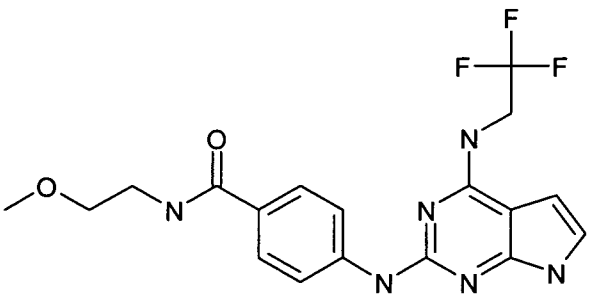
N^2-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]-7-[(4-methylphenyl)sulfonyl]-N^4-(2,2,2-tri fluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-(4-methyl-1,3-oxazol-5-yl)aniline (52mg, Syngene International) and potassium carbonate (48mg) in t-butanol (4.5ml) and degassed with nitrogen for 10min. 2-Dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (18mg) and tris(dibenzylideneacetone)dipalladium (0) (23mg) were added and the stirred mixture was heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature and was partitioned between phosphate buffer solution (pH6.5, 20ml) and ethyl acetate (20ml). The organic phase was dried (sodium sulphate) and the solvent was removed by evaporation *in vacuo*. The residue was purified by chromatography on a silica cartridge (10g), eluting with DCM, methanol / DCM (0.2:10) then (0.5:10). Combination of the appropriate fractions and evaporation of the solvents *in vacuo*, gave the title compound as a straw coloured glass (129mg). LC/MS: Rt 3.70min, MH^+ 543.

Example 317

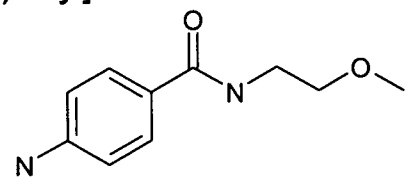
***N*-[2-(methyloxy)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**



A stirred mixture of 4-amino-*N*-[2-(methyloxy)ethyl]benzamide (58mg), 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), potassium carbonate (48mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (6mg) and tris(dibenzylideneacetone)dipalladium (0) (14mg) in in t-butanol (2.5ml) was heated in a sealed vial by microwave irradiation at 120°C for 1h. The cooled reaction was applied to a pre-conditioned SCX-2 cartridge (20g), the column washed with methanol

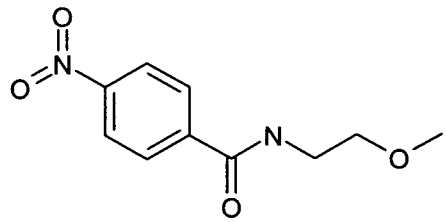
and the product eluted with 2M ammonia in methanol. The ammoniacal fractions were collected and the solvent evaporated under vacuum. The residue was treated with potassium carbonate (344mg), methanol (2ml) and water (1ml) and the stirred mixture was heated at 80°C overnight. Water (5ml) was added and the resulting precipitate was isolated by filtration. The solid was triturated with methanol (1ml) and filtered. This process of trituration with methanol (1ml) and filtration was repeated five more times. The solid was then dissolved in methanol and the solvent was then evaporated under vacuum to give the title compound (14.5mg). LC/MS; Rt 2.66min, MH^+ 408.93.

Intermediate 116
4-amino-*N*-[2-(methyloxy)ethyl]benzamide



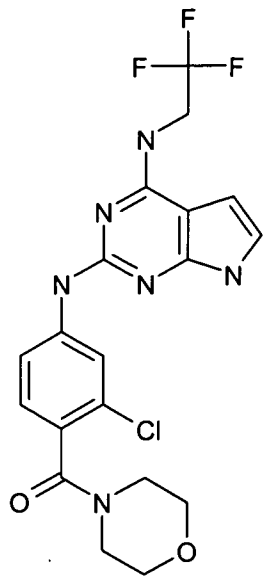
A solution of *N*-[2-(methyloxy)ethyl]-4-nitrobenzamide (401mg) in ethanol (15ml) was hydrogenated (1Atm.) over palladium on carbon (17.9mg) overnight. The reaction mixture was filtered through a Celite pad which was then washed twice with ethanol. The solvent was evaporated from the combined filtrate and washings under vacuum to give the title compound (290mg). LC/MS; Rt 1.54min, MH^+ 195.

Intermediate 117
***N*-[2-(methyloxy)ethyl]-4-nitrobenzamide**



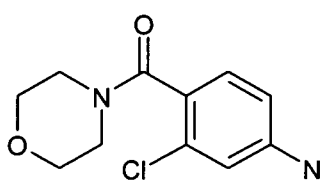
A mixture of 4-nitrobenzoyl chloride (750mg), [2-(methyloxy)ethyl]amine (0.529ml) and potassium carbonate (836mg) in DCM (50ml) was stirred at room temperature under nitrogen overnight. Hydrochloric acid (1M, 50ml) was added and the mixture was stirred for 15min. The phases were separated; the organic phase was washed with saturated aqueous sodium bicarbonate solution (50ml) and water (50ml). The organic phase was reduced to dryness under vacuum to give the title compound (401mg). LC/MS; Rt 2.18min, MH^+ 225.

Example 318
N^2-[3-chloro-4-(4-morpholinylcarbonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



To a stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 3-chloro-4-(4-morpholinylcarbonyl)aniline (111mg) and potassium carbonate (48mg) in t-butanol (4.5ml) under nitrogen was added 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (18mg) and tris(dibenzylideneacetone)dipalladium (0) (23mg) and the stirred mixture was heated at 80°C for 18h. The cooled reaction was partitioned between water (25ml) and ethyl acetate (25ml). The aqueous phase was extracted with ethyl acetate (25ml) and the solvent from the combined organic phases was removed by evaporation *in vacuo*. The residue was treated with a solution of sodium methoxide in methanol (0.5M, 6ml) and the mixture heated at 80°C under nitrogen for 1h. The methanol was evaporated *in vacuo* from the cooled mixture, water (30ml) was added to the residue and the mixture was extracted with ethyl acetate (2x 30ml). The solvent from the combined organic phases was removed by evaporation *in vacuo*. The residue was purified by MDAP. The appropriate fractions were combined and the solvent removed by evaporation *in vacuo* to give the title compound as a white solid (13.3mg). LC/MS; Rt 2.85min, MH^+ 455.

Intermediate 118
3-chloro-4-(4-morpholinylcarbonyl)aniline

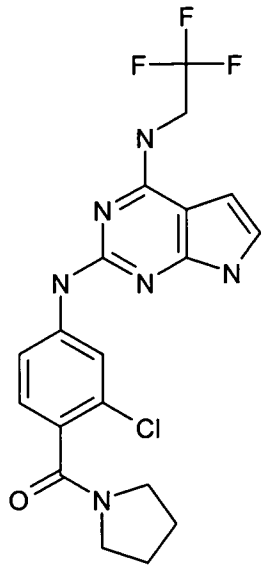


4-Amino-2-chlorobenzoic acid (300mg, Aldrich), PyBOP (1.0g), morpholine (0.73ml) and DIPEA (3.0ml) were stirred in DMF (15ml) at room temperature under nitrogen. The solvent was evaporated *in vacuo*, the residual gum was dissolved in the minimum amount of DCM and was absorbed onto an aminopropyl cartridge (50g) and the

material purified by chromatography, eluting with ethyl acetate / cyclohexane (0-100%) over 30min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound (384mg). LC/MS: Rt 1.93min, MH^+ 241.

Example 319

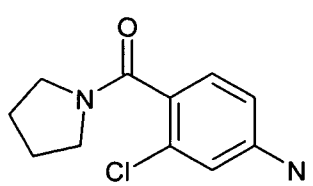
N^2-[3-chloro-4-(1-pyrrolidinylcarbonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



To a stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 3-chloro-4-(1-pyrrolidinylcarbonyl)aniline (111mg) and potassium carbonate (48mg) in t-butanol (4.5ml) under nitrogen was added 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (18mg) and tris(dibenzylideneacetone)dipalladium (0) (23mg) and the stirred mixture was heated at 80°C for 18h. The cooled reaction was partitioned between water (25ml) and ethyl acetate (25ml). The aqueous phase further extracted with ethyl acetate (25ml) and the solvents from the combined organic phases evaporated *in vacuo*. The residue was treated with a solution of sodium methoxide in methanol (0.5M, 6ml) and the mixture heated at 80°C under nitrogen for 1h. The methanol was evaporated *in vacuo* from the cooled reaction, water (30ml) was added and the mixture was extracted with ethyl acetate (2x 30ml). The solvent from the combined organic phases was evaporated *in vacuo* and the residue was purified by MDAP. The appropriate fractions were combined and the solvent removed by evaporation *in vacuo* to give the title compound as a yellow/brown solid (9mg). LC/MS; Rt 3.00min, MH^+ 439.

Intermediate 119

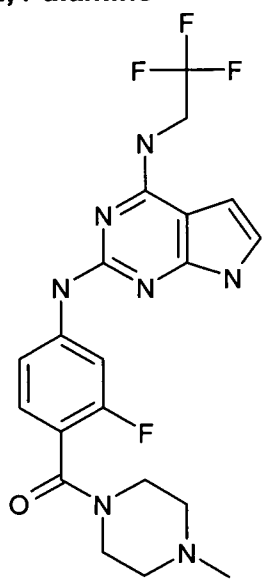
3-chloro-4-(1-pyrrolidinylcarbonyl)aniline



4-Amino-2-chlorobenzoic acid (300mg, Aldrich), PyBOP (1.0g), pyrrolidine (0.70ml) and DIPEA (3.0ml) were stirred in DMF (15ml) at room temperature under nitrogen. The solvent was evaporated *in vacuo*, the residual gum was dissolved in the minimum amount of DCM and was absorbed onto an aminopropyl cartridge (50g) and the material was purified by chromatography, eluting with ethyl acetate / cyclohexane (0-100%) over 30min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound (359mg). LC/MS; Rt 2.21min, MH^+ 225.

Example 320

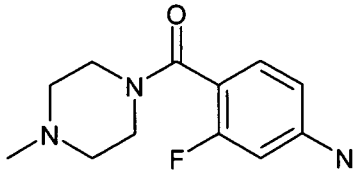
N^2-{3-fluoro-4-[(4-methyl-1-piperazinyl)carbonyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



To a stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 3-fluoro-4-[(4-methyl-1-piperazinyl)carbonyl]aniline (70mg) and potassium carbonate (48mg) in t-butanol (4.5ml) under nitrogen was added 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (18mg) and tris(dibenzylideneacetone)dipalladium (0) (23mg) were added and the stirred mixture was heated in a sealed vial by microwave irradiation at 120°C for 1h. The cooled reaction was partitioned between water (25ml) and ethyl acetate (25ml). The aqueous phase further extracted with ethyl acetate (25ml) and the solvent from the combined organic phases was evaporated *in vacuo*. The residue was treated with a solution of sodium methoxide in methanol (0.5M, 6ml) and the mixture heated at 80°C under nitrogen for 1h. Methanol was evaporated from the cooled reaction *in vacuo*, water (25ml) was added and the mixture was extracted with ethyl acetate (2x 25ml). The solvent from the combined organic phases was removed by evaporation *in vacuo* and the residue was purified by MDAP. The appropriate fractions were combined and the solvent removed by evaporation *in vacuo* to give the title compound as a white solid (4.6mg). LC/MS; Rt 2.21min, MH^+ 452.

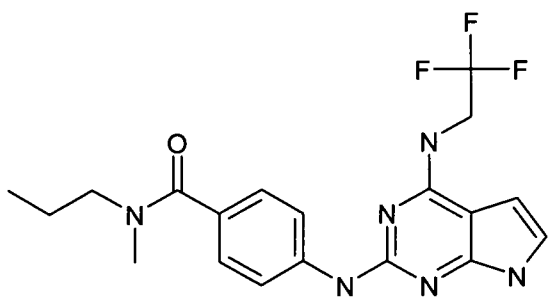
Intermediate 120

3-fluoro-4-[(4-methyl-1-piperazinyl)carbonyl]aniline



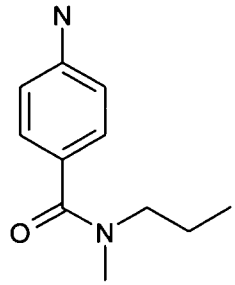
4-Amino-2-fluorobenzoic acid (300mg, Apin) was added to a stirred solution of PyBOP (1.1g), 1-methylpiperazine (1.1ml) and DIPEA (3.37ml) were stirred in DMF (15ml) at room temperature under nitrogen. The solvent was evaporated *in vacuo*, the residual gum was dissolved in the minimum amount of DCM and was absorbed onto an aminopropyl cartridge (50g) and the material was purified by chromatography, eluting with ethyl acetate / cyclohexane (0-100%) over 30min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound (427mg). LC/MS: Rt 0.30min, MH^+ 238.

Example 321
***N*-methyl-*N*-propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**



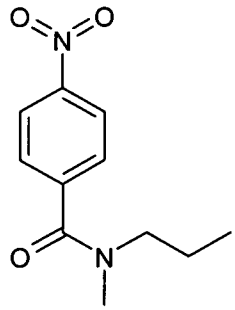
A stirred mixture of 4-amino-*N*-methyl-*N*-propylbenzamide (57mg) , 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), potassium carbonate (48mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (6mg) and tris(dibenzylideneacetone)dipalladium (0) (14mg) in in t-butanol (2.5ml) was heated in a sealed vial by microwave irradiation at 120°C for 1h. The cooled reaction was applied to a pre-conditioned SCX-2 cartridge (20g). The cartridge was washed with methanol and the product eluted with 2M ammonia in methanol. The ammoniacal fractions were collected and the solvent evaporated under vacuum. The residue was treated with potassium carbonate (423.5mg), methanol (2ml) and water (1ml) and the stirred mixture was heated at 80°C overnight. Water (5ml) was added and the precipitate was isolated by filtration. The filtrate was extracted with ethyl acetate (30ml), the organic phase dried (hydrophobic frit) and the solvent evaporated under vacuum. The residue and the precipitate were dissolved in methanol, combined and reduced to dryness *in vacuo*. The resulting residue was purified by MDAP to give, after the appropriate fractions were combined and the solvent evaporated under vacuum, the title compound (19mg). LC/MS; Rt 2.91min, MH^+ 406.9.

Intermediate 121
4-amino-*N*-methyl-*N*-propylbenzamide



A solution of *N*-methyl-4-nitro-*N*-propylbenzamide (330mg) in ethanol (15ml) was hydrogenated (1Atm.) over palladium on carbon (10%, 15.3mg) overnight. The mixture was filtered through a Celite pad which was then washed with ethanol. The solvent was evaporated under vacuum to give the title compound (260mg). LC/MS; Rt 2.02min, MH^+ 193.

Intermediate 122
***N*-methyl-4-nitro-*N*-propylbenzamide**



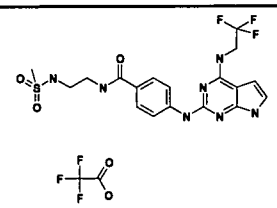
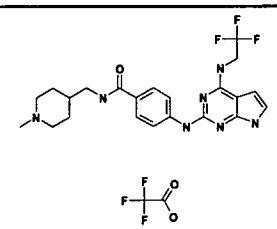
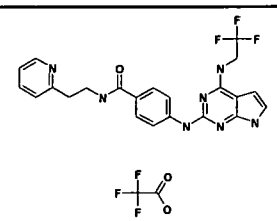
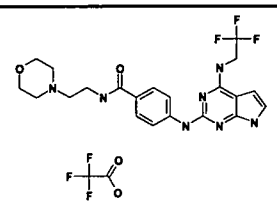
A mixture of 4-nitrobenzoyl chloride (750mg), *N*-methylpropylamine (0.622ml) and potassium carbonate (836mg) in DCM (50ml) was stirred at room temperature under nitrogen overnight. Hydrochloric acid (1M, 50ml) was added and the mixture was stirred for 15min. The phases were separated; the organic phase was washed with water (100ml) and dried (hydrophobic frit). Evaporation of the solvent *in vacuo* gave a residue, which was dissolved in ethyl acetate (25ml) and was washed with sodium hydrogen carbonate solution (50ml). The organic phase was collected through a hydrophobic frit and the solvent was evaporated under vacuum to give the title compound (330mg). LC/MS; Rt 2.58min, MH^+ 223.

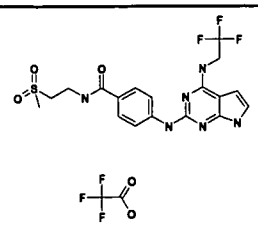
Method 21:

The 4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid (0.21g) and TBTU (0.21g) in DMF (1.5ml) was treated with DIPEA (0.45ml) and left for 30min. The amine (0.2mmol) was suspended in DMF (0.25ml) (amine salts were treated with DIPEA (0.018ml) to obtain the free base). A portion of the activated ester mixture (0.325ml) was added to the amine solution and the reaction mixture left overnight. The volatiles were evaporated in a vacuum centrifuge, the residue

dissolved in methanol (0.5ml) and applied to a pre-conditioned SCX-2 cartridge (1g). The cartridge was washed with methanol, and the product eluted with 2M ammonia in methanol solution. The ammonia fractions were evaporated under vacuum and the residue dissolved in methanol (0.5ml). The solution was applied to an aminopropyl SPE cartridge (methanol pre-conditioned). The cartridge was washed with chloroform, ethyl acetate and methanol. The chloroform fraction was evaporated under vacuum and the residue purified by MDAP. The solvent was evaporated from the appropriate fractions (vacuum centrifuge) to obtain the desired product.

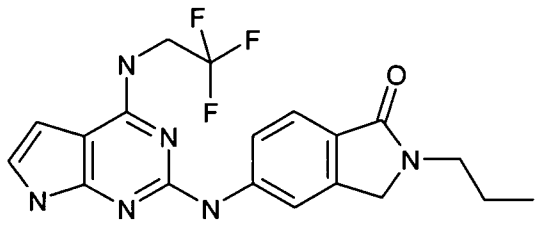
The following examples were prepared using Method 21:

Example	Structure	Name	Starting Material	LC/MS MH^+	LC/MS Rt (min)
322		N-{2-[(methylsulfonyl)amino]ethyl}-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	N-(2-aminoethyl)methanesulfonamide hydrochloride / WO 9802437	471.85	2.57
323		N-[(1-methyl-4-piperidinyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	1-Methyl-4-piperidinylmethylamine / Maybridge	461.98	2.21
324		N-[2-(2-pyridinyl)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	2-(2-Aminoethyl)pyridine / Lancaster	455.89	2.39
325		N-[2-(4-morpholinyl)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	N-(2-Aminoethyl)morpholine / Aldrich	463.94	2.22

		trifluoroacetate			
326		N-[2-(methylsulfonyl)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	2-Aminoethylmethylsulfone / Beta Pharma, Inc.	457	2.55

Example 327

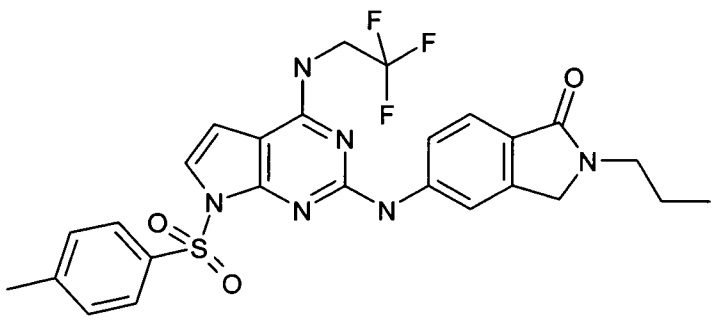
2-Propyl-5-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-2,3-dihydro-1*H*-isoindol-1-one



5-({7-[(4-Methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-2-propyl-2,3-dihydro-1*H*-isoindol-1-one (25mg) was mixed with sodium methoxide in methanol (1.5ml) and the solution heated at 80°C under nitrogen for ~2h. The reaction was allowed to cool, the precipitate isolated by filtration, washed with methanol (~1ml) and water and sucked dry on the sinter, to give the desired product as a pale cream solid (7.5mg). LC/MS; MH^+ 405, Rt 2.95min.

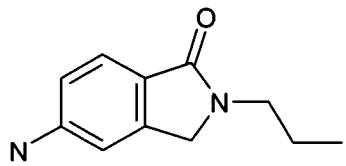
Intermediate 123

5-({7-[(4-Methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-2-propyl-2,3-dihydro-1*H*-isoindol-1-one



2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (56mg), 5-amino-2-propyl-2,3-dihydro-1*H*-isoindol-1-one (32mg), tris(dibenzylideneacetone)dipalladium (0) (12.7mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (6.6mg) and potassium carbonate (26.8mg) were mixed in t-butanol (2.5ml), the mixture degassed and heated at 80°C under nitrogen overnight. The cooled reaction was diluted with ethyl acetate and applied to an SCX-2 SPE (5g), which was washed with ethyl acetate and methanol and the product eluted with 0.880 ammonia / methanol. The basic fraction was reduced to dryness *in vacuo*, the residue dissolved in ethyl acetate and filtered through a silica cartridge (1g) washing with ethyl acetate. The solvent was evaporated from the combined filtrate / washings *in vacuo*, the residue applied to a silica cartridge (10g) and the cartridge eluted with an ethyl acetate / cyclohexane gradient (30-60%). The appropriate fractions were combined and reduced to dryness *in vacuo* to leave the desired product as a cream solid (25mg). LC/MS; MH^+ 559, Rt 3.61min.

Intermediate 124
5-amino-2-propyl-2,3-dihydro-1*H*-isoindol-1-one



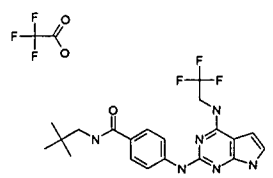
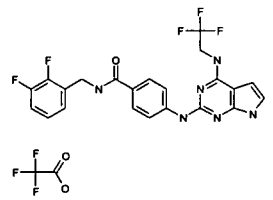
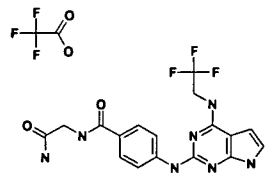
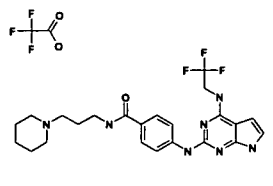
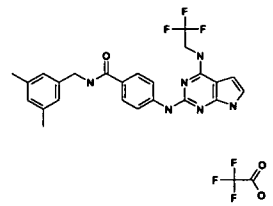
5-Bromo-2-propyl-2,3-dihydro-1*H*-isoindol-1-one (175mg, Synlett (2006), (5), 801-803), tris(dibenzylideneacetone)dipalladium (0) (15.8mg), R-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (32mg) were mixed, the flask flushed with nitrogen and dry toluene (6ml) added. Benzophenone imine (139µl) and sodium t-butoxide (150mg) were added to the mixture, the mixture degassed and heated at 100°C under nitrogen for ~2.5h. The reaction was left to cool overnight, the toluene evaporated *in vacuo* and the residue dissolved in THF (6ml). Hydrochloric acid (1M, 3ml) was added to the THF solution and the reaction stirred at room temperature for ~1.5h. The reaction was partitioned between chloroform and water and the aqueous phase washed with chloroform. The aqueous was basified with sodium hydroxide solution (2N) and extracted with chloroform. The extract was dried (hydrophobic frit) and the solvent evaporated *in vacuo*. The residue was triturated with ethyl acetate / 40-60 petrol and the solid isolated by filtration to give the title compound as a pale yellow solid. LC/MS; MH^+ 191, Rt 2.06min.

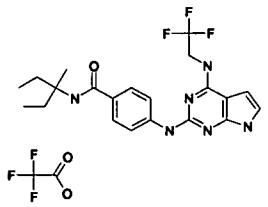
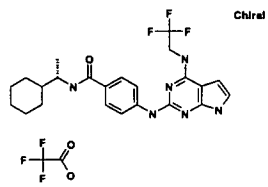
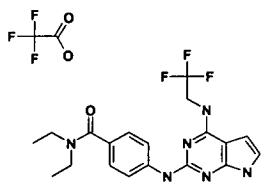
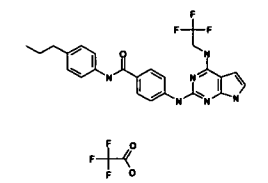
Method 22:

The 4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid (842mg) in anhydrous DMF (6ml) was treated with TBTU (847.2mg) DIPEA (1.7ml) and left at room temperature for 30min. A portion of this solution (0.32ml) was

added to a solution of amine (0.20mM) in DMF (0.25ml). The reaction mixture was left at room temperature for 3.5 days. Further TBTU (32mg) and DIPEA (0.017ml) was added and the reaction left at room temperature overnight. The reaction was purified by MDAP and appropriate fractions combined and evaporated to give the desired product.

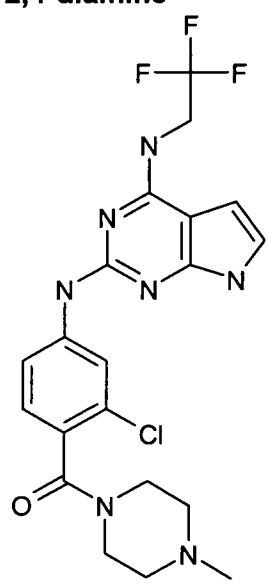
The following compounds were prepared using Method 22:

Example	Structure	Name	Amine / Source	LC/MS MH^+	LC/MS Rt (min)
328		N-(2,2-dimethylpropyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	Neopentylamine / Fluorochem Ltd	420.89	3.16
329		N-[(2,3-difluorophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	2,3-Difluorobenzylamine / Apollo	477	3.21
330		N-(2-amino-2-oxoethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	Glycinamide hydrochloride / Aldrich	408	2.37
331		N-[3-(1-piperidinyl)propyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	1-Amino-3-(N-piperidino)propane / ABCR	476	2.25
332		N-[(3,5-dimethylphenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	3,5-Dimethylbenzylamine / Fluorochem	469.38	3.36

333		N-(1-ethyl-1-methylpropyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	3-Methyl-3-pentanamine / Matrix Scientific	435	3.30
334		N-[(1S)-1-cyclohexylethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	S(+)-1-Cyclohexylethylamine / Aldrich	461	3.41
335		N,N-diethyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	Diethylamine / Aldrich	406.9	2.89
336		N-(4-propylphenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	4-Propylaniline / Aldrich	469	3.61

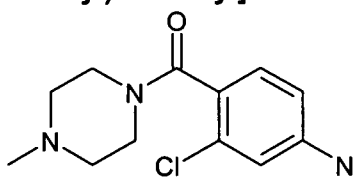
Example 337

N^2-{3-chloro-4-[(4-methyl-1-piperazinyl)carbonyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



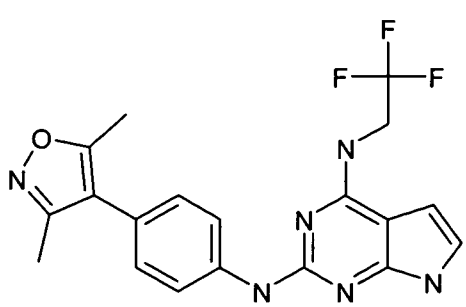
To a stirred mixture of 3-chloro-4-[(4-methyl-1-piperazinyl)carbonyl]aniline (125mg), 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), potassium carbonate (48mg) in t-butanol (4ml) under nitrogen was added 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (18mg) and tris(dibenzylideneacetone)dipalladium (0) (23mg) and the mixture heated at 80°C for 12h. The cooled reaction was partitioned between water (25ml) and ethyl acetate (25ml). The aqueous phase was extracted with ethyl acetate (25ml). The solvent from the combined organic phases was evaporated *in vacuo*. The residue was treated with a solution of sodium methoxide in methanol (0.5M, 6ml) and the mixture heated at 80°C under nitrogen for 1h. The methanol was evaporated from the cooled reaction *in vacuo*, water (25ml) was added to the residue and the mixture was extracted with ethyl acetate (2x 25ml). The solvent from the combined organic phases was evaporated *in vacuo* and the residue purified by MDAP. Combination of the appropriate fractions and evaporation of the solvents *in vacuo* gave the title compound (76.1mg). LC/MS; Rt 2.20min, MH^+ 468.

Intermediate 125
3-chloro-4-[(4-methyl-1-piperazinyl)carbonyl]aniline



4-Amino-2-chlorobenzoic acid (300mg, Aldrich), PyBOP (1.0g), 1-methylpiperazine (0.93ml) and DIPEA (3.0ml) were stirred in DMF (15ml) at room temperature under nitrogen. The solvent was evaporated *in vacuo*, the residual gum was dissolved in the minimum amount of DCM and was absorbed onto an aminopropyl cartridge (50g) and the material was purified by chromatography, eluting with ethyl acetate / cyclohexane (0-100%) over 30min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound (405mg). LC/MS; Rt 0.24min, MH^+ 254.

Example 338
***N*^{2}-[4-(3,5-dimethyl-4-isoxazolyl)phenyl]-*N*^{4}-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine**

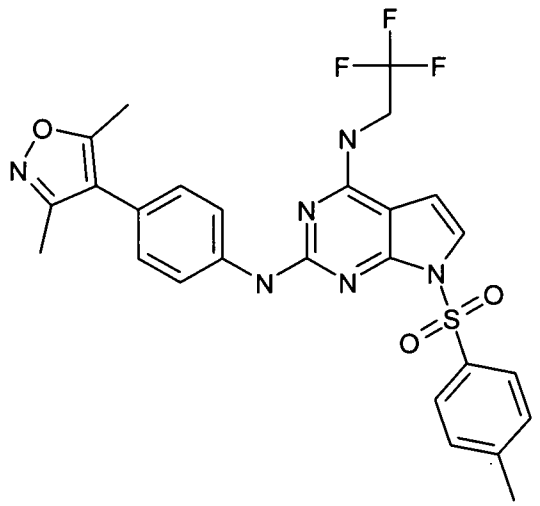


A solution of

N^2-[4-(3,5-dimethyl-4-isoxazolyl)phenyl]-7-[(4-methylphenyl)sulfonyl]-N^4-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine (126mg) in sodium methoxide solution in methanol (0.5M, 4.54ml) under nitrogen was heated at 60°C for 2.5h. The mixture was cooled to room temperature and the solvent evaporated *in vacuo*. The residue was triturated with water (15ml) and filtered under reduced pressure to give a solid (70mg) which was further purified by MDAP. The appropriate fractions were combined and the solvent removed by evaporation *in vacuo* to give the title compound as a white solid (31mg). LC/MS; Rt 3.11min, MH^+ 403.

Intermediate 126

N^2-[4-(3,5-dimethyl-4-isoxazolyl)phenyl]-7-[(4-methylphenyl)sulfonyl]-N^4-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



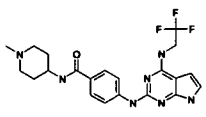
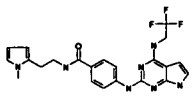
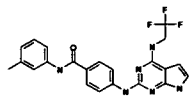
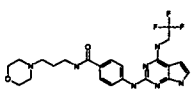
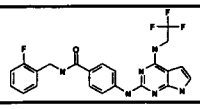
A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-(3,5-dimethyl-4-isoxazolyl)aniline (51mg, Latvijas Kimijas Zurnals, 1991, 85-9.) and potassium carbonate (48mg) in t-butanol (4ml) was degassed with nitrogen for 10min. 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (18mg) and tris(dibenzylideneacetone)dipalladium (0) (23mg) were added and the stirred mixture was heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature and partitioned between phosphate buffer solution (pH6.5, 30ml) and ethyl acetate (30ml). The organic phase was dried (sodium sulphate) and the solvent was evaporated *in vacuo*. The residue was purified by chromatography on a silica cartridge (10g), eluting with DCM, methanol / DCM (0.1:10) then (0.2:10). Combination of the appropriate fractions and evaporation of the solvents *in vacuo*, gave the title compound as a red/brown glass (130mg). LC/MS; Rt 3.74min, MH^+ 557.

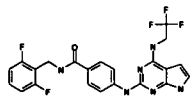
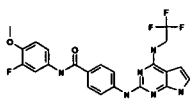
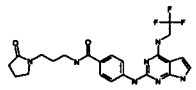
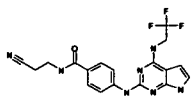
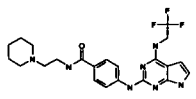
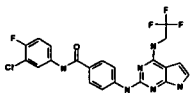
Method 23:

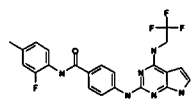
The 4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic

acid (0.42g) was suspended in DMF (3ml). The suspension was treated with DIPEA (0.84ml) followed by TBTU (0.48g) and left for 20min. One twelfth of the activated ester mixture (~0.32ml) was added to the amine suspended in DMF (0.25ml). The reaction mixture was left overnight under nitrogen. The reaction mixture was purified by MDAP and the solvent evaporated from the appropriate fractions by vacuum centrifuge. The residue was dissolved in methanol and filtered through an aminopropyl cartridge (1g, pre-conditioned with methanol). The cartridge was washed with methanol and the combined filtrate and washings reduced to dryness (vacuum centrifuge) to give the desired compound.

The following compounds were prepared using Method 23:

Example	Structure	Name	Amine / Source	LC/MS MH^+	LC/MS Rt (min)
339		N-(1-methyl-4-piperidinyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	1-Methylpiperidin-4-amine / Matrix	447.98	2.25
340		N-[2-(1-methyl-1H-pyrrol-2-yl)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	2-(2-Aminoethyl)-1-methylpyrrole / ANDAChem, Inc.	457.99	3.12
341		N-(3-methylphenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	m-Toluidine / Aldrich	440.95	3.46
342		N-[3-(4-morpholinyl)propyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	4-(3-Aminopropyl)morpholine / Acros	478	2.26
343		N-[(2-fluorophenyl)methyl]-4-({4-[(2,	2-Fluorobenzylamine /	458.96	3.25

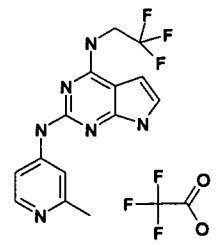
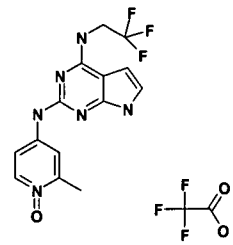
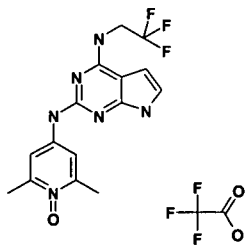
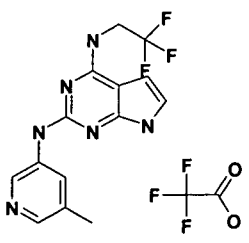
		2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	Aldrich		
344		N-[(2,6-difluorophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	2,6-Difluorobenzylamine / Acros	476.94	3.24
345		N-[3-fluoro-4-(methyloxy)phenyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	3-Fluoro-p-anisidine / Aldrich	474.93	3.39
346		N-[3-(2-oxo-1-pyrrolidinyl)propyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	1-(3-Aminopropyl)-2-pyrrolidone / Acros	476	2.69
347		N-(2-cyanoethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	3-Aminopropionitrile / Alfa	401.93	2.74
348		N-[2-(1-piperidinyl)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	1-(2-Aminoethyl)piperidine / Aldrich	462	2.35
349		N-(3-chloro-4-fluorophenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-	3-Chloro-4-fluoroaniline / Acros	478.92	3.66

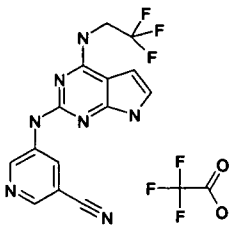
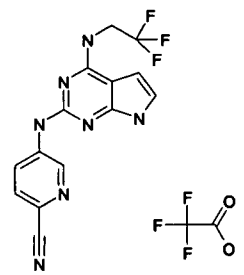
		2-yl}amino)benzamide			
350		N-(2-fluoro-4-methylphenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	2-fluoro-4-methylaniline / Aldrich	458.97	3.44

Method 24:

A mixture of potassium carbonate (1.4g), tris(dibenzylideneacetone)dipalladium (0) (450mg) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (350mg) was stirred for 2h to give a homogeneous solid. This solid (~44mg) was added to an aliquot (1ml) of a suspension of 2-chloro-*N*-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (850mg) in t-butanol (34ml), followed by the amine (2eq). The resultant mixture was heated at 90°C overnight. The reaction was diluted with ethanol and filtered through a pad of Celite. The solvent was removed under a stream of nitrogen and the residue was purified by MDAP. Combination of appropriate fractions and evaporation of the solvents gave the desired product.

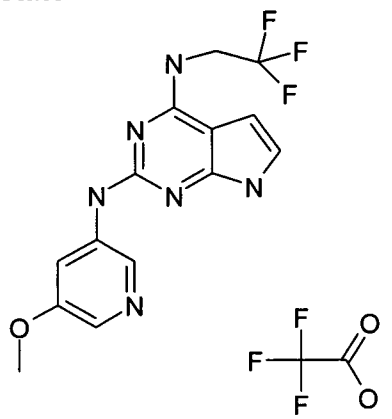
The following compounds were prepared using Method 24:

Example	Structure	Name	Amine/ Source	LC/MS Rt (min)	LC/MS MH^+
351		N^2-(2-methyl-4-pyridinyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-Methyl-4-pyridinamine / Fluorochem	2.27	323
352		N^2-(2-methyl-1-oxido-4-pyridinyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2-Methyl-4-pyridinamine 1-oxide / WO 8808842	2.47	339
353		N^2-(2,6-dimethyl-1-oxido-4-pyridinyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	2,6-Dimethyl-4-pyridinamine 1-oxide / Chem. And Pharm. Bull 1956, 4, 174-177	2.55	353
354		N^2-(5-methyl-3-pyridinyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	5-Methyl-3-pyridinamine [washed into reaction with t-butanol (1ml)] / Matrix Scientific	2.31	323

355		5-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-3-pyridinecarbonitrile trifluoroacetate	5-Amino-3-pyridinecarbonitrile / ChemPacific	2.96	334
356		5-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-2-pyridinecarbonitrile trifluoroacetate	5-amino-2-pyridinecarbonitrile/ ABCR	3.07	333.99

Example 357

N^2-[5-(methyloxy)-3-pyridinyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate



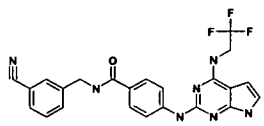
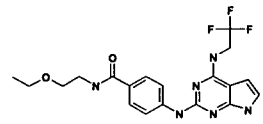
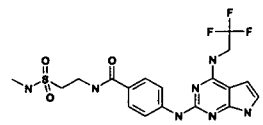
A mixture of potassium carbonate (1.4g), tris(dibenzylideneacetone)dipalladium (0) (450mg) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (350mg) was stirred for 2h to give a homogeneous solid. This solid (~44mg) was added to an aliquot (1ml) of a suspension of 2-chloro-*N*-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (850mg) in t-butanol (34ml), followed by addition of 5-(methyloxy)-3-pyridinamine hydrobromide (41mg, Heterocycles, 15(2), 871-4; 1981). The resultant mixture was heated at 90°C overnight. Potassium carbonate (840mg), tris(dibenzylideneacetone)dipalladium (0) (270mg) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (210mg) were stirred for 2h to give a homogeneous solid. This solid (~44mg) was added to the reaction and heating repeated at 90°C overnight. The reaction was diluted with ethanol and filtered through a pad of Celite. The solvent was removed under a stream of nitrogen and the residue was purified by MDAP. Combination of

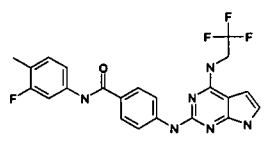
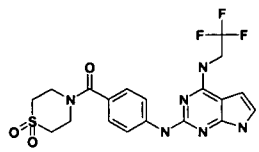
appropriate fractions and evaporation of the solvents gave the desired product (4mg). LC/MS; Rt 2.50min, MH^+ 339.

Method 25:

4-({4-[(2,2,2-Trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid (0.42g) was suspended in DMF (3ml). The suspension was treated with DIPEA (0.84ml) followed by TBTU (0.48g) and left for 20min. Amine (0.2mmol) was suspended in DMF (0.25ml) and one twelfth (~0.25ml) of the activated ester mixture was added. The reaction mixtures were left at room temperature under nitrogen. The reaction mixture was purified by MDAP, the appropriate fractions combined and the solvent evaporated by vacuum centrifuge. The residue was dissolved in a small amount of methanol and filtered through an aminopropyl cartridge (1g, pre-conditioned with methanol). The cartridge was washed with methanol and the solvent evaporated from the combined filtrate and washings under vacuum to give the desired product.

The following compounds were prepared using Method 25:

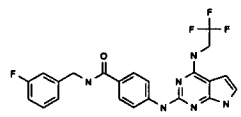
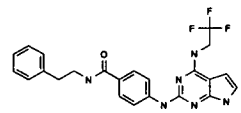
Example	Structure	Name	Starting Material	LC/MS MH^+	LC/MS Rt (min)
358		N-[(3-cyanophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	3-(Aminomethyl)benzonitrile / Apin	465.9	3.08
359		N-[2-(ethyloxy)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	2-(Ethyloxy)ethanamine / Matrix	422.92	2.79
360		N-{2-[(methylamino)sulfonyl]ethyl}-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)	2-Amino-N-methylethanesulfonamide	471.85	2.64

		benzamide			
361		N-(3-fluoro-4-methylphenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	3-Fluoro-4-methylaniline / Aldrich	458.9	3.49
362		N~2~-{4-[(1,1-dioxido-4-thiomorpholinyl)carbonyl]phenyl}-N~4~-(2,2,2-trifluoroethyl)-1H-pyrrolo[2,3-d]pyrimidine-2,4-diamine	thiomorpholine 1,1-dioxide / Syntech	468.84	2.60

Method 26:

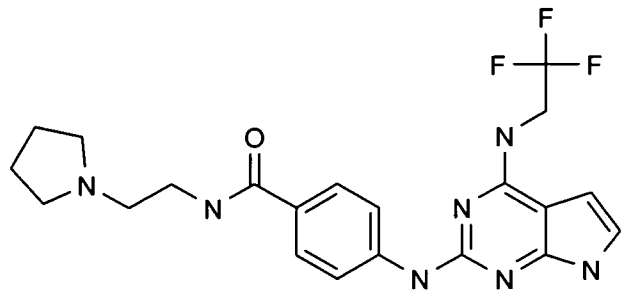
4-({4-[(2,2,2-Trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid (0.42g) was suspended in DMF (3ml). The suspension was treated with DIPEA (0.84ml) followed by TBTU (0.48g) and left for 20min. Amine (0.2mmol) was suspended in DMF (0.25ml) and one twelfth (~0.25ml) of the activated ester mixture was added. The reaction mixtures were left at room temperature under nitrogen. The reaction mixture was purified by MDAP, the appropriate fractions combined and the solvent evaporated by vacuum centrifuge. The residue was dissolved in a small amount of methanol and filtered through an aminopropyl cartridge (1g, pre-conditioned with methanol). The cartridge was washed with methanol and the solvent evaporated from the combined filtrate and washings under vacuum. The residue was applied an aminopropyl cartridge (1g, methanol pre-conditioned) and the cartridge eluted with DCM. The eluent was reduced to dryness and the residue purifed by MDAP. The appropriate fractions combined and the solvents evaporated *in vacuo* to give the desired product

The following compounds were prepared using Method 26:

Example	Structure	Name	Starting Material	LC/MS MH^+	LC/MS Rt (min)
363		*N*-[(3-fluorophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide	[(3-Fluorophenyl)methyl]amine / Aldrich	459	3.14
364		*N*-(2-phenylethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide	2-Phenylethanamine / Aldrich	454.94	3.20

Example 365

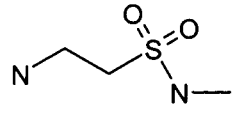
***N*-[2-(1-pyrrolidinyl)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**



4-({4-[(2,2,2-Trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid (0.42g) was suspended in DMF (3ml). The suspension was treated with DIPEA (0.84ml) followed by TBTU (0.48g) and left for 20min. [2-(1-Pyrrolidinyl)ethyl]amine (0.2mmol, Lancaster) was suspended in DMF (0.25ml) and one twelfth (~0.25ml) of the activated ester mixture was added. The reaction mixtures were left at room temperature under nitrogen. The reaction mixture was purified by MDAP, the appropriate fractions combined and the solvent evaporated by vacuum centrifuge. The residue was dissolved in a small amount of methanol and filtered through an aminopropyl cartridge (1g, pre-conditioned with methanol). The cartridge was washed with methanol and the solvent evaporated from the combined filtrate and washings under vacuum. The residue was applied an aminopropyl cartridge (1g, methanol pre-conditioned) and the cartridge eluted with DCM. The eluent was reduced to dryness and the residue purifed by MDAP. The appropriate fractions combined and the solvents evaporated *in vacuo*. The residue was dissolved in methanol (1ml)

andapplied to a pre-conditioned SCX-2 cartridge (0.5g) which was washed with methanol. Elution with 2N ammonia in methanol and evaporation of the solvents under vacuum gave the title compound. LC/MS; Rt 2.20min, MH^+ 448.

Intermediate 127
2-Amino-N-methylethanesulfonamide hydrochloride



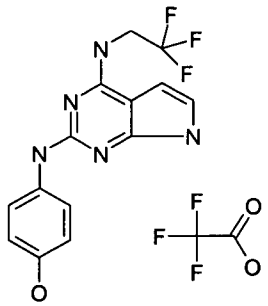
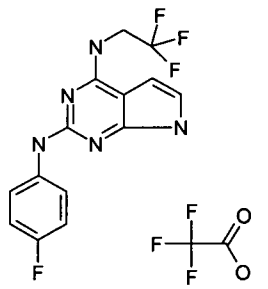
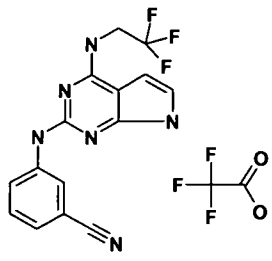
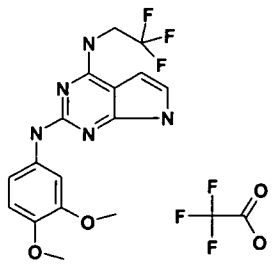
Cl

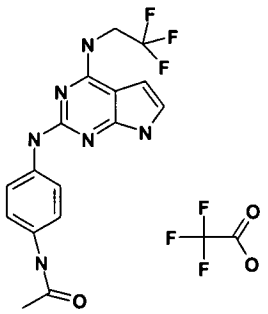
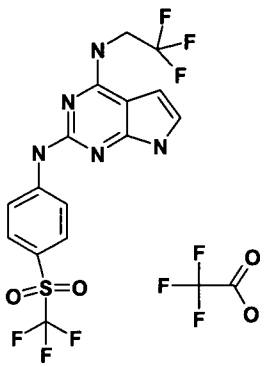
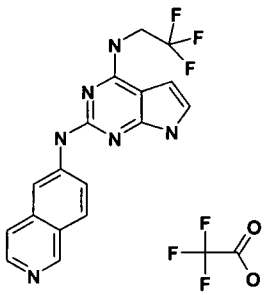
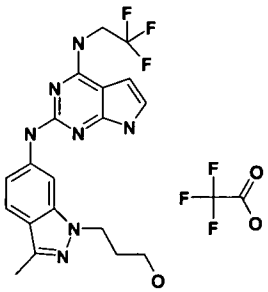
Methylamine was passed into a stirred solution of 2-phthalimidoethanesulfonyl chloride (20g, Alfa Aesar) in dioxane (200ml) for 10min at 45°C. With the continued passing of methylamine, the reaction mixture was heated to reflux for 4.5h and then allowed to cool. The flask was stoppered with a vent and left to stand for 22h. The white solid was filtered and the opaque filtrate concentrated *in vacuo*. Water (100ml) was added and the solution acidified to pH1 with hydrochloric acid (2N, 35ml). The mixture was concentrated *in vacuo* to give a white solid which was recrystallised from ethanol (720ml) to give the title compound as a white crystalline solid (7.8g). MS; MH^+ 139.

Method 27:

Potassium carbonate (700mg), tris(dibenzylideneacetone)dipalladium (0) (225mg) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (350mg) were stirred for ~1h to give a homogeneous solid. This solid (~44mg) was added to an aliquot (1ml) of a solution of 2-chloro-*N*-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (475mg) dissolved in t-butanol (19ml), followed by the amine (2eq). The mixture was heated under nitrogen, at 90°C overnight. The reaction was diluted with ethanol, filtered through a plug of Celite and the filtrate reduced to dryness under a stream of nitrogen. The residue was purified by MDAP, which after combination of appropriate fractions and evaporation of the solvents under a stream of nitrogen, gave the desired product.

The following compounds were prepared using Method 27:

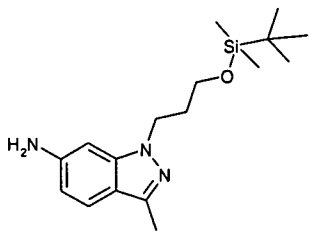
Example	Structure	Name	Amine/ Source	LC/MS Rt (min)	LC/MS MH^+
366		4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenol trifluoroacetate (salt)	4-aminophenol / Aldrich	2.43	324
367		N^2-(4-fluorophenyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	(4-fluorophenyl)amine / Avocado	3.08	326
368		3-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzonitrile trifluoroacetate	3-aminobenzonitrile / Avocado	3.20	333
369		N^2-[3,4-bis(methyloxy)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	[3,4-bis(methyloxy)phenyl]amine / Avocado	2.68	368

370		*N*-[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetamide trifluoroacetate	*N*-(4-aminophenyl)acetamide / Aldrich	2.49	365
371		*N*4-(2,2,2-trifluoroethyl)-*N*2-{4-[(trifluoromethyl)sulfonyl]phenyl}-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	{4-[(trifluoromethyl)sulfonyl]phenyl}amine / Apollo	3.59	440
372		N^2-6-isoquinolinyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	6-isoquinolinamine / Pharm Lab Product List	2.44	359
373		3-[3-methyl-6-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-1*H*-indazol-1-yl]-1-propanol trifluoroacetate (salt)	1-(3-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}propyl)-3-methyl-1*H*-indazol-6-amine (deprotected during purificatio	2.73	420

			n)		

Intermediate 128

1-(3-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}propyl)-3-methyl-1*H*-indazol-6-amine

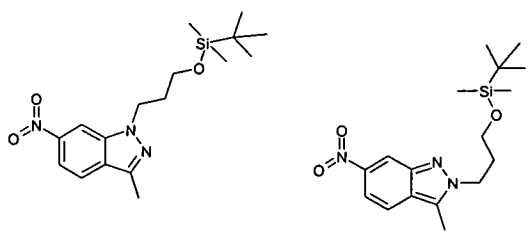


1-(3-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}propyl)-3-methyl-6-nitro-1*H*-indazole (6.4g) in dry ethanol (150ml) was added to palladium on carbon (10%, 650mg) and stirred under 1Atm. of hydrogen for 4h. The mixture was filtered through Celite and the filtrate evaporated to dryness. The residue was purified by chromatography on a silica cartridge (100g), eluting with an ethyl acetate / cyclohexane gradient (0 -100%) over 40min. to give, after evaporation of the solvents, the title compound (5.17g). LC/MS; MH^+ 320, Rt 3.53min.

Intermediates 129 and 130

2-(3-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}propyl)-3-methyl-6-nitro-2*H*-indazole and

1-(3-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}propyl)-3-methyl-6-nitro-1*H*-indazole



3-Methyl-6-nitro-1*H*-indazole (5g, WO 2002059110) in dry DMF (40ml) was cooled in an ice / water bath to ~5°C, stirring under nitrogen. Sodium hydride (60% in mineral oil 1.13g) was added portionwise. The reaction mixture was stirred for a further 30min. in the ice / water bath and

[(3-bromopropyl)oxy](1,1-dimethylethyl)dimethylsilane (6.72ml) in dry DMF (5ml) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 18h. The reaction mixture was quenched with water and extracted with ethyl acetate (x3). The organic phases were combined, dried (magnesium sulphate), and evaporated to dryness. The residue was purified by chromatography on a silica cartridge (100g), eluting with an ethyl acetate / cyclohexane gradient (0 - 50%) over 40min to give a mixture of the two products (9.07g).

The mixture was dissolved in cyclohexane and applied to a silica cartridge (100g), the cartridge was eluted with cyclohexane (200ml), 10% ethyl acetate / cyclohexane (200ml) and then 30% ethyl acetate / cyclohexane. Appropriate fractions were combined and reduced to dryness to give the two title compounds:-

The eluting product first, 1-(3-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}propyl)-3-methyl-6-nitro-1*H*-indazole (6.4g). NMR; [$CDCl_3$] δH 8.39,(1H, s), 7.98-7.96,(1H, d), 7.74-7.72,(1H, d), 4.52-4.51,(2H, t), 3.58-3.55,(2H, t), 2.62,(3H, s), 2.16-2.10,(2H, m), 0.92,(9H, s), 0.04,(6H, s). LC/MS; MH^+ 350, Rt 4.24min.

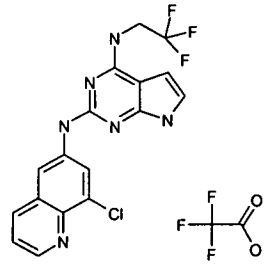
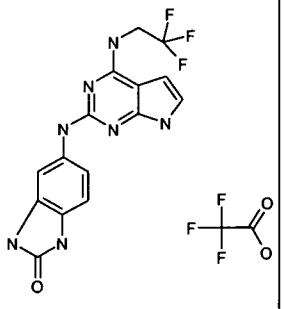
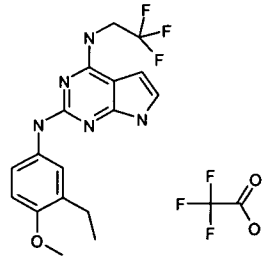
The eluting product second was purified further by trituation with cyclohexane and filtration to give 2-(3-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}propyl)-3-methyl-6-nitro-2*H*-indazole (2.08g). NMR; [$CDCl_3$] δH 8.63,(1H,,s), 7.85-7.83,(1H, d), 7.67-7.65,(1H, d), 4.55-4.52,(2H, t), 3.62-3.60,(2H, t), 2.69,(3H, s), 2.23-2.17,(2H, m), 0.91,(9H, s), 0.06,(6H, s). LC/MS; MH^+ 350, Rt 4.24min.

Method 28:

Potassium carbonate (700mg), tris(dibenzylideneacetone)dipalladium(0) (225mg) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (350mg) were stirred for ~1h to give a homogeneous solid. This solid (~44mg) was added to an aliquot (1ml) of a solution of 2-chloro-*N*-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (475mg) dissolved in t-butanol (19ml), followed by the amine (2eq). The mixture was heated under nitrogen, at 90°C overnight. Potassium carbonate (28mg), tris(dibenzylideneacetone)dipalladium (0) (9mg) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (7mg) were added to the reaction and heating repeated under nitrogen at 90°C overnight. The reaction was

diluted with ethanol, filtered through a plug of Celite and the filtrate reduced to dryness under nitrogen. The residue was purified by MDAP, which after combination of appropriate fractions and evaporation of the solvents under a stream of nitrogen, gave the desired product.

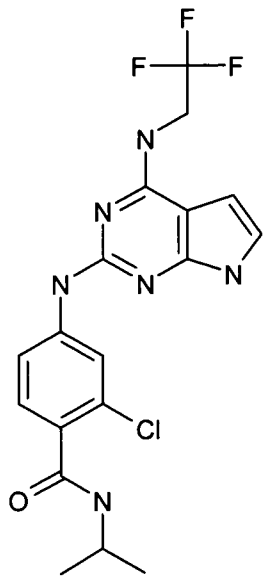
The following compounds were prepared using Method 28:

Example	Structure	Name	Amine / Source	LC/MS Rt (min)	LC/MS MH^+
374		N^2-(8-chloro-6-quinolinyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	8-chloro-6-quinolinamine / J Chem Soc 3543-8; 1953	3.24	393
375		5-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-1,3-dihydro-2*H*-benzimidazol-2-one trifluoroacetate	5-amino-1,3-dihydro-2*H*-benzimidazol-2-one / Matrix	2.31	364
376		N^2-[3-ethyl-4-(methyloxy)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	[3-ethyl-4-(methyloxy)phenyl]amine hydrochloride / WO2003035065	3.15	366

Example 377

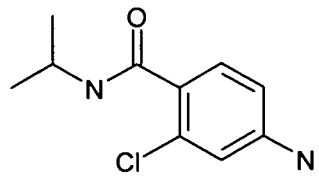
2-chloro-*N*-(1-methylethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]

pyrimidin-2-yl}amino)benzamide



A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-amino-2-chloro-*N*-(1-methylethyl)benzamide (106mg) and potassium carbonate (52mg) in t-butanol (4ml) under nitrogen, was treated with 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (17.9mg) and tris(dibenzylideneacetone)dipalladium (0) (22.9mg) and the stirred mixture was heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature and was partitioned between water (30ml) and ethyl acetate (30ml). The aqueous phase was further extracted with ethyl acetate (30ml) and the solvent was evaporated from the combined organics *in vacuo*. The residue was treated with a solution of sodium methoxide in methanol (0.5M, 5ml) and the mixture heated at 80°C under nitrogen for 1h. The methanol was evaporated *in vacuo* from the cooled reaction and the residue was purified by MDAP. The appropriate fractions were combined to give, after solvent evaporation *in vacuo*, partially purified material. This was further purified by MDAP on a Supelco ABZ +plus column (100 x 21.2mm, 5um). Gradient elution with ethyl 0.1% trifluoroacetic acid / acetonitrile in 0.2% trifluoroacetic acid / water (20- 99%) over 15min gave, after combination of the appropriate fractions and evaporation of the solvent *in vacuo*, the title compound. LC/MS; Rt 3.02min, MH^+ 427.

Intermediate 131

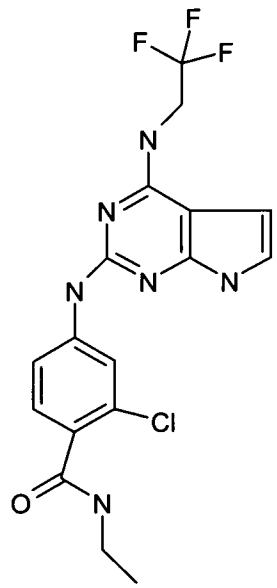


4-amino-2-chloro-*N*-(1-methylethyl)benzamide

4-Amino-2-chlorobenzoic acid (300mg, Aldrich) was added to a stirred solution of PyBOP (1.0g), isopropylamine (0.745ml) and DIPEA (2.26g) in DMF (15ml) at room temperature under nitrogen and the mixture was stirred overnight. The solvent was evaporated *in vacuo*, the residual gum was dissolved in the minimum amount of DCM and was absorbed onto an aminopropyl cartridge (50g) and the material was purified by chromatography, eluting with ethyl acetate / cyclohexane (0-100%) over 30min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound (339mg). LC/MS; Rt 2.13min, MH^+ 213.

Example 378

2-chloro-*N*-ethyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

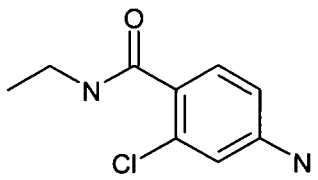


A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-amino-2-chloro-*N*-ethylbenzamide (99mg) and potassium carbonate (52mg) in t-butanol (4ml) under nitrogen, was treated with 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (17.9mg) and

tris(dibenzylideneacetone)dipalladium (0) (22.9mg) and the stirred mixture was heated in a sealed vial by microwave irradiation at 120°C for 1h. The mixture was cooled to room temperature and was partitioned between water (30ml) and ethyl acetate (30ml). The aqueous phase was further extracted with ethyl acetate (30ml) and the solvent was evaporated from the combined organics *in vacuo*. The residue was treated with a solution of sodium methoxide in methanol (0.5M, 5ml) and the mixture heated at 80°C under nitrogen for 1h. The methanol was evaporated *in vacuo* from the cooled reaction and the residue was purified by MDAP. The appropriate fractions were combined to give, after solvent evaporation *in vacuo*, partially purified material. The MDAP was repeated and the residue further purified by MDAP on a Supelco ABZ +plus column (100 x 21.2mm, 5um). Gradient elution with ethyl 0.1% trifluoroacetic acid / acetonitrile in 0.2% trifluoroacetic acid / water (20- 99%) over 15min gave, after combination of the appropriate fractions and evaporation of the solvent *in vacuo*, the title compound (2.7mg). LC/MS; Rt 2.93min, MH^+ 412.85.

Intermediate 132

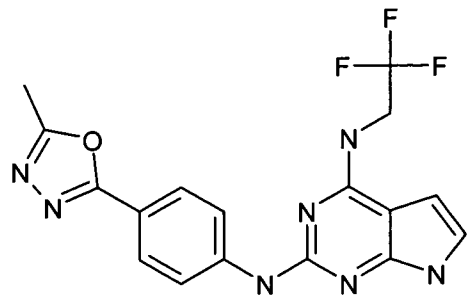
4-amino-2-chloro-*N*-ethylbenzamide



4-Amino-2-chlorobenzoic acid (300mg, Aldrich) was added to a stirred solution of PyBOP (1.0g), ethylamine hydrochloride (714mg) and DIPEA (3.39g) in DMF (15ml) at room temperature under nitrogen and the mixture was stirred overnight. The solvent was evaporated *in vacuo*, the residual gum was dissolved in the minimum amount of DCM and was absorbed onto an aminopropyl cartridge (50g) and the material was purified by chromatography, eluting with ethyl acetate / cyclohexane (0-100%) over 30min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound (293mg). LC/MS; Rt 1.83min, MH^+ 199.

Example 379

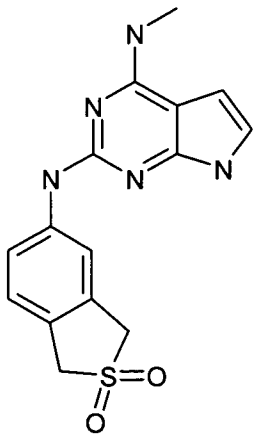
***N*^{2}-[4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-*N*^{4}-(2,2,2-trifluoroethyl)-1*H*-pyrrolo [2,3-*d*]pyrimidine-2,4-diamine**



4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid (100mg) was dissolved in DMF (0.5ml) and was treated with *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (119.2mg). The mixture was stirred under nitrogen for 10min. A solution of acetic hydrazide (31.7mg) in DMF (0.5ml) was added and the mixture was stirred under nitrogen overnight. The solvent was evaporated under vacuum and DCM (5ml) was added to the residue. The solvent was evaporated under vacuum, the residue was dissolved in methanol (5ml) and was filtered through an aminopropyl cartridge (5g, pre-conditioned with methanol). The cartridge was washed with methanol and the combined filtrate and washes reduced to dryness under vacuum. The residue was dissolved in methanol (5ml) and applied to a pre-conditioned SCX-2 cartridge (5g). The cartridge was washed with methanol and the product eluted with 2M ammonia in methanol. The basic fractions were combined and the solvent evaporated under vacuum. The residue was treated with THF (2.5ml) and (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt (60.8mg, Burgess reagent, Aldrich) was added. The mixture was heated at 70°C under nitrogen for 5h. The solvent was evaporated under vacuum and the residue purified by MDAP to give, after the appropriate fractions were combined and the solvent evaporated under vacuum, the title compound (2.7mg). LC/MS; Rt 2.78min, MH^+ 390.

Example 380

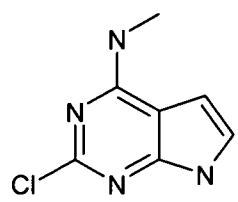
N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-N^4-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



2-Chloro-*N*-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (87mg), 1,3-dihydro-2-benzothiophen-5-amine-2,2-dioxide (104mg, Maybridge), tris(dibenzylideneacetone)dipalladium (0) (44.0mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (34.1mg), potassium carbonate (133mg) and t-butanol (10ml) were heated by microwave in a sealed vial at 140°C for 40min. The cooled reaction was diluted with ethanol, filtered through a plug of Celite and the filtrate reduced to dryness under a stream of nitrogen. The residue was dissolved in methanol / DCM and loaded on to a SCX-2 SPE cartridge (10g, pre-conditioned with methanol). The cartridge was eluted with methanol followed by a 2M solution of ammonia in methanol. The methanolic ammonia fraction was concentrated under a stream of nitrogen. The residue was purified by chromatography on a silica cartridge (20g), eluting with a methanol / DCM gradient (0-15%) + 1% triethylamine over 40min. Combination of the appropriate fractions and evaporation of the solvents gave the title compound (25mg). LC/MS; Rt 2.24min, MH^+ 329.94.

Intermediate 133

2-Chloro-*N*-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

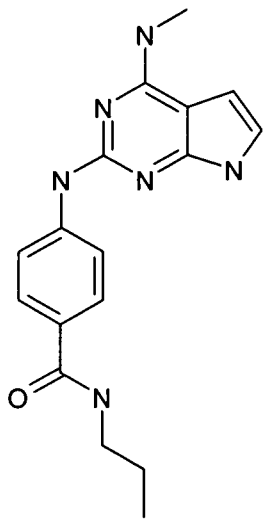


2,4-Dichloro-1*H*-pyrrolo[2,3-*d*]pyrimidine (400mg, Pharm Lab Product List) and a solution of methylamine in ethanol (33%, 10ml) were heated by microwave in a sealed vial at 80°C for 10min. The reaction was evaporated *in vacuo* and the

resultant solid was suspended in water and stirred for 5min. The solid was isolated by filtration and dried under vacuum at 40°C overnight to give the title compound (311mg). LC/MS; Rt 2.22min, MH^+ 183, 185.

Example 381

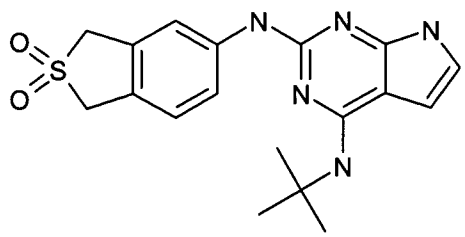
4-{[4-(Methylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-propylbenzamide



2-Chloro-*N*-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-amino-*N*-propylbenzamide (98mg), tris(dibenzylideneacetone)dipalladium (0) (50.4mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (39.1mg), potassium carbonate (152mg) and t-butanol (10ml) were combined and heated by microwave in a sealed vessel at 140°C for 40min. The reaction was diluted with ethanol, filtered through Celite and the filtrate reduced to dryness under a stream of nitrogen. The residue was dissolved in DCM / methanol and loaded on to an SCX-2 cartridge (10g, pre-conditioned with methanol). The cartridge was eluted with methanol and 2M ammonia in methanol. The solvent was evaporated from the methanolic ammonia fraction under a stream of nitrogen. The residue was purified by chromatography on a silica cartridge (20g), eluting with a gradient of methanol / DCM (0-15%) + 1% triethylamine over 30min to give the title compound (41mg). LC/MS; Rt 2.32min, MH^+ 325.

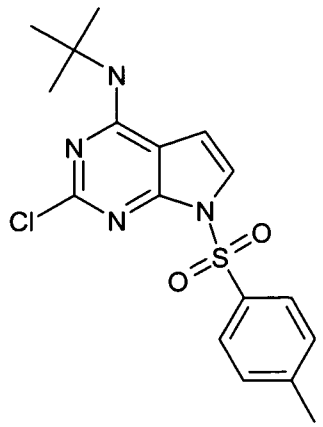
Example 382

N^4-(1,1-dimethylethyl)-N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine



To a stirred mixture of 2-chloro-*N*-(1,1-dimethylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (170mg), potassium carbonate (124.4mg) and 1,3-dihydro-2-benzothiophen-5-amine 2,2-dioxide (123.7mg, Maybridge) in t-butanol (12ml) at room temperature under nitrogen was added 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (32.2mg) and tris(dibenzylideneacetone)dipalladium (0) (41.2mg) and the stirred mixture was heated in a sealed vial by microwave irradiation at 120°C for 40min. The cooled mixture was partitioned between water (25ml) and ethyl acetate (25ml). The organic phase was concentrated *in vacuo* and the residue (300mg) was treated with a solution of sodium methoxide in methanol (0.5M, 5ml) and the mixture heated at 80°C under nitrogen for 40min. A further portion of sodium methoxide in methanol (0.5M, 5ml) was added and the mixture heated at 80°C under nitrogen for 1h. The methanol was evaporated from the cooled reaction, water (30ml) was added and the mixture was extracted with ethyl acetate (2x 25ml). The solvent from the combined organic phases was evaporated *in vacuo* and the residue was purified by chromatography on a silica cartridge (50g), eluting with an ethyl acetate / cyclohexane gradient (0-100%) over 60min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound (48mg). LC/MS; Rt 2.56min, MH^+ 372.

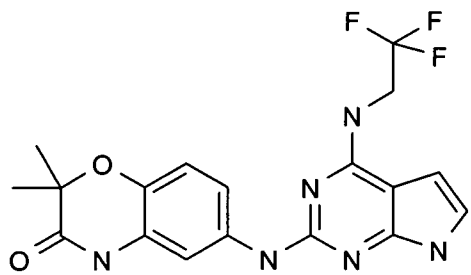
Intermediate 134
2-chloro-*N*-(1,1-dimethylethyl)-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



A mixture of 2,4-dichloro-7-[(4-methylphenyl)sulfonyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (300mg), DIPEA (0.92ml) and t-butylamine (0.56ml) in ethanol (15ml) was heated at 80°C for 24h. The mixture was treated with water (25ml) and extracted with ethyl acetate (2x 25ml). The solvent from the combined organic portions was evaporated *in vacuo* to give a residue which was purified by chromatography on a silica cartridge (50g), eluting with an ethyl acetate / cyclohexane gradient (0-100%) over 60min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound (170mg). LC/MS; Rt 3.85min, MH^+ 379, 381.

Example 383

2,2-dimethyl-6-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl} amino)-2*H*-1,4-benzoxazin-3(4*H*)-one

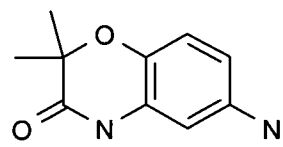


2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (50mg), 6-amino-2,2-dimethyl-2*H*-1,4-benzoxazin-3(4*H*)-one (28.4mg), potassium carbonate (23.9mg), tris(dibenzylideneacetone)dipalladium (0) (6.8mg) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (2.9mg) in t-butanol (1.5ml) were combined in a sealed vial and heated at 120°C for 45min by microwave

irradiation. The reaction was heated at 120°C for a further 45min with added 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (~2mg), 6-amino-2,2-dimethyl-2*H*-1,4-benzoxazin-3(4*H*)-one (~5mg) and tris(dibenzylideneacetone)dipalladium (0) (~2mg). The mixture was diluted with ethyl acetate and filtered through Celite. The filtrate was evaporated and was purified on MDAP. The appropriate fractions were combined and evaporated and then dissolved in sodium methoxide in methanol solution (0.5N, 2ml) and stirred at 80°C for 1.5h. The solvent was evaporated and the residue partitioned between chloroform (2ml) and water (2ml). The organic phase was reduced to dryness and the residue purified by MDAP. Evaporation of the appropriate fraction gave the title compound (2.1mg). LC/MS; MH^+ 407, Rt 3.07min.

Intermediate 135

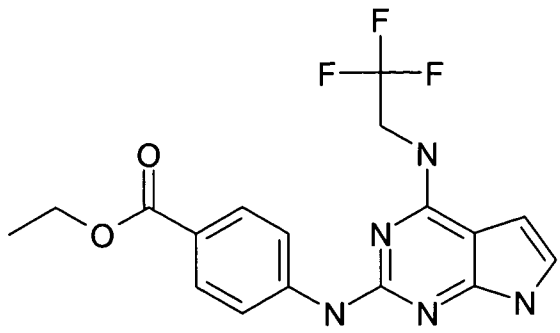
6-amino-2,2-dimethyl-2*H*-1,4-benzoxazin-3(4*H*)-one



2,2-Dimethyl-6-nitro-4H-benzo[1,4]oxazin-3-one (1.5g, ChemOvation Ltd.) was partially dissolved in ethyl acetate (30ml) and stirred with palladium on carbon (10%, 350mg) under 1 Atm. pressure of hydrogen for 5h. The reaction mixture was filtered through Celite and the filtrate evaporated to give a pale brown solid. The crude material was applied to a SCX-2 cartridge (50g) and the cartridge eluted with methanol and 8% ammonia in methanol solution. The methanolic ammonia fraction was evaporated to give the title compound as a salmon pink powder (1.17g). LC/MS; MH^+ 193, Rt 1.75min.

Example 384

Ethyl 4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoate



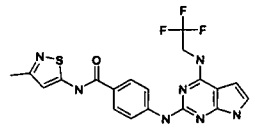
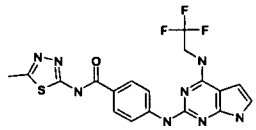
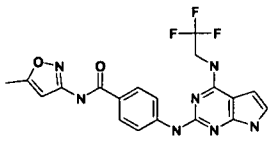
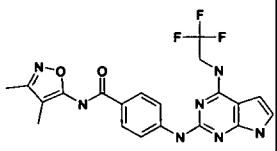
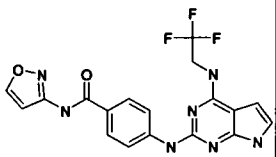
Ethyl 4-({7-[(4-methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoate (38.0mg) in a solution of tetrabutylammonium fluoride in THF (1N, 0.427ml) was stirred at room temperature. Further tetrabutylammonium fluoride in THF solution (1N, 0.4ml) was added and the reaction left to stir overnight. The reaction mixture was then heated to 50°C for 21h and then cooled to room temperature. The mixture was diluted with ethyl acetate and the solvents evaporated. The residue was adsorbed onto Florisil from ethyl acetate and purified by chromatography on a silica cartridge (20g), eluting with an ethyl acetate / cyclohexane gradient (5-70%). The appropriate fraction was evaporated to give the title compound as an off-white solid (10.9mg). LC/MS; MH^+ 380, Rt 3.35min.

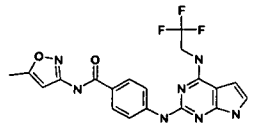
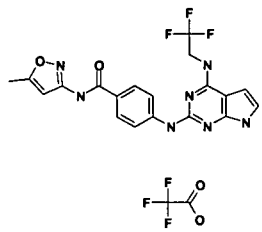
Method 29:

The 4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoyl chloride (55.5mg) was added to each amine and the mixture suspended in acetone (1ml). The reaction was treated with pyridine (23.7mg), stoppered and stirred at room temperature for 2.5 days. The solvent was evaporated under a stream of nitrogen and the residue purified by MDAP. The appropriate fractions were combined and the solvents evaporated. The residue was dissolved in methanol, the solution loaded onto an aminopropyl cartridge (0.5g, methanol pre-conditioned) and the cartridge eluted with methanol (3ml). The solvent was evaporated (vacuum centrifuge) to leave the title compound.

The following compounds were all prepared using Method 29:

Example	Structure	Name	Amine	LCMS MH^+	LCMS Rt (min)

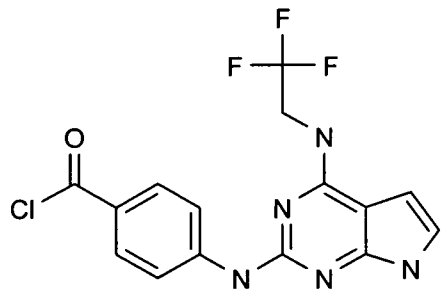
385		N-(3-methyl-5-isothiazolyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	5-Amino-3-methylisothiazole hydrochloride / Aldrich	448	3.20
386		N-(5-methyl-1,3,4-thiadiazol-2-yl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	2-Amino-5-methyl-1,3,4-thiadiazole / Acros	449	3.00
387		N-(5-methyl-3-isoxazolyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	3-Amino-5-methylisoxadiaole / Aldrich	432	3.08
388		N-(3,4-dimethyl-5-isoxazolyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	5-Amino-3,4-dimethylisoxadiazole / Alfa	446	3.03
389		N-3-isoxazolyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	3-Aminoisoxazole / Aldrich	418	2.99

390		N-(5-methyl-3-isoxazolyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide	3-Amino-5-methylisoxazole / Aldrich	431.88	3.07
391*		N-(5-methyl-3-isoxazolyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide trifluoroacetate	3-Amino-5-methylisoxazole / Aldrich	432.16	3.08

* Example originates from precipitate on top of NH2 cartridge.

Intermediate 136

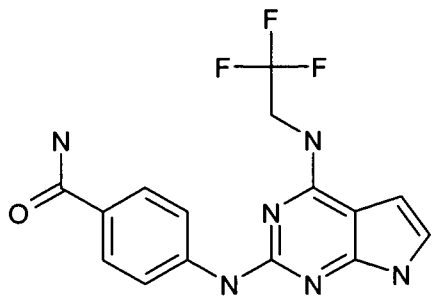
4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoyl chloride



The 4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid (1.2g) was suspended in anhydrous toluene (20ml) and treated with thionyl chloride (20ml). The reaction mixture was stirred at room temperature under nitrogen overnight. The volatiles were evaporated *in vacuo* and the residue azeotroped with anhydrous toluene to give the title compound as a light brown solid (1.15g). NMR; [D_6-DMSO] δH 11.99,(1H, bs), 10.42,(1H, bs), 9.15,(1H, bs), 7.90,(2H, d), 7.82,(2H, d), 7.04,(1H, s), 6.73,(1H, s), 4.47,(2H, m).

Example 392

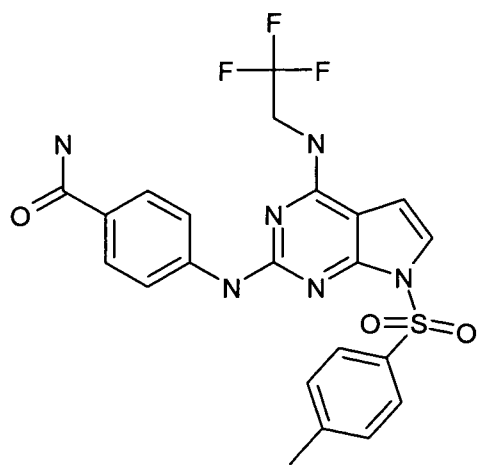
4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide



4-({7-[(4-Methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide (229mg) was dissolved in sodium methoxide in methanol (0.5M, 3ml) and the solution heated at 80°C under nitrogen for ~1h and then left overnight at room temperature. The reaction was diluted with water (~5ml) and the precipitate isolated by filtration. The solid was washed with water, sucked dry on the sinter and further dried at 45°C under vacuum to give the desired product as a cream solid (133mg). LC/MS; MH^+ 350.93, Rt 2.51min.

Intermediate 137

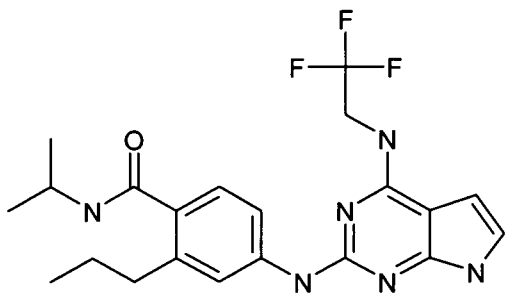
4-({7-[(4-Methylphenyl)sulfonyl]-4-[(2,2,2-trifluoroethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide



2-Chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (200mg), 4-aminobenzamide (81mg), tris(dibenzylideneacetone)dipalladium (0) (12mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (6mg) and potassium carbonate (100mg) were mixed in t-butanol (7.5ml), the mixture degassed and heated at 85°C under nitrogen for ~20h. Tris(dibenzylideneacetone)dipalladium (0) (12mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (6mg) were added to the reaction and heating continued for 3h at 85°C and then at 95°C for ~20h. The cooled reaction was diluted with ethyl acetate, adsorbed onto silica and applied to a silica cartridge (20g). The cartridge was eluted with an ethyl acetate / cyclohexane gradient (0-100%), the appropriate fractions combined and the solvents evaporated *in vacuo* to give the desired product as a pale yellow solid (230mg). NMR; [D_6-DMSO] δH 9.51,(1H, s), 8.32,(1H, t), 7.98-7.93,(4H, m), 7.86-7.84,(3H, m), 7.40-7.37,(3H, m), 7.15,(1H, bs), 6.85,(1H, d), 4.35,(2H, m), 2.32,(3H, s).

Example 393

***N*-(1-methylethyl)-2-propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide**

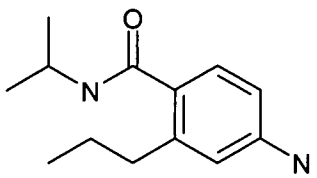


A stirred mixture of 2-chloro-7-[(4-methylphenyl)sulfonyl]-*N*-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100mg), 4-amino-*N*-(1-methylethyl)-2-propylbenzamide (65mg) and potassium carbonate (48mg) in t-butanol (5ml) under nitrogen was treated with 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (18mg) and tris(dibenzylideneacetone)dipalladium (0) (23mg) and the stirred mixture was heated in a sealed vial by microwave irradiation at 120°C for 1h. The cooled mixture was partitioned between water (25ml) and ethyl acetate (25ml). The aqueous phase further extracted with ethyl acetate (25ml). The solvent was evaporated from the

combined organic phases *in vacuo*. The residue was treated with sodium methoxide solution in methanol (0.5M) and heated at 80°C for 2h. The mixture was cooled to room temperature and the solvent was evaporated *in vacuo*. The residue was purified by MDAP. The appropriate fractions were combined and the solvent evaporated *in vacuo* to leave the title compound (27mg). LC/MS; Rt 3.05min, MH^+ 435.

Intermediate 138

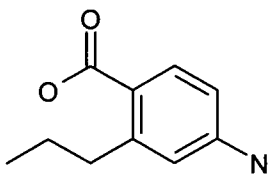
4-amino-*N*-(1-methylethyl)-2-propylbenzamide



A mixture of PyBOP (958mg), DIPEA (2.92ml), isopropylamine (0.71ml) and 4-amino-2-propylbenzoic acid (300mg) in DMF (10ml) at room temperature under nitrogen was stirred for 10h. The solvent was evaporated *in vacuo* and the residue was dissolved in the minimum amount of DCM and absorbed onto an aminopropyl cartridge (50g). The cartridge was eluted with an ethyl acetate / cyclohexane gradient (0-100%) over 30min. Combination of the appropriate fractions and evaporation of the solvent *in vacuo*, gave the title compound (183mg). LC/MS; Rt 2.24min, MH^+ 221.

Intermediate 139

4-Amino-2-propylbenzoic acid

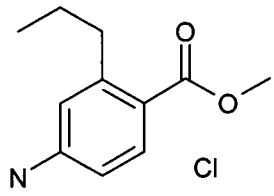


Methyl 4-amino-2-propylbenzoate hydrochloride (1.0g) was dissolved in methanol (20ml) and sodium hydroxide solution (2M, 10ml) added. The solution was stirred at room temperature for 3h and then heated at 80°C for 5h. The cooled solution was neutralised with hydrochloric acid (2M), the methanol evaporated *in vacuo* and the residue treated with water (40ml). The mixture was extracted with ethyl acetate (2x

40ml) and the solvent from the combined organic portions was evaporated *in vacuo* to leave the title compound (800mg). LC/MS; Rt 2.41min, MH^+ 180.

Intermediate 140

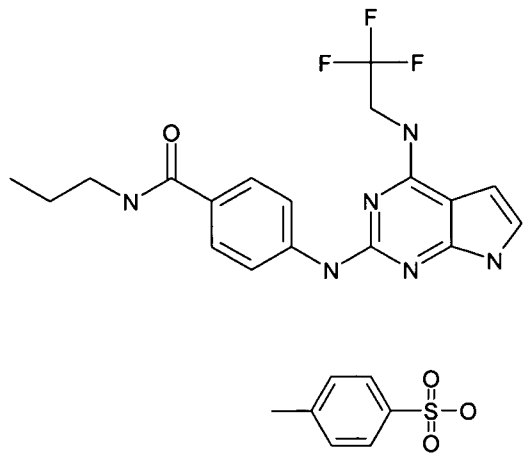
Methyl 4-amino-2-propylbenzoate hydrochloride



A solution of methyl 2-bromo-4-nitrobenzoate (5.00g, Bioorg. and Med. Chem. 2004, 12(24), 6517-6526) in dry toluene (25ml) was treated with allyltributyltin (7.40ml). Tetrakis(triphenylphosphine)palladium (0) (665mg) was added and the mixture under nitrogen was heated at ~100°C for 4h. The mixture was applied to a silica column (160g). Elution with hexane / ethyl acetate (4:1) gave, after combination the appropriate fractions and evaporation of the solvent *in vacuo*, an oil (4.1g). The oil (3.1g) was dissolved in ethyl acetate (60ml) and hydrogenated over platinum on carbon overnight (5%, 1.5g). The mixture was filtered through Celite and the filtrate was treated with ethereal hydrogen chloride (1M, 25ml). Solvent evaporation *in vacuo* gave the title compound (2.23g). NMR; [D_6-DMSO] δH 7.77,(1H, d), 6.91,(2H, m), 3.77,(3H, t), 2.82,(2H, t), 1.51,(2H, m), 0.90,(3H, t).

Example 394

***N*-propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide 4-methylbenzenesulfonate**



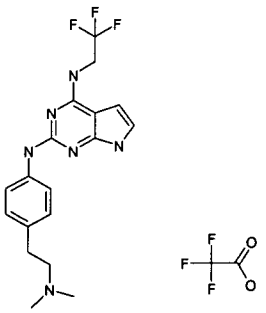
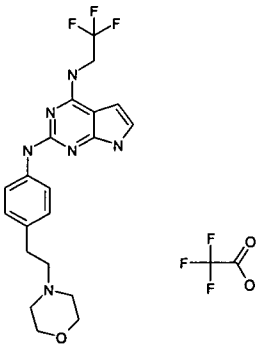
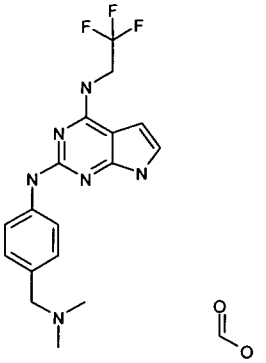
N-Propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide (350mg) was dissolved with heating and sonication in THF (7ml). p-Toluenesulphonic acid hydrate (162mg) was dissolved with heating in THF (1ml) and the resulting solution added to the *N*-propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide. The mixture was warmed gently to give a solution and then allowed to cool to room temperature. The mixture was rewarmed to 40°C, allowed to cool and the heating cooling cycle repeated (x2). The mixture was left at room temperature over the weekend, the white solid isolated by filtration, washed with THF (1ml) and sucked dry on the sinter. Solid further dried under vacuum at ~40°C for 2h to give the title compound as a white solid (425mg). NMR; [D_6-DMSO] δH 11.46,(1H, b), 9.44,(1H, b), 8.47,(1H, b), 8.28,(1H, t), 7.79,(4H, s), 7.48,(2H, d), 7.11,(2H, d), 6.96,(1H, m), 6.60,(1H, m), 4.40,(2H, m), 3.21,(2H, q), 2.29,(3H, s), 1.53,(2H, m), 0.89,(3H, t).

Method 30:

Potassium carbonate (420mg), tris(dibenzylideneacetone)dipalladium (0) (135mg) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (105mg) were mixed and stirred for 2h. To an aliquot of this mixture (~44mg), was added 2-chloro-*N*-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (25mg) dissolved in methanol, and the aniline (0.2mmol). The methanol was evaporated under a stream of nitrogen, t-butanol added and the mixture heated at 90°C overnight. The reaction was diluted with ethanol, filtered through Celite, the Celite washed with ethanol and the combined filtrate and washingsreduced to dryness under a stream of nitrogen. The residue was dissolved in DMSO / methanol (1:1,

1ml) and purified by MDAP. MP-carbonate resin was added to the eluted fractions and the fractions allowed to stand at room temperature overnight. Appropriate fractions were combined and reduced to dryness *in vacuo* to give the desired compound.

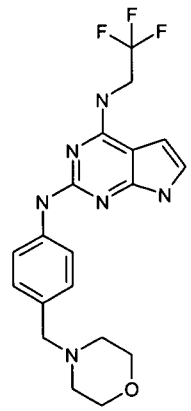
The following examples were prepared using Method 30.

Example	Structure	Name	Aniline	LCMS MH^+	LCMS Rt (min)
395		N^2-{4-[2-(dimethylamino)ethyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	[2-(4-aminophenyl)ethyl]dimethylamine / PharmLab Product List	379	2.13
396		N^2-{4-[2-(4-morpholinyl)ethyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	{4-[2-(4-morpholinyl)ethyl]phenyl}amine / PharmLab Product List	421	2.15
397		formic acid - N^2-{4-[(dimethylamino)methyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine	[(4-aminophenyl)methyl]dimethylamine / PharmLab Product List	365	2.45

Example 398

formic acid -

N^2-[4-(4-morpholinylmethyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]p

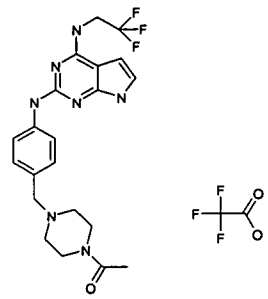
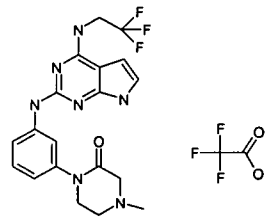
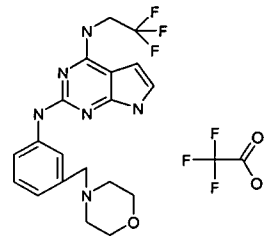
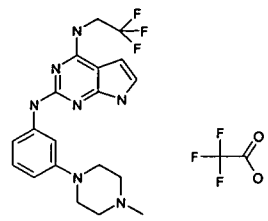


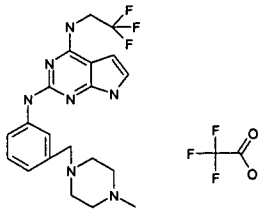
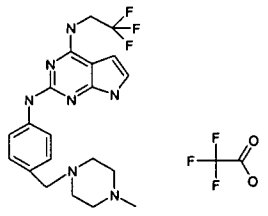
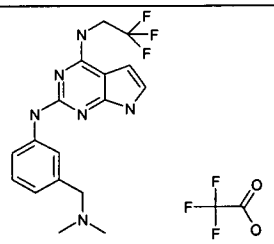
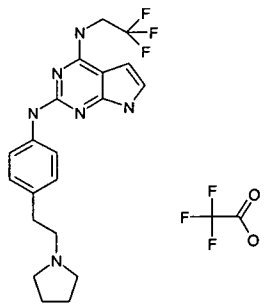
yrimidine-2,4-diamine Potassium carbonate (420mg), tris(dibenzylideneacetone)dipalladium (0) (135mg) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (105mg) were mixed and stirred for 2h. To an aliquot of this mixture (~44mg), was added 2-chloro-*N*-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (25mg) dissolved in methanol, and [4-(4-morpholinylmethyl)phenyl]amine (38mg, PharmLab Product List). The methanol was evaporated under a stream of nitrogen, t-butanol added and the mixture heated at 90°C overnight. A further aliquot (~44mg) of the catalyst mixture was added to the reaction and heating continued for 24h. The reaction was diluted with ethanol, filtered through Celite, the Celite washed with ethanol and the combined filtrate and washingsreduced to dryness under a stream of nitrogen. The residue was dissolved in DMSO / methanol (1:1, 1ml) and purified by MDAP. MP-carbonate resin was added to the eluted fractions and the fractions allowed to stand at room temperature overnight. Appropriate fractions were combined and reduced to dryness *in vacuo* to give the title compound.

Method 31:

Potassium carbonate (420mg), tris(dibenzylideneacetone)dipalladium (0) (135mg) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (105mg) were mixed and stirred for 2h. To an aliquot of this mixture (~44mg), was added 2-chloro-*N*-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (25mg) dissolved in t-butanol (1ml), and the aniline (0.2mmol). The mixture was heated at 90°C overnight. The reaction was diluted with ethanol, filtered through Celite, the Celite washed with ethanol and the combined filtrate and washings reduced to dryness under a stream of nitrogen. The residue was dissolved in DMSO / methanol (1:1, 1ml) and purified by MDAP. Appropriate fractions were combined and reduced to dryness *in vacuo* to give the desired compound.

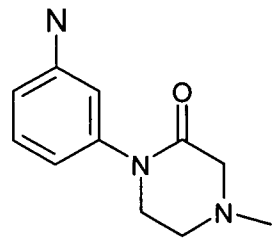
The following examples were prepared using Method 31.

Example	Structure	Name	Aniline	LCMS MH^+	LCMS Rt (min)
399		N^2-{4-[(4-acetyl-1-piperazinyl)methyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	{4-[(4-acetyl-1-piperazinyl)methyl]phenyl}amine	448	2.42
400		4-methyl-1-[3-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]-2-piperazinone trifluoroacetate	1-(3-aminophenyl)-4-methyl-2-piperazinone	420	2.35
401		N^2-[3-(4-morpholinylmethyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	[3-(4-morpholinylmethyl)phenyl]amine / PharmLab Product List	407	2.50
402		N^2-[3-(4-methyl-1-piperazinyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	[3-(4-methyl-1-piperazinyl)phenyl]amine / Maybridge	406	2.52

403		N^2-{3-[(4-methyl-1-piperazinyl)methyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	{3-[(4-methyl-1-piperazinyl)methyl]phenyl}amine / PharmLab Product List	420	2.49
404		N^2-{4-[(4-methyl-1-piperazinyl)methyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	{4-[(4-methyl-1-piperazinyl)methyl]phenyl}amine / PharmLab Product List	420	2.44
405		N^2-{3-[(dimethylamino)methyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	[(3-aminophenyl)methyl]dimethylamine / PharmLab Product List	365	2.50
406		N^2-{4-[2-(1-pyrrolidinyl)ethyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	{4-[2-(1-pyrrolidinyl)ethyl]phenyl}amine / PharmLab Product List	405	2.51

Intermediate 141

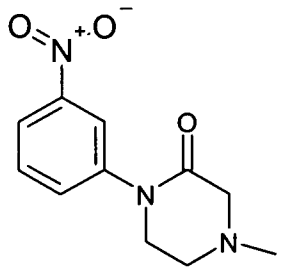
1-(3-aminophenyl)-4-methyl-2-piperazinone



To a solution of 4-methyl-1-(3-nitrophenyl)-2-piperazinone (37.38g) dissolved in warm methanol (500ml) was added a paste of palladium on carbon (5%, 3g) in toluene. The autoclave was charged with hydrogen (40Atm). After 10min the catalyst was filtered off and the filtrate concentrated to a solid. The solid was dissolved in DCM, dried (magnesium sulphate) and concentrated until almost solid. The oil was treated with hexane and the resulting solid isolated by filtration and dried to give the title compound (29.24g).

Intermediate 142

4-methyl-1-(3-nitrophenyl)-2-piperazinone



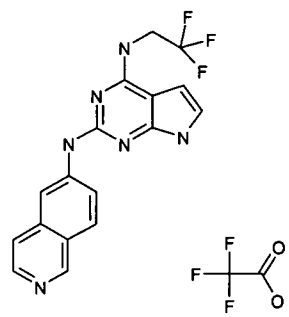
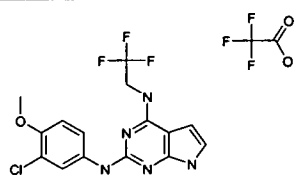
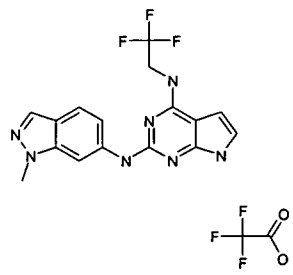
1-(3-Nitrophenyl)-2-piperazinone (32g, Tet. Lett. 1998 39(41) 7459-62) was dissolved in DCM (450ml). To the solution was added aqueous formaldehyde (37%, 12.16g) and then sodium triacetoxyborohydride (118.7g) portionwise. The reaction was stirred overnight, quenched by addition of sodium hydroxide solution and saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate (500ml) and the extract dried and reduced to dryness. The residue was triturated with ethyl acetate / hexane and the resulting solid isolate by filtration to give the title compound (26.65g).

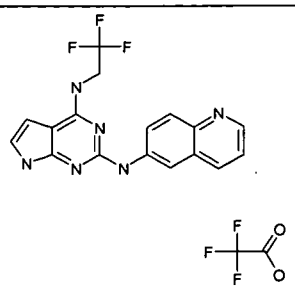
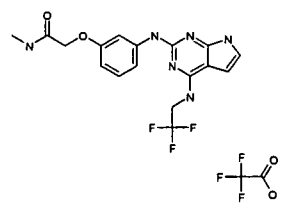
Method 32:

Potassium carbonate (1.38g), tris(dibenzylideneacetone)dipalladium (0) (450mg) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (350mg) were mixed and stirred for 2h. To an aliquot of this mixture (~87mg), was added

2-chloro-*N*-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (50mg), t-butanol (2ml), and the aniline (0.2mmol). The mixture was heated at 90°C overnight. The reaction was diluted with ethanol, filtered through Celite, the Celite washed with ethanol and the combined filtrate and washings reduced to dryness under a stream of nitrogen. The residue was dissolved in DMSO / methanol (1:1, 2ml) and purified by MDAP. Appropriate fractions were combined and reduced to dryness *in vacuo* to give the desired compound.

The following examples were prepared using Method 32.

Example	Structure	Name	Aniline	LCMS MH^+	LCMS Rt (min)
407		N^2-6-isoquinolinyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	6-isoquinolinamine / Pharm Lab Product List	359	2.59
408		N^2-[3-chloro-4-(methyloxy)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	[3-chloro-4-(methyloxy)phenyl]amine / Aldrich	372	3.26
409		N^2-(1-methyl-1*H*-indazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	1-methyl-1*H*-indazol-6-amine / Pharm Lab Product List	362	2.96

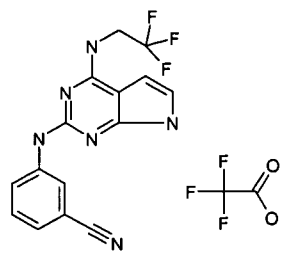
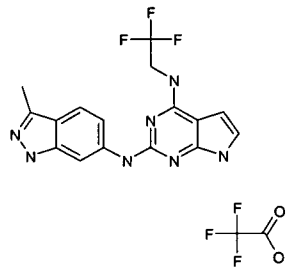
410		N^2-6-quinolinyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	6-quinolinamine / Aldrich	359	2.72
411		*N*-methyl-2-{[3-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]oxy}acetamide trifluoroacetate	2-[(3-aminophenyl)oxy]-*N*-methylacetamide	395	2.74

Method 33:

Potassium carbonate (1.38g), tris(dibenzylideneacetone)dipalladium (0) (450mg) and 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (350mg) were mixed and stirred for 2h. To an aliquot of this mixture (~87mg), was added 2-chloro-*N*-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (50mg), t-butanol (2ml), and the aniline (0.2mmol). The mixture was heated at 90°C overnight, a further aliquot of the catalyst mixture (~87mg) added and heating continued for 24h. The reaction was diluted with ethanol, filtered through Celite, the Celite washed with ethanol and the combined filtrate and washings reduced to dryness under a stream of nitrogen. The residue was dissolved in DMSO / methanol (1:1, 2ml) and purified by MDAP. Appropriate fractions were combined and reduced to dryness *in vacuo* to give the desired compound.

The following examples were prepared using Method 33.

Example	Structure	Name	Aniline	LCMS MH^+	LCMS Rt (min)

412		3-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzonitrile trifluoroacetate	3-aminobenzonitrile / Avocado	333	3.20
413		N^2-(3-methyl-1*H*-indazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine trifluoroacetate	3-methyl-1*H*-indazol-6-amine	362	2.89

Biological test methods

Compounds of the invention may be tested for *in vitro* activity in accordance with the following assays:

1. Enzyme Assay - Time-resolved fluorescence resonance energy transfer kinase assay

Recombinant human Syk was expressed as a His-tagged protein*. The activity of Syk was assessed using a time-resolved fluorescence resonance energy transfer (TR-FRET) assay.

Version A - 3µl of substrate reagent containing biotinylated peptide, Biotin-AAAEEIYGEI (0.5µM final), ATP (30µM final) and $MgCl_2$ (10mM final) in HEPES pH 7.4, (40mM final), were added to wells containing 0.2µl of various concentrations of compound or DMSO vehicle (3.3% final) in Greiner low volume 384 well black plate. The reaction was initiated by the addition of 3µl of Syk (20nM final) in HEPES pH 7.4 (40mM final). The reaction was incubated for 40min at room temperature, then terminated by the addition of 3µl of read reagent containing 60 mM EDTA, 150mM NaCl, 50nM Streptavidin APC (Prozyme, San Leandro,

California, USA), 0.5nM antiphosphotyrosine antibody labelled with W-1024 europium chelate (Wallac OY, Turku, Finland) in 40mM HEPES pH 7.4, 0.03% BSA. The reaction was further incubated for 60min at room temperature. The degree of phosphorylation of Biotin-AAAEEIYGEI was measured using a BMG Rubystar plate reader (BMG LabTechnologies Ltd, Aylesbury, UK) as a ratio of specific 665 nm energy transfer signal to reference europium 620 nm signal.

Version B - Syk was pre-activated at room temperature for 30 mins in the presence of 16.6mM $MgCl_2$, 8.3mM ATP and then diluted to 4nM in 40mM Hepes pH 7.4, 0.01% BSA. 3µl of substrate reagent containing biotinylated peptide, Biotin-AAAEEIYGEI (0.5µM final), ATP (30µM final) and $MgCl_2$ (10mM final) in 40mM HEPES pH 7.4, 0.01% BSA, were added to wells containing 0.1µl of various concentrations of compound or DMSO vehicle (1.7% final) in Greiner low volume 384 well black plate. The reaction was initiated by the addition of 3µl of diluted Syk (2nM final). The reaction was incubated for 60min at room temperature, then terminated by the addition of 3µl of read reagent containing 60 mM EDTA, 150mM NaCl, 50nM Streptavidin APC (Prozyme, San Leandro, California, USA), 0.5nM antiphosphotyrosine antibody labelled with W-1024 europium chelate (Wallac OY, Turku, Finland) in 40mM HEPES pH 7.4, 0.03% BSA. The reaction was further incubated for 45min at room temperature. The degree of phosphorylation of Biotin-AAAEEIYGEI was measured using a BMG Rubystar plate reader (BMG LabTechnologies Ltd, Aylesbury, UK) as a ratio of specific 665 nm energy transfer signal to reference europium 620 nm signal.

Compounds according to the present invention were assayed in this, or a similar Time-resolved fluorescence resonance energy transfer kinase assay, and gave IC_{50} values less than 10µM.

<u>* Preparation of Recombinant Human Full Length Spleen Tyrosine Kinase (Syk)</u>

Full length human Syk was expressed with a 6His tag on the N-terminal using the baculovirus system (Invitrogen, Paisley, Scotland). The cells were disrupted by dounce homogenisation, the debris removed by centrifugation and the lysate contacted with NiNTA Superflow (Qiagen, Crawley, UK). The NiNTA was packed into a column and eluted using 10 column volumes each of buffer (20mM Tris pH8.0,

300mM NaCl, 10mM βMcEtOH, 10% glycerol), buffer + 1M NaCl, buffer + 20mM Imidazole and buffer + 300mM imidazole. The 300mM Imidazole fractions were pooled buffer exchanged using G25M (Amersham Biosciences, Buckinghamshire, UK) into 20mM MES pH 6.0, 20mM NaCl, 10mM βMcEtOH,10% glycerol. The buffer exchanged 6His-Syk was loaded onto a Source15S column (Amersham Biosciences, Buckinghamshire, UK) and the column eluted using a NaCl gradient 0-500mM over 50 column volumes. The 6His-Syk containing fractions were pooled and concentrated by ultra-filtration. The identity of 6His-Syk was confirmed by peptide mass finger printing and intact LC-MS.

2. Whole Cell Assay - cFms assay

Principle of the assay

Cells of the mouse fibroblast cell line NIH-3T3 are stably transfected with a cFms-SYK chimera. Addition of the ligand (MCSF) produces dimerisation of the chimera resulting in autophosphorylation of the SYK kinase domain. Following cell lysis phosphorylated SYK is detected by ELISA.

Stimulation of cFms-SYK cells with MCSF Version A

Cells are plated at a density of $1x10^5$/well in a volume of 200µl growth medium (DMEM containing 10% heat inactivated foetal calf serum, 1% L-glutamine, 400µg/ml geneticin and 400µg/ml zeocin) in 96 well Collagen 1 coated tissue culture plates. Following incubation at 37°C, 10% CO_2, for 20h, the cell supernatant is removed and replaced with 200µl DMEM containing 1% penicillin/streptomycin (serum free DMEM). The cells are incubated for one hour under the conditions described above. The medium is removed, 50µl appropriately diluted compound solution added and the plate incubated for a further hour. Cells are stimulated with 25µl MCSF (0.66µg/ml final) for 20min at 37°C. After removal of the supernatant, the cells are washed with cold PBS and lysed with 100µl lysis buffer for 4h at 4°C.

Stimulation of cFms-SYK cells with MCSF Version B

Cells are plated at a density of 1x105/well in a volume of 200µl growth medium (DMEM containing 10% heat inactivated foetal calf serum, 1% L-glutamine, 400µg/ml geneticin and 400µg/ml zeocin) in 96 well Collagen 1 coated tissue culture plates. Following incubation at 37°C, 10% CO2, for 20h the cell supernatant is

removed and 50µl appropriately diluted compound solution added and the plate incubated for an hour. Cells are stimulated with 25µl MCSF (0.66µg/ml final) for 20min at 37°C. After removal of the supernatant, the cells are washed with cold PBS and lysed with 100µl lysis buffer for 4h at 4°C.

cFms ELISA

85µl cell lysate is transferred to a 96 well ELISA plate coated with goat anti human M-CSF R capture antibody and incubated for 16 hours at 4°C. The plate is washed and a biotinylated anti-phosphotyrosine detection antibody added (100µl/well) for 2h at room temperature. This is removed and replaced with 100µl Streptavidin-HRP for 30min. Captured phosphorylated SYK is visualised using 100µl TMB substrate. The reaction is terminated with 50µl 1M sulphuric acid and the absorbance measured at 450nm.

Compound Preparation

Compound is prepared as a 10mM stock in DMSO and a dilution series prepared in DMSO using 9 successive 5-fold dilutions. This dilution series is diluted a further 1:333 with serum free DMEM to give the concentration range to be tested of $1x10^{-5}$ to $1.54x10^{-11}$M. Compound dilutions are prepared using the Biomek 2000 or Biomek Nx automated robotic pipetting systems.

3. B Cell Proliferation Assay

Background

The population of B cells observed in this assay are the naïve mature IgM/IgD expressing population. These form at least 70% of the purified B cell population (the rest being isotype switched memory B cells) and are the only cells that proliferate as the cells are stimulated with anti-IgM.

Anti-IgM drives signalling through the B cell receptor which is Syk dependant. Proliferation is a functional measure of B cell signalling that can be measured by observing the incorporation of tritiated methyl thymidine into the cells.

Protocol

Purified human tonsillar B cells are resuspended in Buckleys* medium at a

concentration of 1.25 x 10^6 ml.

160µl of cells re-suspended in Buckley's medium is added to the compound and control wells of a 96 well plate. The control wells are located on column 11 and 12 of the 96 well plate. The background wells are located in column 12 and 20µl of 10µM control is added to provide an appropriate background control. 20µl of 1% DMSO is added to the wells in column 11 for the stimulated control.

The compound titrations are located between columns 1 and 10. Three compounds are run in duplicate on each plate and row A and B are used for the control compound titration.

The final concentration of DMSO is 0.1% in the assay. The cells are left for 45min, after 45min the proliferative stimulus is added to the first 11 wells of the 96 well plate and 20µl of medium is added to column 12. F(ab')2 fragments of a polyclonal goat anti-sera raised to human IgM is used at a final concentration of 15µg/ ml to stimulate the cells. (Biosource. Cat no: AMI 4601).

Tritiated methyl thymidine is added to the cells at a concentration of 1µCi per well. (Amersham, TRK 758). The radioactivity is added 65 hours after the initial stimulus and is left on the cells for 6 to 8 hours. After pulsing with methyl thymidine the cells are harvested on a Skatron 96 well cell harvester onto glass fibre mats. Once these have dried these are counted on a Wallac 1450 Microbeta scintillation counter.

Data is downloaded as an XL file and IC50's determined using Activity base.

* Buckleys Medium: 450 ml Iscoves (Sigma I 3390), 50ml FCS, 2.5 g BSA, 5ml Pen/ strep, 5ml Glutamine (200mM), 500µl Apo transferrin (50mg/ml) Sigma (T 1147), 100µl Bovine Insulin (10mg/ml) Sigma (I 1882).

Compound Preparation

Compound is prepared as a 10mM stock in DMSO and a dilution series prepared in DMSO using 9 successive 3-fold dilutions. This dilution series is diluted a further 1:100 with Buckleys medium to give the concentration range to be tested of 100µM to 5nM. This is added as 20µl to 96 well plates in duplicate to generate two IC50's for each compound tested. Each plate is run in the presence of a control compound,

which acts as an internal standard.

4. LAD2 Assay

Principle of the assay

LAD2 is a stem cell factor (SCF)-dependent human mast cell line that was established by the NIH from bone marrow aspirates from a patient with mast cell sarcoma/leukaemia. LAD2 cells resemble CD34+-derived human mast cells and express functional FcεRI. The FcεRI is up-regulated in the presence of IL-4, SCF and IgE, subsequent cross linking of cell-bound IgE results in degranulation which can be measured as hexosaminidase release.

Priming LAD2 cells to up-regulate FcεRI

LAD2 cells are re-suspended at $1x10^5$/ml in complete stem pro-34SFM (Gibco Cat 10640-019 media containing Stem Pro-34 nutrient supplement (1:40), glutamine (2mM), penicillin (100µg/ml), streptomycin (100µg/ml)) with additional supplements of human recombinant SCF (100ng/ml; R&D systems), human recombinant Interleukin-4 (6ng/ml; R&D Systems) and IgE (100µg/ml; Calbiochem). Cells are then maintained for 5 days at 37°C, 5% CO2 in a humidified atmosphere.

Compound Preparation

Compounds are titrated from a 2mM stock in 100% DMSO to give 9 successive 1:3 dilutions (V 96-well Nunc; Biomek 2000). From this master plate 3µl is dispensed into a daughter plate (flat 96-well NuncBiomek Fx) which is then diluted 1:40 in RPMI with 2mM glutamine, and 20µl of the diluted compound transferred into the Greiner cell plate. Therefore the final compound concentration range is $1x10^{-5}$M to $5x10^{-10}$M in a constant 0.5% DMSO. Control wells are treated with 0.5% DMSO.

Activation of LAD2 cells with anti-IgE Version A

Primed LAD2 cells are centrifuged (300g, 5min), the supernatant discarded and the cell pellet re-suspended at $1x10^4$ cells/ml in RPMI supplemented with glutamine (2mM). Following a further centrifugation (300g, 5min) the cells are re-suspended in fresh RPMI with glutamine (2mM), adjusted to a density of $2.85x10^5$/ml, and pipetted into sterile V-well plates (70µl/well; Greiner) containing 20µl diluted compound (prepared as detailed above). Cells are then incubated for 1h (37°C, 5%

CO_2 in a humidified atmosphere) before activating with a sub-maximal concentration of anti-IgE (10µl volume to give a final assay dilution of 1:2700; Sigma). Following a 40min incubation (37°C, 5% CO_2 in a humidified atmosphere), plates are centrifuged (1200g, 10min, 4°C) and the supernatant removed for hexosaminidase assay. The cell pellet is lysed in 100µl/well triton-X (0.5% in RPMI 2mM glutamine) at 37°C for 30min.

Activation of LAD2 cells with anti-IgE Version B

Primed LAD2 cells are centrifuged (400g, 5min), the supernatant discarded and the cell pellet re-suspended at $1x10^4$ cells/ml in RPMI supplemented with glutamine (2mM). Following a further centrifugation (400g, 5min) the cells are re-suspended in fresh RPMI with glutamine (2mM), adjusted to a density of 5.7 $x10^5$/ml, and pipetted into sterile V-well plates (70µl/well; Greiner) containing 20µl diluted compound (prepared as detailed above). Cells are then incubated for 1h (37°C, 5% CO_2 in a humidified atmosphere) before activating with a sub-maximal concentration of anti-IgE (10µl volume to give a final assay dilution of 1:2700; Sigma). Following a 40min incubation (37°C, 5% CO_2 in a humidified atmosphere), plates are centrifuged (1200g, 10min, 4°C) and the supernatant removed for hexosaminidase assay. The cell pellet is lysed in 100µl/well triton-X (0.5% in RPMI 2mM glutamine) at 37°C for 30min.

Beta-hexosaminidase assay

Beta-hexosaminidase activity is measured by the conversion of 4-methylumbelliferyl N-acetyl-ε-D glucosaminide (Sigma) to a fluorescent product.

Supernatant or lysate (25µl) is incubated with an equal volume of 4-methylumbelliferyl N-acetyl-ε-D glucosaminide (500µM in 0.2M sodium citrate buffer, pH 4.5) in black 96-well plate (Nunc) for 1h at 37°C. The reaction is then terminated by addition of Trizma pH9 (90µl) and the fluorescent product measured using excitation 356nm and emission 450nm (Tecan Safire)

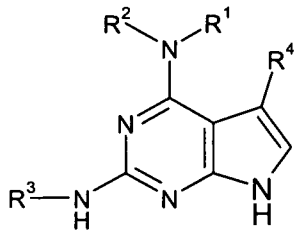
A useful screening strategy comprises assay 1 (enzyme assay (pKi), assay 2 and then assay 3 (B Cell Proliferation) or assay 4 (LAD2).

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) or a salt or solvate thereof:



(I)

wherein:

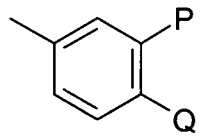
R^1 is H or C_{1-3} alkyl;

R^2 is C_{1-6} alkyl, C_{1-6}-haloalkyl, C_{3-7} cycloalkyl, C_{1-3} alkyleneC_{3-7} cycloalkyl wherein each cycloalkyl may be substituted by one or more substituents independently selected from C_{1-3} alkyl or halogen;

R^3 is:

(a) a six membered heteroaryl group selected from 3-pyridinyl, 4-pyridinyl or 5-pyrimidinyl (each of which may be optionally substituted by one or more substituents independently selected from OH, =O, C_{1-3} alkyl, $NHCOC_{1-3}$ alkyl, C_{1-6} alkoxy, COC_{1-6} alkyl, C_{0-3} alkylene $COOC_{1-3}$ alkyl), CN;

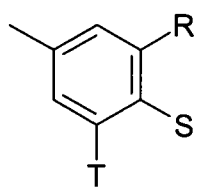
(b) a group



wherein P and Q together form a 5 - 7 membered carbocyclic, heterocyclic or heteroaryl ring, which thus formed bicyclic ring may be optionally substituted by one or more substituents independently selected from; on each carbon by up two C_{1-3}alkyl groups or halogen or by =O or by OH, C_{1-3}alkoxy, C_{1-3}haloalkyl,C_{0-3} alkyleneNR^{5}R^6, on each nitrogen by C_{1-3}alkyl, COC_{1-3}alkyl, C_{1-3}alkyleneC_{3-7}cycloalkyl, phenyl (optionally substituted by fluorine), C_{1-3}alkylOR^5, C_{0-3} alkyleneNR^{5}R^6 or SO_2R^5 or on sulphur by =O or $(=O)_2$;

R^5 and R^6 are independently H or C_{1-3} alkyl;

(d) a group



wherein one of R, S and T is H and the remaining substituents are independently selected from:

H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, OH, C_{1-6} hydroxyalkyl, CN, C_{3-7}cycloalkyl, Ophenyl, OCH_2phenyl, halogen, $COOR^7$, C_{1-3}alkyleneCOOR^7, XNR^8R^9, $XCONR^8R^9$, $XSO_2NR^8R^9$, NR^7COC_{1-6}alkyl, $NR^7SO_2C_{1-6}$alkyl, $OCH_2CONR^8R^9$, SO_2C_{1-3}alkyl, SO_2C_{1-3}haloalkyl, a monocyclic heteroaryl group (optionally substituted by methyl);

R^7 is H or -C_{1-3} alkyl;

X is a bond or C_{1-3}alkylene;

R^8 and R^9 are independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{3-7}cycloalkyl, C_{1-3} alkyleneC_{3-7} cycloalkyl, phenyl (optionally substituted by one or more substitutents independently selected from halogen, -C_{1-3} alkyl, OC_{1-3} alkyl, CN, or SO_2CF_3), C_{1-3} alkylenephenyl, C_{1-3} alkyleneOC_{1-3} alkyl; or

R^8 and R^9 are independently heteroaryl (optionally substituted by one or more substituents independently selected from -C_{1-3} alkyl), heterocyclyl (optionally substituted by one or more substituents independently selected from -C_{1-3} alkyl, =O), C_{1-3} alkylenephenyl (substituted by one or more substitutents independently selected from halogen, -C_{1-3} alkyl or OC_{1-3} alkyl, CN, SO_2CF_3), C_{1-3} alkyleneheteroaryl (optionally substituted by one or more substituents independently selected from -C_{1-3} alkyl), C_{1-3} alkyleneheterocyclyl (optionally substituted by one or more substituents independently selected from -C_{1-3} alkyl, =O), C_{1-3} alkyleneSO_2C_{1-3} alkyl, C_{1-3} alkyleneCONH2, C_{1-3} alkyleneCN, C_{1-3} alkyleneSO_2NC_{1-3} alkyl, alkyleneNSO_2C_{1-3} alkyl; or

R^8 and R^9; together with N to which they are joined form a 4-, 5- or 6 membered heterocyclic group, optionally containing a further heteroatom selected from O, S, or N and optionally substituted by on each carbon by up to two C_{1-6} alkyl or halogen, or by =O or C_{1-6} alkoxy, on any optional nitrogen by C_{1-6}alkyl, COC_{1-3}alkyl or $COOC_{1-6}$ alkyl and on any optional sulphur by =O, $(=O)_2$; and

R^4 is H or -C_{1-3} alkyl.

2. A compound as claimed in claim 1 in which R^1 represents H or methyl.

3. A compound as claimed in claim 1 or 2 in which R^1 represents H.

4. A compound as claimed in any one of claims 1 to 3 in which R^2 represents cyclobutyl, cyclopentyl, cyclohexyl, C_{1-3} alkyl, or C_{1-3} haloalkyl.

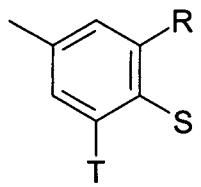
5. A compound as claimed in any one of claims 1 to 4 in which R^2 represents C_{1-3} alkyl or C_{1-3} haloalkyl.

6. A compound as claimed in any one of claims 1 to 5 in which R^1 represents H and R^2 is cyclobutyl, cyclopentyl, cyclohexyl, C_{1-3} alkyl, C_{1-3} haloalkyl.

7. A compound as claimed in any one of claims 1 to 6 in which R^4 is H or CH_3.

8. A compound as claimed in any one of claims 1 to 7 in which R^2 represents C_{1-3} alkyl, or C_{1-3} haloalkyl and R^4 is H.

9. A compound as claimed in any one of claims 1 to 8 in which R^3 is a group:

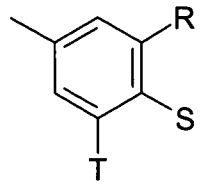


wherein one of R, S and T is H and the remaining substituents are independently selected from: H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, OH, C_{1-6} hydroxyalkyl, CN, C_{3-7}cycloalkyl, Ophenyl, OCH_2phenyl, halogen, $COOR^7$, C_{1-3}alkyleneCOOR^7, XNR^8R^9, $XCONR^8R^9$, $XSO_2NR^8R^9$, NR^7COC_{1-6}alkyl, $NR^7SO_2C_{1-6}$alkyl, $OCH_2CONR^8R^9$, SO_2C_{1-3}alkyl, a monocyclic heteroaryl group (optionally substituted by methyl), and

excluding compounds in which R and T is each hydrogen, S is $CONR^8R^9$ and R^8 and R^9 are independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{3-7}cycloalkyl, C_{1-3} alkyleneC_{3-7} cycloalkyl, phenyl (optionally substituted by one or more substitutents independently selected from halogen, -C_{1-3} alkyl CN, or SO_2CF_3), C_{1-3} alkylenephenyl, C_{1-3} alkyleneOC_{1-3} alkyl; or

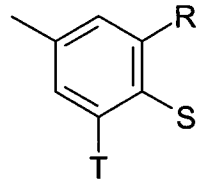
R^8 and R^9; together with N to which they are joined form a 4-, 5- or 6- membered heterocyclic group, optionally containing a further heteroatom selected from O, S, or N and optionally substituted on each carbon by up to two C_{1-6} alkyl or halogen, or by =0 or C_{1-6} alkoxy, on any optional nitrogen by C_{1-6}alkyl, COC_{1-3}alkyl or $COOC_{1-6}$ alkyl and on any optional sulphur by =O, or $(=O)_2$.

10. A compound as claimed in any one of claims 1 to 8 in which R^3 is a group:



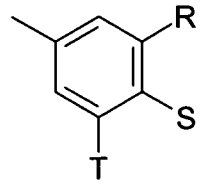
wherein R and T is each hydrogen, S is $CONR^8R^9$,
and R^8 and R^9 are independently heteroaryl (optionally substituted by one or more substituents independently selected from $-C_{1-3}$ alkyl), heterocyclyl (optionally substituted by one or more substituents independently selected from $-C_{1-3}$ alkyl, =O), C_{1-3} alkylenephenyl (substituted by one or more substitutents independently selected from halogen, $-C_{1-3}$ alkyl or OC_{1-3} alkyl, CN, SO_2CF_3), C_{1-3} alkyleneheteroaryl (optionally substituted by one or more substituents independently selected from $-C_{1-3}$ alkyl), C_{1-3} alkyleneheterocyclyl (optionally substituted by one or more substituents independently selected from $-C_{1-3}$ alkyl, =O), C_{1-3} alkyleneSO_2C_{1-3} alkyl, C_{1-3} alkyleneCONH2, C_{1-3} alkyleneCN, C_{1-3} alkyleneSO_2NC_{1-3} alkyl, alkyleneNSO_2C_{1-3} alkyl.

11. A compound as claimed in any one of claims 1 to 8 in which R^3 is a group:



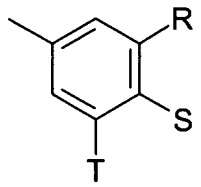
wherein R is hydrogen, T is halogen and S is $CONR^8R^9$.

12. A compound as claimed in any one of claims 1 to 8 in which R^3 is a group:



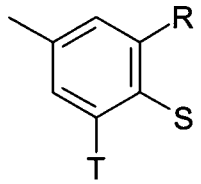
wherein R and T is H and S is NR^7COC_{1-6}alkyl.

13. A compound as claimed in any one of claims 1 to 8 in which R^3 is a group:



wherein R and T is H and S is NR^8R^9 in which R^8 and R^9 together with the N to which they are joined form a 6 membered heterocyclic group, optionally containing a further heteroatom selected from O, S, or N and optionally substituted by on each carbon by up to two C_{1-6} alkyl or halogen, or by =O or C_{1-6} alkoxy, on any optional nitrogen by C_{1-6}alkyl, COC_{1-3}alkyl or $COOC_{1-6}$ alkyl and on any optional sulphur by =O, or $(=O)_2$.

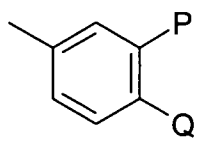
14 A compound as claimed in any one of claims 1 to 8 in which R^3 is a group:



wherein R and T is H, and S is $OCH_2CONR^8R^9$.

15. A compound as claimed in any one of claims 1 to 8 in which R^3 is a six membered heteroaryl group selected from 3-pyridinyl, 4-pyridinyl or 5-pyrimidinyl (each of which may be optionally substituted by one or more substituents independently selected from =O, C_{1-3} alkyl, $NHCOC_{1-3}$ alkyl, C_{1-6} alkoxy, COC_{1-6} alkyl, C_{0-3} alkylene $COOC_{1-3}$ alkyl), CN.

16. A compound as claimed in any one of claims 1 to 8 in which R^3 is a group:



wherein P and Q together form a 5 - 7 membered carbocyclic, heterocyclic or heteroaryl ring, which rings may be optionally substituted by one or more substituents independently selected from; on each carbon by up two C_{1-3}alkyl groups or halogens or by =O or by OH, C_{1-3}alkoxy, C_{1-3}haloalkyl,C_{0-3} alkyleneNR^{5}R^6, on each nitrogen by C_{1-3}alkyl, COC_{1-3}alkyl, C_{1-3}alkyleneC_{3-7}cycloalkyl, phenyl (optionally substituted by fluorine), C_{1-3}alkylOR^5, C_{0-3} alkyleneNR^{5}R^6 or SO_2R^5 or on sulphur by =O or $(=O)_2$.

17. A compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof selected from:

N^4-cyclobutyl-N^2-[4-(1,1-dimethylethyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;;

1-methylethyl (3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)acetate

N^4-cyclobutyl-N^2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-(1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-(2,3-dihydro-1-benzofuran-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

6-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-2,3-dihydro-1*H*-inden-1-one

3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide

6-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-2*H*-chromen-2-one

7-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-4-methyl-2(1*H*)-quinolinone

N^2-(1-acetyl-2,3-dihydro-1*H*-indol-5-yl)-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-1*H*-isoindole-1,3(2*H*)-dione

N^4-cyclobutyl-N^2-1*H*-indazol-5-yl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-(2-methyl-1*H*-benzimidazol-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-1*H*-indazol-6-yl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-[4-(phenyloxy)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide

6-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-3,4-dihydro-1(2*H*)-naphthalenone

N^4-cyclobutyl-N^2-{3-[(1-methylethyl)oxy]phenyl}-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-[3,5-bis(methyloxy)phenyl]-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-[4-(1-methylethyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-[4-(4-methyl-1-piperazinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-(4-cyclohexylphenyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-(3-methylphenyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzenesulfonamide

N^4-cyclobutyl-N^2-{4-[(1-methylethyl)oxy]phenyl}-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-6-quinolinyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-(4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)-*N*-ethylacetamide

N^2-1,3-benzothiazol-6-yl-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-(2-methyl-1,3-benzothiazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-(cyclobutylmethyl)-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclopentyl-N^4-methyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-[4-(dimethylamino)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-1*H*-1,2,3-benzotriazol-5-yl-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-1,3-dihydro-2*H*-benzimidazol-2-one

N^4-cyclobutyl-N^2-[4-(1*H*-tetrazol-5-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-(2-methyl-1,3-benzothiazol-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(1-methylethyl)benzamide

N^4-cyclobutyl-N^2-[3-(1,3-oxazol-5-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-[3,4-bis(methyloxy)phenyl]-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide

N^4-cyclobutyl-N^2-3-pyridinyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-(4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)-*N*-methylacetamide

N^4-cyclobutyl-N^2-4-pyridinyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenol

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*,*N*-diethylbenzamide

N^4-cyclobutyl-N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-methylbenzamide

Ethyl
4-(4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)-1-piperazinecarboxylate

N^4-cyclobutyl-N^2-(3,5-dimethylphenyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-[3-chloro-4-(methyloxy)phenyl]-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-(4-methylphenyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-{3-[(phenylmethyl)oxy]phenyl}-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

4-({4-[(1-Methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide formate

4-{[4-(cyclopentylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide formate

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide formate

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-ethylbenzamide formate

N^2-[4-(1-azetidinylcarbonyl)phenyl]-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine formate

N^4-cyclobutyl-N^2-1*H*-indazol-6-yl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-[4-(trifluoromethyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-(2,3-dihydro-1*H*-inden-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoic acid

(3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)acetic acid

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoic acid

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-2-(hydroxymethyl)benzoic acid

N^4-cyclobutyl-N^2-[3-(methyloxy)-4-(4-methyl-1-piperazinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

6-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-1,4-dihydro-2*H*-3,1-benzoxazin-2-one

methyl 3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoate

methyl 4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoate

5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-2-benzofuran-1(3*H*)-one

N^4-cyclobutyl-N^2-(2,3-dihydro-1,4-benzodioxin-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-(3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)methanesulfonamide

N^4-cyclobutyl-N^2-[4-(methyloxy)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzonitrile

N^4-cyclobutyl-N^2-[3-(trifluoromethyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-2-[2-(dimethylamino)ethyl]-1*H*-isoindole-1,3(2*H*)-dione

N^4-cyclobutyl-N^2-{2-[(dimethylamino)methyl]-1,3-benzoxazol-5-yl}-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-[4-(1,3-oxazol-2-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-1,3-dimethyl-1,3-dihydro-2*H*-benzimidazol-2-one

N^4-cyclobutyl-N^2-(2-methyl-1,3-benzoxazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-[4-(1,3-oxazol-5-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-(4-chlorophenyl)-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-(5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-3-pyridinyl)acetamide

N^4-cyclobutyl-N^2-(1,2-dimethyl-1*H*-benzimidazol-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

3-({4-[(2-methylpropyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzenesulfonamide

N^4-methyl-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-(1-methyl-1*H*-indazol-6-yl)-N^4-[(1*R*)-1-methylpropyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-methyl-4-[(4-{[(1*R*)-1-methylpropyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino]benzamide

N^4-cyclopentyl-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

4-{[4-(ethylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-methylbenzamide.

N^2-1,3-benzothiazol-6-yl-N^4-(cyclopropylmethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

4-({4-[(cyclopropylmethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-methylbenzamide

N-methyl-4-({4-[(2-methylpropyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N^2-(3-methyl-1*H*-indazol-6-yl)-N^4-(2-methylpropyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-N^4-[(1*R*)-1-methylpropyl]-1*H*-pyrrolo[

2,3-*d*]pyrimidine-2,4-diamine

N^2-(3-methyl-1*H*-indazol-6-yl)-N^4-[(1*R*)-1-methylpropyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-1,3-benzothiazol-6-yl-N^4-cyclopentyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

3-{[4-(cyclopentylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzenesulfonamide

4-{[4-(cyclopentylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-methylbenzamide

N^4-ethyl-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-1,3-benzothiazol-6-yl-N^4-ethyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-(cyclopropylmethyl)-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

3-({4-[(cyclopropylmethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzenesulfonamide

N^4-(cyclopropylmethyl)-N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-methyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-(1-methylethyl)-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclopropyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-ethyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclohexyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclopentyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-(2,2-dimethylpropyl)-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4,N^4-dimethyl-N^2-[4-(4-morpholinyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

4-{[4-(cyclopropylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide

4-{[4-(methylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide

4-({4-[(2-methylpropyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-[(4-{[(1*R*)-1-methylpropyl]amino}-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)amino]benzamide

4-({4-[(2,2-dimethylpropyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-({4-[cyclopentyl(methyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-({4-[methyl(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-{[4-(cyclohexylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide

4-({4-[(cyclopropylmethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-{[4-(propylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide

4-{[4-(ethylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide

4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-({4-[(2,2-Difluoropropyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-({4-[(3-methylbutyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-({4-[(1-ethylpropyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-({4-[(2-methylcyclopentyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-({4-[(2-fluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-{[4-(dimethylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzamide

4-({4-[(1,1-dimethylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-({4-[ethyl(methyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-({4-[(3,3,3-trifluoropropyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-({4-[(2,2-difluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N^4-(1-methylethyl)-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N2-1,3-benzothiazol-6-yl-N4-(1-methylethyl)-1H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

4-({4-[(1-methylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-ethyl-N-[4-({4-[(1-methylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]acetamide

N-methyl-N-[4-({4-[(1-methylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]acetamide

3-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzenesulfonamide

N^2-(1-acetyl-2,3-dihydro-1*H*-indol-5-yl)-N^4-(1-methylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-N^4-(1-methylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

6-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-1,4-dihydro-2*H*-3,1-benzoxazin-2-one

1-[4-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]-2-pyrrolidinone

N^2-1,3-benzothiazol-6-yl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

3-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzenesulfonamide

N^2-(1-acetyl-2,3-dihydro-1*H*-indol-5-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-(1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-methyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

6-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-1,4-dihydro-2*H*-3,1-benzoxazin-2-one

1-[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]-2-pyrrolidinone

N^4-(1-methylethyl)-N^2-6-quinolinyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

4-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-[2-(methyloxy) ethyl]benzamide

N^2-(1-methyl-1*H*-indazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2, 4-diamine

N^2-6-quinolinyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-methyl-*N*-[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino) phenyl]acetamide

6-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-3,4-dihydro-1(2*H*)-naphthalenone

N^2-(3-methyl-1*H*-indazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2, 4-diamine

N-propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)be nzamide

N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-5-methyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-methyl-4-({5-methyl-4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl} amino)benzamide

N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-5-methyl-N^4-(1-methylethyl)-1*H*-pyrro lo[2,3-*d*]pyrimidine-2,4-diamine

5-methyl-N^4-(1-methylethyl)-N^2-(3-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidi ne-2,4-diamine

N-methyl-4-({5-methyl-4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amin o)benzamide

N^2-1,3-benzothiazol-6-yl-5-methyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin e-2,4-diamine

4-({5-methyl-4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)be nzamide

N-methyl-*N*-[4-({5-methyl-4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2 -yl}amino)phenyl]acetamide

N^4-cyclobutyl-N^2-(3-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-(3-methyl-1*H*-indazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-(4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}phenyl)-*N*-methyla cetamide

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-[2-(methyloxy)ethyl]benzamide

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(2-hydroxyethyl)be nzamide

N^4-cyclobutyl-N^2-[4-(1-pyrrolidinylcarbonyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-d iamine

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(4-fluorophenyl)be nzamide

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(phenylmethyl)ben zamide

N^4-cyclobutyl-N^2-[4-(1-piperidinylcarbonyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-di amine

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-propylbenzamide

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(2-methylpropyl)be
nzamide

4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzoic acid

Formic acid –
4-({5-methyl-4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzam
ide

5-methyl-N^4-(1-methylethyl)-N^2-(3-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidi
ne-2,4-diamine

N^4-cyclobutyl-N^2-[4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidi
ne-2,4-diamine

3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(2-methylpropyl)be
nzamide

3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-propylbenzamide

3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*,*N*-dimethylbenzami
de

3-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-ethylbenzamide

N^4-cyclobutyl-N^2-[4-(4-morpholinylcarbonyl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-
diamine

N-Propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)be
nzamide

N-cyclobutyl-4-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}benzami
de

N-(5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-2-pyridinyl)acetamide

methyl (5-{[4-(cyclobutylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-2-pyridinyl)acetate

N^4-cyclobutyl-N^2-[3-(4-methyl-1,3-oxazol-5-yl)phenyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-[6-(methyloxy)-3-pyridinyl]-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-cyclobutyl-N^2-5-pyrimidinyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-methyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N^2-[3,4-bis(methyloxy)phenyl]-N^4-cyclobutyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-[3,4-bis(methyloxy)phenyl]-N^4-cyclopentyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-[3,4-bis(methyloxy)phenyl]-N^4-cyclobutyl-5-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-Propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N-Propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide 4-methylbenzenesulfonate

4-({4-[(1-Methylethyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide
N-methyl-N-[3-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)

phenyl]acetamide

3,3-dimethyl-5-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-1,3-dihydro-2H-indol-2-one

N-methyl-2-{[3-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]oxy}acetamide

N^2-[1-(4-fluorophenyl)-1*H*-indazol-5-yl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-[2-methyl-7-(trifluoromethyl)-1-benzofuran-5-yl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

5-methyl-N^4-(1-methylethyl)-N^2-(1-methyl-1H-indazol-6-yl)-1H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

N-methyl-N-[4-({5-methyl-4-[(1-methylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]acetamide

5-methyl-N^2-(1-methyl-1*H*-indazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

4-({4-[(1,1-dimethylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-*N*-methylbenzamide

N^4-(1,1-dimethylethyl)-N^2-(1-methyl-1*H*-indazol-6-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-1,3-benzothiazol-6-yl-N^4-(1,1-dimethylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^4-(1,1-dimethylethyl)-N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-[4-({4-[(1,1-dimethylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]-N-methylacetamide

N,*N*-Dimethyl-4-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzenesulfonamide

N^4-(1-methylethyl)-N^2-phenyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-(2-propyl-1-benzofuran-5-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-[1-(1-methylethyl)-1*H*-indazol-5-yl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-[1-(cyclopropylmethyl)-1*H*-indazol-5-yl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-[3-(methylsulfonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-[4-(methylsulfonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

2-[4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]acetamide

2-[3-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]acetamide

1-[3-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]methanesulfonamide

1-[4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]methanesulfonamide

N^2-[2-(1-methylethyl)-4-(methyloxy)-6-quinolinyl]-N^4-(2,2,2-trifluoroethyl)-1H-pyrrolo[

2,3-d]pyrimidine-2,4-diamine

N^2-6-quinoxalinyl-*N*^{4}-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-(1,1-dioxido-2,3-dihydro-1-benzothien-6-yl)-N^4-(2,2,2-trifluoroethyl)-1H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

N^2-(1-methyl-1*H*-indazol-5-yl)-*N*^{4}-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-1,2-benzisoxazol-5-yl-*N*^{4}-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzenesulfonamide

N,N-dimethyl-3-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzenesulfonamide

3-methyl-5-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenol

N^2-4-pyridinyl-*N*^{4}-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-3-pyridinyl-*N*^{4}-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-5-pyrimidinyl-*N*^{4}-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N-[5-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-3-pyridinyl]acetamide;

N^2-phenyl-*N*^{4}-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

4-methyl-6-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-2(1H)-quinolinone;

7-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-4(1H)-quinazolinone;

N^2-(2-methyl-7-quinolinyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N,N-dimethyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzenesulfonamide;

N^2-(2-methyl-6-quinolinyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-[3-chloro-4-(methyloxy)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N2-(3-Methyl-1,2-benzisoxazol-6-yl)-N4-(2,2,2-trifluoroethyl)-1H-pyrrolo[2,3-d]pyrimidine-2,4-diamine;

N-(1-methylethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N-(2-methylpropyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N-ethyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N-[3-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)phenyl]acetamide;

N^2-[3-(4-pyridinyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

6-({4-[(2,2,2-Trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-2*H*-1,4-benzoxazin-3(4*H*)-one;

4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-2-(trifluoro methyl)benzamide;
4-({4-[(1-methylethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid
N-ethyl-*N*-methyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}a mino)benzamide

2-fluoro-*N*-propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}a mino)benzamide

2-Chloro-*N*-propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl} amino)benzamide
2-Fluoro-*N*-(2-methylpropyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyri midin-2-yl}amino)benzamide

N^2-[4-(1-Piperidinylcarbonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimid ine-2,4-diamine

N^2-[4-(1-azetidinylcarbonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidi ne-2,4-

2-Fluoro-*N*-methyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl} amino)benzamide

2-chloro-*N*-(2-methylpropyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrim idin-2-yl}amino)benzamide

2-chloro-*N*-methyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl} amino)benzamide
Formic
acid-N^2-[4-(1,3-oxazol-5-yl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidi ne-2,4-diamine (1:1)

N,*N*-Dimethyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amin o)benzamide3-({4-[(1-methylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)ben zonitrile (1:1)

N-[5-({4-[(1-methylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-2-pyridinyl]acetamide (1:1)

N^2-(4-fluorophenyl)-N^4-(1-methylethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-(2,2,2-trifluoroethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)

2-Fluoro-*N*-(1-methylethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

2-fluoro-*N*-(2,2,2-trifluoroethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N-Ethyl-2-fluoro-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N-(cyclopropylmethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N^2-{4-[(4-Methyl-1-piperazinyl)carbonyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetic acid

N^2-[3-fluoro-4-(4-morpholinylcarbonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-[3-Fluoro-4-(1-pyrrolidinylcarbonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-

N-propyl-2-[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetamide

N-methyl-2-[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)

phenyl]acetamide

N^2-4*H*-1,3-benzodioxin-6-yl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

5-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-2-benzofuran-1(3*H*)-one;

N^2-[4-(methyloxy)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-[1-(methylsulfonyl)-2,3-dihydro-1*H*-indol-5-yl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N-(1-methylethyl)-2-{[3-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]oxy}acetamide;

N-(1-methylethyl)-2-{[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]oxy}acetamide;

N^2-(2-methyl-1,3-benzothiazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

2-hydroxy-5-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzonitrile;

N^2-[3-methyl-4-(methyloxy)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N-[2-methyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetamide;

N-1,3-thiazol-2-yl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}a

mino)benzamide;
4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoic acid

N^2-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-[(3,4-difluorophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-[(2,4-difluorophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-[3-(methyloxy)propyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-[(6-methyl-2-pyridinyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-(1,2,4-oxadiazol-3-ylmethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-(4-fluorophenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-cyclohexyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-cyclopentyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-(tetrahydro-2H-pyran-4-yl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-methyl-N-[2-(methyloxy)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-methyl-N-(1-methylethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-(1,1-dimethylethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-[(5-methyl-2-furanyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-cyclobutyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N^2-[4-(4-methyl-1,3-oxazol-5-yl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-[2-(methyloxy)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N^2-[3-chloro-4-(4-morpholinylcarbonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-[3-chloro-4-(1-pyrrolidinylcarbonyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-{3-fluoro-4-[(4-methyl-1-piperazinyl)carbonyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-methyl-*N*-propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N-{2-[(methylsulfonyl)amino]ethyl}-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-[(1-methyl-4-piperidinyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-[2-(2-pyridinyl)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-[2-(4-morpholinyl)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-[2-(methylsulfonyl)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

2-Propyl-5-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-2,3-dihydro-1*H*-isoindol-1-one

N-(2,2-dimethylpropyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-[(2,3-difluorophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-(2-amino-2-oxoethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-[3-(1-piperidinyl)propyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-[(3,5-dimethylphenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-(1-ethyl-1-methylpropyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N-[(1S)-1-cyclohexylethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

N,N-diethyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino) benzamide;

N-(4-propylphenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl} amino)benzamide;

N^2-{3-chloro-4-[(4-methyl-1-piperazinyl)carbonyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-[4-(3,5-dimethyl-4-isoxazolyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N-(1-methyl-4-piperidinyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-[2-(1-methyl-1H-pyrrol-2-yl)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-(3-methylphenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl }amino)benzamide

N-[3-(4-morpholinyl)propyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-[(2-fluorophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-[(2,6-difluorophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-[3-fluoro-4-(methyloxy)phenyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d] pyrimidin-2-yl}amino)benzamide

N-[3-(2-oxo-1-pyrrolidinyl)propyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d] pyrimidin-2-yl}amino)benzamide

N-(2-cyanoethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}a

mino)benzamide.

N-[2-(1-piperidinyl)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-(3-chloro-4-fluorophenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-(2-fluoro-4-methylphenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-(3-methylphenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-[3-(4-morpholinyl)propyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-[(2-fluorophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-[(2,6-difluorophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-[3-fluoro-4-(methyloxy)phenyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-[3-(2-oxo-1-pyrrolidinyl)propyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-(2-cyanoethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-[2-(1-piperidinyl)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-(3-chloro-4-fluorophenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimi

din-2-yl}amino)benzamide

N-(2-fluoro-4-methylphenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N^2-(2-methyl-4-pyridinyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-(2-methyl-1-oxido-4-pyridinyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-(2,6-dimethyl-1-oxido-4-pyridinyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-(5-methyl-3-pyridinyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

5-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-3-pyridinecarbonitrile;

5-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)-2-pyridinecarbonitrile;

N^2-[5-(methyloxy)-3-pyridinyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N-[(3-cyanophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-[2-(ethyloxy)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-{2-[(methylamino)sulfonyl]ethyl}-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-(3-fluoro-4-methylphenyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrim

idin-2-yl}amino)benzamide

N~2~-{4-[(1,1-dioxido-4-thiomorpholinyl)carbonyl]phenyl}-N~4~-(2,2,2-trifluoroethyl)-1H-pyrrolo[2,3-d]pyrimidine-2,4-diamine

N-[(3-fluorophenyl)methyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N-(2-phenylethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N-[2-(1-pyrrolidinyl)ethyl]-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenol;

N^2-(4-fluorophenyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

3-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzonitrile;

N^2-[3,4-bis(methyloxy)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N-[4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]acetamide;

*N*4-(2,2,2-trifluoroethyl)-*N*2-{4-[(trifluoromethyl)sulfonyl]phenyl}-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-6-isoquinolinyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

3-[3-methyl-6-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-1*H*-indazol-1-yl]-1-propanol;

N^2-(8-chloro-6-quinolinyl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

5-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-1,3-dihydro-2*H*-benzimidazol-2-one;

N^2-[3-ethyl-4-(methyloxy)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

2-chloro-*N*-(1-methylethyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

2-chloro-*N*-ethyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N^2-[4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-N^4-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

4-{[4-(Methylamino)-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]amino}-*N*-propylbenzamide

N^4-(1,1-dimethylethyl)-N^2-(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

2,2-dimethyl-6-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)-2*H*-1,4-benzoxazin-3(4*H*)-one

Ethyl
4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzoate

N-(3-methyl-5-isothiazolyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-(5-methyl-1,3,4-thiadiazol-2-yl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-(5-methyl-3-isoxazolyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-(3,4-dimethyl-5-isoxazolyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-3-isoxazolyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-(5-methyl-3-isoxazolyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide

N-(5-methyl-3-isoxazolyl)-4-({4-[(2,2,2-trifluoroethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-2-yl}amino)benzamide;

4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N-(1-methylethyl)-2-propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide

N-propyl-4-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzamide 4-methylbenzenesulfonate

N^2-{4-[2-(dimethylamino)ethyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-{4-[2-(4-morpholinyl)ethyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

formic acid – N^2-{4-[(dimethylamino)methyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-[4-(4-morpholinylmethyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine

N^2-{4-[(4-acetyl-1-piperazinyl)methyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

4-methyl-1-[3-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino) phenyl]-2-piperazinone;

N^2-[3-(4-morpholinylmethyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-[3-(4-methyl-1-piperazinyl)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-{3-[(4-methyl-1-piperazinyl)methyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-{4-[(4-methyl-1-piperazinyl)methyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-{3-[(dimethylamino)methyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-{4-[2-(1-pyrrolidinyl)ethyl]phenyl}-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-6-isoquinolinyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-[3-chloro-4-(methyloxy)phenyl]-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-(1-methyl-1*H*-indazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N^2-6-quinolinyl-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diamine;

N-methyl-2-{[3-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)phenyl]oxy}acetamide;

3-({4-[(2,2,2-trifluoroethyl)amino]-1*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}amino)benzonitrile; and

N^2-(3-methyl-1*H*-indazol-6-yl)-N^4-(2,2,2-trifluoroethyl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2, 4-diamine.

18. A pharmaceutical composition comprising a compound according to any one of claims 1 to 17 or a pharmaceutically acceptable salt or solvate, thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

19. A compound according to according to any one of claims 1 to 17 or a pharmaceutically acceptable salt or solvate thereof for use in therapy.

20. A compound of formula (I) according to according to any one of claims 1 to 17 or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of a disease or condition mediated by inappropriate Syk activity.

21. A method of treating a disease or condition mediated by inappropriate Syk activity in a mammal comprising administering to said mammal a compound of formula (I) or a salt or solvate thereof.

22. A method as claimed in claim 21 in which the disease or condition mediated by inappropriate Syk activity is rheumatoid arthritis.

23. A method as claimed in claim 21 in which the disease or condition mediated by inappropriate Syk activity is allergic rhinitis.

24. A method as claimed in claim 21 in which the disease or condition mediated by inappropriate Syk activity is chronic obstructive pulmonary disease (COPD),

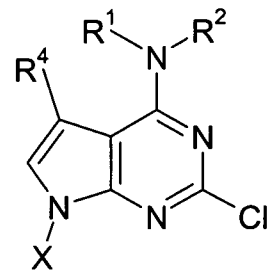
25. A method as claimed in claim 21 in which the disease or condition mediated by inappropriate Syk activity is adult respiratory distress syndrome (ARDs).

26. The use of a compound according to according to any one of claims 1 to 17 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a

medicament for use in the treatment of a disease or condition mediated by inappropriate Syk activity.

27. A process for preparing a compound of formula (I) as claimed in any one of claims 1 to 17 which process comprises:

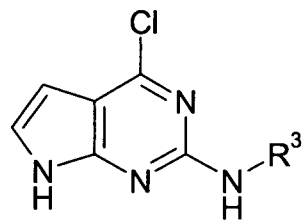
(i) reacting a compound of formula (II):



(II)

wherein X is H or a protecting group such as p-toluenesulphonyl, with an amine R^3NH_2 and thereafter, if present, removing the protecting group;

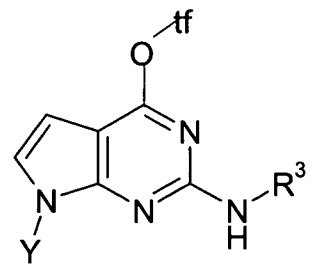
(ii) reacting a compound of formula (III):



(III)

with an amine R^1R^2NH;

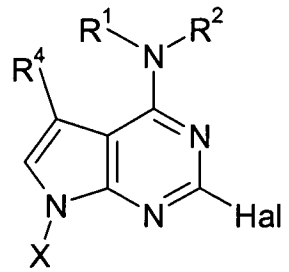
(iii) when R^4-H, reacting a compound of formula (IV):



(IV)

wherein Y is a protecting group such as triflate, with an amine HNR^1R^2 and thereafter removing the protecting group;

(iv) reacting a compound of formula (V):



(V)

wherein Hal is Cl or I, with an amine R^3NH_2 and thereafter removing the protecting group.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/009870

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519 A61P37/08

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y A	WO 01/09134 A (NOVARTIS AG) 8 February 2001 (2001-02-08) page 1, line 1 - page 2, line 15	1-14, 16-27 15
Y A	WO 01/83485 A (BAYER AKTIENGESELLSCHAFT) 8 November 2001 (2001-11-08) page 5, line 12 - page 12, line 16	1-14, 16-27 15
A	WO 03/057695 A (BOEHRINGER INGELHEIM PHARMACEUTICALS INC.) 17 July 2003 (2003-07-17) page 4, line 1 - page 6, line 14	1-27
A	NAKASHIMA K ET AL: EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 505, 2004, pages 223-228, XP004649387 the whole document	1-27

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2007	07/02/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Usuelli, Ambrogio

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/009870

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

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

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

Although claims 21-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/009870

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0109134 A	08-02-2001	AR 029175 A1	18-06-2003
		AT 251160 T	15-10-2003
		AU 767349 B2	06-11-2003
		AU 6567700 A	19-02-2001
		BR 0012888 A	09-04-2002
		CA 2379560 A1	08-02-2001
		CN 1365360 A	21-08-2002
		CZ 20020299 A3	17-04-2002
		DE 60005684 D1	06-11-2003
		DE 60005684 T2	29-07-2004
		DK 1200435 T3	02-02-2004
		EP 1200435 A1	02-05-2002
		ES 2208395 T3	16-06-2004
		HU 0201935 A2	28-11-2002
		JP 2003506375 T	18-02-2003
		MX PA02001102 A	20-08-2002
		NO 20020467 A	20-03-2002
		NZ 516667 A	28-05-2004
		PL 354477 A1	26-01-2004
		PT 1200435 T	27-02-2004
		SK 1262002 A3	02-07-2002
		TR 200200234 T2	21-06-2002
		TW 255268 B	21-05-2006
		US 6589950 B1	08-07-2003
		ZA 200200783 A	12-02-2003
WO 0183485 A	08-11-2001	AR 033367 A1	17-12-2003
		AT 272639 T	15-08-2004
		AU 783043 B2	22-09-2005
		AU 6220401 A	12-11-2001
		BG 107166 A	30-06-2003
		BR 0110404 A	11-02-2003
		CA 2407531 A1	25-10-2001
		CN 1439009 A	27-08-2003
		CZ 20023551 A3	15-01-2003
		DE 60104671 D1	09-09-2004
		DE 60104671 T2	29-12-2005
		EE 200200606 A	15-04-2004
		EP 1278750 A1	29-01-2003
		ES 2225546 T3	16-03-2005
		HR 20020943 A2	28-02-2005
		HU 0300846 A2	28-08-2003
		JP 2001302667 A	31-10-2001
		JP 2003535067 T	25-11-2003
		MA 25746 A1	01-04-2003
		MX PA02010579 A	14-05-2003
		NO 20025154 A	25-10-2002
		NZ 522241 A	30-04-2004
		NZ 526221 A	28-01-2005
		PL 358106 A1	09-08-2004
		PT 1278750 T	30-11-2004
		SK 15332002 A3	03-06-2003
		TR 200402300 T4	21-12-2004
		TW 222974 B	01-11-2004
		UA 72615 C2	15-03-2005
		US 2004054179 A1	18-03-2004
		ZA 200207676 A	25-09-2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/009870

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03057695 A	17-07-2003	AU 2002357773 A1	24-07-2003
		US 2003158195 A1	21-08-2003
		US 2003229090 A1	11-12-2003