METHODS OF TREATING OR PREVENTING AUTOIMMUNE DISEASES WITH 2,4–PYRIMIDINEDIAMINE COMPOUNDS

1. CROSS REFERENCE TO RELATED APPLICATIONS

This application claims benefit under 35 U.S.C. § 119(e) to application Serial No. 60/399,673 filed July 29, 2002; Serial No. 60/443,949 filed January 31, 2003 and Serial No. 60/452,339 filed March 6, 2003.

2. FIELD OF THE INVENTION

The present invention relates generally to 2,4-pyrimidinediamine compounds, pharmaceutical compositions comprising the compounds, intermediates and synthetic methods of making the compounds and methods of using the compounds and compositions in a variety of contexts, such as in the treatment or prevention of autoimmune diseases and/or the symptoms associated therewith.

3. BACKGROUND OF THE INVENTION

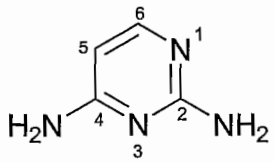
Crosslinking of Fc receptors, such as the high affinity receptor for IgE (FcεRI) and/or the high affinity receptor for IgG (FcγRI) activates a signaling cascade in mast, basophil and other immune cells that results in the release of chemical mediators responsible for numerous adverse events. For example, such crosslinking leads to the release of preformed mediators of Type I (immediate) anaphylactic hypersensitivity reactions, such as histamine, from storage sites in granules *via* degranulation. It also leads to the synthesis and release of other mediators, including leukotrienes, prostaglandins and platelet-activating factors (PAFs), that play important roles in inflammatory reactions. Additional mediators that are synthesized and released upon crosslinking Fc receptors include cytokines and nitric oxide.

The signaling cascade(s) activated by crosslinking Fc receptors such as FcεRI and/or FcγRI comprises an array of cellular proteins. Among the most important intracellular signal propagators are the tyrosine kinases. And, an important tyrosine kinase involved in the signal transduction pathways associated with crosslinking the FcεRI and/or FcγRI receptors, as well as other signal transduction cascades, is Syk kinase (*see* Valent *et al.*, 2002, *Intl. J. Hematol.* 75(4):257-362 for review).

As the mediators released as a result of FcεRI and FcγRI receptor cross-linking are responsible for, or play important roles in, the manifestation of numerous adverse events, the availability of compounds capable of inhibiting the signaling cascade(s) responsible for their release would be highly desireable. Moreover, owing to the critical role that Syk kinase plays these and other receptor signaling cascade(s), the availability of compounds capable of inhibiting Syk kinase would also be highly desirable.

4. SUMMARY OF THE INVENTION

In one aspect, the present invention provides novel 2,4-pyrimidinediamine compounds that, as will be discussed in more detail below, have myriad biological activities. The compounds generally comprise a 2,4-pyrimidinediamine "core" having the following structure and numbering convention:



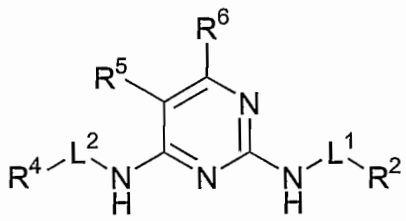
The compounds of the invention are substituted at the C2 nitrogen (N2) to form a secondary amine and are optionally further substituted at one or more of the following positions: the C4 nitrogen (N4), the C5 position and/or the C6 position. When substituted at N4, the substituent forms a secondary amine. The substituent at N2, as well as the optional substituents at the other positions, may range broadly in character and physico-chemical properties. For example, the substituent(s) may be a branched, straight-chained or cyclic alkyl, a branched, straight-chained or cyclic heteroalkyl, a mono- or polycyclic aryl a mono- or polycyclic heteroaryl or combinations of these groups. These substituent groups may be further substituted, as will be described in more detail below.

The N2 and/or N4 substituents may be attached directly to their respective nitrogen atoms, or they may be spaced away from their respective nitrogen atoms *via* linkers, which may be the same or different. The nature of the linkers can vary widely, and can include virtually any combination of atoms or groups useful for spacing one molecular moiety from another. For example, the linker may be an acyclic hydrocarbon bridge (*e.g.* a saturated or unsaturated alkyleno such as methano, ethano, etheno, propano, prop[1]eno, butano, but[1]eno, but[2]eno, buta[1,3]dieno, and the like), a monocyclic or polycyclic hydrocarbon bridge (*e.g.*, [1,2]benzeno, [2,3]naphthaleno, and the like), a simple acyclic heteroatomic or

heteroalkyldiyl bridge (*e.g.*, -O-, -S-, -S-O-, -NH-, -PH-, -C(O)-, -C(O)NH-, -S(O)-, -$S(O)_2$-, -S(O)NH-, -$S(O)_2$NH-, -O-CH_2-, -CH_2-O-CH_2-, -O-CH=CH-CH_2-, and the like), a monocyclic or polycyclic heteroaryl bridge (*e.g.*, [3,4]furano, pyridino, thiopheno, piperidino, piperazino, pyrazidino, pyrrolidino, and the like) or combinations of such bridges.

The substituents at the N2, N4, C5 and/or C6 positions, as well as the optional linkers, may be further substituted with one or more of the same or different substituent groups. The nature of these substituent groups may vary broadly. Non-limiting examples of suitable substituent groups include branched, straight–chain or cyclic alkyls, mono- or polycyclic aryls, branched, straight–chain or cyclic heteroalkyls, mono- or polycyclic heteroaryls, halos, branched, straight–chain or cyclic haloalkyls, hydroxyls, oxos, thioxos, branched, straight-chain or cyclic alkoxys, branched, straight-chain or cyclic haloalkoxys, trifluoromethoxys, mono- or polycyclic aryloxys, mono- or polycyclic heteroaryloxys, ethers, alcohols, sulfides, thioethers, sulfanyls (thiols), imines, azos, azides, amines (primary, secondary and tertiary), nitriles (any isomer), cyanates (any isomer), thiocyanates (any isomer), nitrosos, nitros, diazos, sulfoxides, sulfonyls, sulfonic acids, sulfamides, sulfonamides, sulfamic esters, aldehydes, ketones, carboxylic acids, esters, amides, amidines, formadines, amino acids, acetylenes, carbamates, lactones, lactams, glucosides, gluconurides, sulfones, ketals, acetals, thioketals, oximes, oxamic acids, oxamic esters, etc., and combinations of these groups. Substituent groups bearing reactive functionalities may be protected or unprotected, as is well-known in the art.

In one illustrative embodiment, the 2,4-pyrimidinediamine compounds of the invention are compounds according to structural formula (I):



including salts, hydrates, solvates and N-oxides thereof, wherein:

L^1 and L^2 are each, independently of one another, selected from the group consisting of a direct bond and a linker;

R^2 is selected from the group consisting of (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^4 is selected from the group consisting of hydrogen, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^5 is selected from the group consisting of R^6, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C1-C4) alkanyl optionally substituted with one or more of the same or different R^8 groups, (C2-C4) alkenyl optionally substituted with one or more of the same or different R^8 groups and (C2-C4) alkynyl optionally substituted with one or more of the same or different R^8 groups;

each R^6 is independently selected from the group consisting of hydrogen, an electronegative group, $-OR^d$, $-SR^d$, (C1-C3) haloalkyloxy, (C1-C3) perhaloalkyloxy, $-NR^cR^c$, halogen, (C1-C3) haloalkyl, (C1-C3) perhaloalkyl, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$; $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)NR^cR^c$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-OC(O)R^d$, $-SC(O)R^d$, $-OC(O)OR^d$, $-SC(O)OR^d$, $-OC(O)NR^cR^c$, $-SC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-SC(NH)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$ and $-[NHC(NH)]_nNR^cR^c$, (C5-C10) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups, (C6-C16) arylalkyl optionally substituted with one or more of the same or different R^8 groups, 5-10 membered

heteroaryl optionally substituted with one or more of the same or different R^8 groups and 6-16 membered heteroarylalkyl optionally substituted with one or more of the same or different R^8 groups;

R^8 is selected from the group consisting of R^a, R^b, R^a substituted with one or more of the same or different R^a or R^b, $-OR^a$ substituted with one or more of the same or different R^a or R^b, $-B(OR^a)_2$, $-B(NR^cR^c)_2$, $-(CH_2)_m-R^b$, $-(CHR^a)_m-R^b$, $-O-(CH_2)_m-R^b$, $-S-(CH_2)_m-R^b$, $-O-CHR^aR^b$, $-O-CR^a(R^b)_2$, $-O-(CHR^a)_m-R^b$, $-O-(CH_2)_m-CH[(CH_2)_mR^b]R^b$, $-S-(CHR^a)_m-R^b$, $-C(O)NH-(CH_2)_m-R^b$, $-C(O)NH-(CHR^a)_m-R^b$, $-O-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-S-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-O-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-S-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-NH-(CH_2)_m-R^b$, $-NH-(CHR^a)_m-R^b$, $-NH[(CH_2)_mR^b]$, $-N[(CH_2)_mR^b]_2$, $-NH-C(O)-NH-(CH_2)_m-R^b$, $-NH-C(O)-(CH_2)_m-CHR^bR^b$ and $-NH-(CH_2)_m-C(O)-NH-(CH_2)_m-R^b$;

each R^a is independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C3-C8) cycloalkyl, cyclohexyl, (C4-C11) cycloalkylalkyl, (C5-C10) aryl, phenyl, (C6-C16) arylalkyl, benzyl, 2-6 membered heteroalkyl, 3-8 membered cycloheteroalkyl, morpholinyl, piperazinyl, homopiperazinyl, piperidinyl, 4-11 membered cycloheteroalkylalkyl, 5-10 membered heteroaryl and 6-16 membered heteroarylalkyl;

each R^b is a suitable group independently selected from the group consisting of =O, $-OR^d$, (C1-C3) haloalkyloxy, $-OCF_3$, =S, $-SR^d$, $=NR^d$, $=NOR^d$, $-NR^cR^c$, halogen, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-C(NR^a)NR^cR^c$, $-C(NOH)R^a$, $-C(NOH)NR^cR^c$, $-OC(O)R^d$, $-OC(O)OR^d$, $-OC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-OC(NR^a)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NR^aC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NR^aC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$, $-[NR^aC(O)]_nNR^cR^c$, $-[NHC(NH)]_nNR^cR^c$ and $-[NR^aC(NR^a)]_nNR^cR^c$;

each R^c is independently a protecting group or R^a, or, alternatively, each R^c is taken together with the nitrogen atom to which it is bonded to form a 5 to 8-membered cycloheteroalkyl or heteroaryl which may optionally include one or more of the same or different additional heteroatoms and which may optionally be substituted with one or more of the same or different R^a or suitable R^b groups;

each R^d is independently a protecting group or R^a;

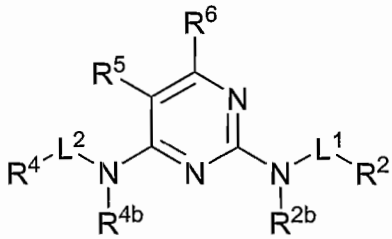
each *m* is independently an integer from 1 to 3; and

each *n* is independently an integer from 0 to 3.

In another aspect, the present invention provides prodrugs of the 2,4-pyrimidinediamine compounds. Such prodrugs may be active in their prodrug form, or may be inactive until converted under physiological or other conditions of use to an active drug form. In the prodrugs of the invention, one or more functional groups of the 2,4-pyrimidinediamine compounds are included in promoieties that cleave from the molecule under the conditions of use, typically by way of hydrolysis, enzymatic cleavage or some other cleavage mechanism, to yield the functional groups. For example, primary or secondary amino groups may be included in an amide promoiety that cleaves under conditions of use to generate the primary or secondary amino group. Thus, the prodrugs of the invention include special types of protecting groups, termed "progroups," masking one or more functional groups of the 2,4-pyrimidinediamine compounds that cleave under the conditions of use to yield an active 2,4-pyrimidinediamine drug compound. Functional groups within the 2,4-pyrimidinediamine compounds that may be masked with progroups for inclusion in a promoiety include, but are not limited to, amines (primary and secondary), hydroxyls, sulfanyls (thiols), carboxyls, carbonyls, phenols, catechols, diols, alkynes, phosphates, etc. Myriad progroups suitable for masking such functional groups to yield promoieties that are cleavable under the desired conditions of use are known in the art. All of these progroups, alone or in combinations, may be included in the prodrugs of the invention. Specific examples of promoieties that yield primary or secondary amine groups that can be included in the prodrugs of the invention include, but are not limited to amides, carbamates, imines, ureas, phosphenyls, phosphoryls and sulfenyls. Specific examples of promoieties that yield sulfanyl groups that can be included in the prodrugs of the invention include, but are not limited to, thioethers, for example S-methyl derivatives (monothio, dithio, oxythio, aminothio acetals), silyl thioethers, thioesters, thiocarbonates, thiocarbamates, asymmetrical disulfides, etc. Specific examples of promoieties that cleave to yield hydroxyl groups that can be included in the prodrugs of the invention include, but are not limited to, sulfonates, esters and carbonates. Specific examples of promoieties that yield carboxyl groups that can be included in the prodrugs of the invention included, but are not limited to, esters (including silyl esters, oxamic acid esters and thioesters), amides and hydrazides.

In one illustrative embodiment, the prodrugs of the invention are compounds according to structural formula (I) in which the protecting group of R^c and R^d is a progroup.

Replacing the hydrogens attached to N2 and N4 in the 2,4-pyrimidinediamines of structural formula (I) with substituents adversely affects the activity of the compounds. However, as will be appreciated by skilled artisans, these nitrogens may be included in promoieties that, under conditions of use, cleave to yield 2,4-pyrimidinediamines according to structural formula (I). Thus, in another illustrative embodiment, the prodrugs of the invention are compounds according to structural formula (II):



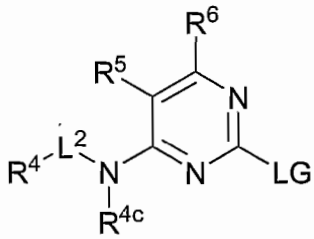
including salts, hydrates, solvates and N-oxides thereof, wherein:

R^2, R^4, R^5, R^6, L^1 and L^2 are as previously defined for structural formula (I); and

R^{2b} and R^{4b} are each, independently of one another, a progroup.

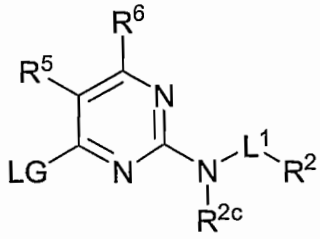
In another aspect, the present invention provides compositions comprising one or more compounds and/or prodrugs of the invention and an appropriate carrier, excipient or diluent. The exact nature of the carrier, excipient or diluent will depend upon the desired use for the composition, and may range from being suitable or acceptable for veterinary uses to being suitable or acceptable for human use.

In still another aspect, the present invention provides intermediates useful for synthesizing the 2,4-pyrimidinediamine compounds and prodrugs of the invention. In one embodiment, the intermediates are 4-pyrimidineamines according to structural formula (III):



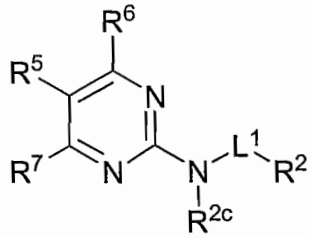
including salts, hydrates, solvates and N-oxides thereof, wherein R^4, R^5, R^6 and L^2 are as previously defined for structural formula (I); LG is a leaving group such as, for example, $-S(O)_2Me$, -SMe or halo (*e.g.*, F, Cl, Br, I); and R^{4c} is hydrogen or a progroup.

In another embodiment, the intermediates are 2-pyrimidineamines according to structural formula (IV):



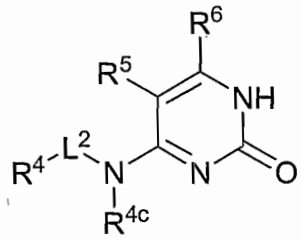
including salts, hydrates, solvates and N-oxides thereof, wherein R^2, R^5, R^6 and L^1 are as previously defined for structural formula (I); LG is a leaving group, such as, for example, $-S(O)_2Me$, -SMe or halo (*e.g.*, F, Cl, Br, I) and R^{2c} is hydrogen or a progroup.

In yet another embodiment, the intermediates are 4-amino- or 4-hydroxy-2-pyrimidineamines according to structural formula (V):



including salts, hydrates, solvates and N-oxides thereof, wherein R^2, R^5, R^6 and L^1 are as previously defined for structural formula (I), R^7 is an amino or hydroxyl group and R^{2c} is hydrogen or a progroup.

In another embodiment, the intermediates are N4-substituted cytosines according to structural formula (VI):



including salts, hydrates, solvates and N-oxides thereof, wherein R^4, R^5, R^6 and L^2 are as previously defined for structural formula (I) and R^{4c} is hydrogen or a progroup.

In yet another aspect, the present invention provides methods of synthesizing the 2,4-pyrimidinediamine compounds and prodrugs of the invention. In one embodiment, the method involves reacting a 4-pyrimidineamine according to structural formula (III) with an amine of the formula $HR^{2c}N\text{-}L^1\text{-}R^2$, where L^1, R^2 and R^{2c} are as previously defined for

structural formula (IV) to yield a 2,4-pyrimidinediamine according to structural formula (I) or a prodrug according to structural formula (II).

In another embodiment, the method involves reacting a 2-pyrimidineamine according to structural formula (IV) with an amine of the formula R^4-L^2-NHR^{4c} where L^4, R^4 and R^{4c} are as previously defined for structural formula (III) to yield a 2,4-pyrimidinediamine according to structural formula (I) or a prodrug according to structural formula (II).

In yet another embodiment, the method involves reacting a 4-amino-2-pyrimidineamine according to structural formula (V) (in which R^7 is an amino group) with an amine of the formula R^4-L^2-NHR^{4c}, where L^2, R^4 and R^{4c} are as defined for structural formula (III), to yield a 2,4-pyrimidinediamine according to structural formula (I) or a prodrug according to structural formula (II). Alternatively, the 4-amino-2-pyrimidineamine may be reacted with a compound of the formula R^4-L^2-LG, where R^4 and L^2 are as previously defined for structural formula (I) and LG is a leaving group.

In still another embodiment, the method involves halogenating a 4-hydroxy-2-pyrimidineamine according to structural formula (V) (R^7 is a hydroxyl group) to yield a 2-pyrimidineamine according to structural formula (IV) and reacting this pyrimidineamine with an appropriate amine, as described above.

In yet another embodiment, the method involves halogenating an N4-substituted cytosine according to structural formula (VI) to yield a 4-pyrimidineamine according to structural formula (III) and reacting this pyrimidineamine with an appropriate amine, as described above.

The 2,4-pyrimidinediamine compounds of the invention are potent inhibitors of degranulation of immune cells, such as mast, basophil, neutrophil and/or eosinophil cells. Thus, in still another aspect, the present invention provides methods of regulating, and in particular inhibiting, degranulation of such cells. The method generally involves contacting a cell that degranulates with an amount of a 2,4-pyrimidinediamine compound or prodrug of the invention, or an acceptable salt, hydrate, solvate, N-oxide and/or composition thereof, effective to regulate or inhibit degranulation of the cell. The method may be practiced in *in vitro* contexts or in *in vivo* contexts as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by or associated with cellular degranulation.

While not intending to be bound by any theory of operation, biochemical data confirm that the 2,4-pyrimidinediamine compounds exert their degranulation inhibitory

effect, at least in part, by blocking or inhibiting the signal transduction cascade(s) initiated by crosslinking of the high affinity Fc receptors for IgE ("FcεRI") and/or IgG ("FcγRI"). Indeed, the 2,4-pyrimidinediamine compounds are potent inhibitors of both FcεRI-mediated and FcγRI-mediated degranulation. As a consequence, the 2,4-pyrimidine compounds may be used to inhibit these Fc receptor signalling cascades in any cell type expressing such FcεRI and/or FcγRI receptors including but not limited to macrophages, mast, basophil, neutrophil and/or eosinophil cells.

The methods also permit the regulation of, and in particular the inhibition of, downstream processes that result as a consequence of activating such Fc receptor signaling cascade(s). Such downstream processes include, but are not limited to, FcεRI-mediated and/or FcγRI-mediated degranulation, cytokine production and/or the production and/or release of lipid mediators such as leukotrienes and prostaglandins. The method generally involves contacting a cell expressing an Fc receptor, such as one of the cell types discussed above, with an amount of a 2,4-pyrimidinediamine compound or prodrug of the invention, or an acceptable salt, hydrate, solvent, N-oxide and/or composition thereof, effective to regulate or inhibit the Fc receptor signaling cascade and/or a downstream process effected by the activation of this signaling cascade. The method may be practiced in *in vitro* contexts or in *in vivo* contexts as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by or associated with the Fc receptor signaling cascade, such as diseases effected by the release of granule specific chemical mediators upon degranulation, the release and/or synthesis of cytokines and/or the release and/or synthesis of lipid mediators such as leukotrienes and prostaglandins.

In yet another aspect, the present invention provides methods of treating and/or preventing diseases characterized by, caused by or associated with the release of chemical mediators as a consequence of activating Fc receptor signaling cascades, such as FcεRI and/or FcγRI- signaling cascades. The methods may be practiced in animals in veterinary contexts or in humans. The methods generally involve administering to an animal subject or human an amount of a 2,4-pyrimidinediamine compound or prodrug of the invention, or an acceptable salt, hydrate, solvate, N-oxide and/or composition thereof, effective to treat or prevent the disease. As discussed previously, activation of the FcεRI or FcγRI receptor signaling cascade in certain immune cells leads to the release and/or synthesis of a variety of chemical substances that are pharmacological mediators of a wide variety of diseases.

Any of these diseases may be treated or prevented according to the methods of the invention.

For example, in mast cells and basophil cells, activation of the FcεRI or FcγRI signaling cascade leads to the immediate (*i.e.,* within 1-3 min. of receptor activation) release of preformed mediators of atopic and/or Type I hypersensitivity reactions (*e.g.,* histamine, proteases such as tryptase, etc.) *via* the degranulation process. Such atopic or Type I hypersensitivity reactions include, but are not limited to, anaphylactic reactions to environmental and other allergens (*e.g.,* pollens, insect and/or animal venoms, foods, drugs, contrast dyes, etc.), anaphylactoid reactions, hay fever, allergic conjunctivitis, allergic rhinitis, allergic asthma, atopic dermatitis, eczema, urticaria, mucosal disorders, tissue disorders and certain gastrointestinal disorders.

The immediate release of the preformed mediators *via* degranulation is followed by the release and/or synthesis of a variety of other chemical mediators, including, among other things, platelet activating factor (PAF), prostaglandins and leukotrienes (e.g., LTC4) and the *de novo* synthesis and release of cytokines such as TNFα, IL-4, IL-5, IL-6, IL-13, etc. The first of these two processes occurs approximately 3-30 min. following receptor activation; the latter approximately 30 min. – 7 hrs. following receptor activation. These "late stage" mediators are thought to be in part responsible for the chronic symptoms of the above-listed atopic and Type I hypersensitivity reactions, and in addition are chemical mediators of inflammation and inflammatory diseases (e.g., osteoarthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, idiopathic inflammatory bowel disease, irritable bowel syndrome, spastic colon, etc.), low grade scarring (e.g., scleroderma, increased fibrosis, keloids, post-surgical scars, pulmonary fibrosis, vascular spasms, migraine, reperfusion injury and post myocardial infarction), and sicca complex or syndrome. All of these diseases may be treated or prevented according to the methods of the invention.

Additional diseases which can be treated or prevented according to the methods of the invention include diseases associated with basophil cell and/or mast cell pathology. Examples of such diseases include, but are not limited to, diseases of the skin such as scleroderma, cardiac diseases such as post myocardial infarction, pulmonary diseases such as pulmonary muscle changes or remodeling and chronic obstructive pulmonary disease (COPD) and diseases of the gut such as inflammatory bowel syndrome (spastic colon).

The 2,4-pyrimidinediamine compounds of the invention are also potent inhibitors of the tyrosine kinase Syk kinase. Thus, in still another aspect, the present invention provides

methods of regulating, and in particular inhibiting, Syk kinase activity. The method generally involves contacting a Syk kinase or a cell comprising a Syk kinase with an amount of a 2,4-pyrimidinediamine compound or prodrug of the invention, or an acceptable salt, hydrate, solvate, N-oxide and/or composition thereof, effective to regulate or inhibit Syk kinase activity. In one embodiment, the Syk kinase is an isolated or recombinant Syk kinase. In another embodiment, the Syk kinase is an endogenous or recombinant Syk kinase expressed by a cell, for example a mast cell or a basophil cell. The method may be practiced in *in vitro* contexts or in *in vivo* contexts as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by or associated with Syk kinase activity.

While not intending to be bound by any particular theory of operation, it is believed that the 2,4-pyrimdinediamine compounds of the invention inhibit cellular degranulation and/or the release of other chemical mediators primarily by inhibiting Syk kinase that gets activated through the gamma chain homodimer of FcεRI (*see, e.g.,* FIG. 2). This gamma chain homodimer is shared by other Fc receptors, including FcγRI, FcγRIII and FcαRI. For all of these receptors, intracellular signal transduction is mediated by the common gamma chain homodimer. Binding and aggregation of those receptors results in the recruitment and activation of tyrosine kinases such as Syk kinase. As a consequence of these common signaling activities, the 2,4-pyrimidinediamine compounds described herein may be used to regulate, and in particular inhibit, the signaling cascades of Fc receptors having this gamma chain homodimer, such as FcεRI, FcγRI, FcγRIII and FcαRI, as well as the cellular responses elicited through these receptors.

Syk kinase is known to play a critical role in other signaling cascades. For example, Syk kinase is an effector of B-cell receptor (BCR) signaling (Turner *et al.,* 2000, Immunology Today 21:148-154) and is an essential component of integrin beta(1), beta(2) and beta(3) signaling in neutrophils (Mocsai *et al.,* 2002, Immunity 16:547-558). As the 2,4-pyrimidinediamine compounds described herein are potent inhibitors of Syk kinase, they can be used to regulate, and in particular inhibit, any signaling cascade where Syk plays a role, such as, fore example, the Fc receptor, BCR and integrin signaling cascades, as well as the cellular responses elicited through these signaling cascades. The particular cellular response regulated or inhibited will depend, in part, on the specific cell type and receptor signaling cascade, as is well known in the art. Non-limiting examples of cellular responses that may be regulated or inhibited with the 2,4-pyrimidinediamine compounds

include a respiratory burst, cellular adhesion, cellular degranulation, cell spreading, cell migration, phagocytosis (*e.g.,* in macrophages), calcium ion flux (*e.g.,* in mast, basophil, neutrophil, eosinophil and B-cells), platelet aggregation, and cell maturation (*e.g.,* in B-cells).

Thus, in another aspect, the present invention provides methods of regulating, and in particular inhibiting, signal transduction cascades in which Syk plays a role. The method generally involves contacting a Syk-dependent receptor or a cell expressing a Syk-dependent receptor with an amount of a 2,4-pyrimidinediamine compound or prodrug of the invention, or an acceptable salt, hydrate, solvate, N-oxide and/or composition thereof, effective to regulate or inhibit the signal transduction cascade. The methods may also be used to regulate, and in particular inhibit, downstream processes or cellular responses elicited by activation of the particular Syk-dependent signal transduction cascade. The methods may be practiced to regulate any signal transduction cascade where Syk is not known or later discovered to play a role. The methods may be practiced in *in vitro* contexts or in *in vivo* contexts as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by or associated with activation of the Syk-dependent signal transduction cascade. Non-limited examples of such diseases include those previously discussed.

Cellular and animal data also confirm that the 2,4-pyrimidinediamine compounds of the invention may also be used to treat or prevent autoimmune diseases and/or symptoms of such diseases. The methods generally involve administering to a subject suffering from an autoimmune disease or at risk of developing an autoimmune disease an amount of a 2,4-pyrimidinediamine method or prodrug of the invention, or an acceptable salt, N-oxide, hydrate, solvate or composition thereof, effective to treat or prevent the autoimmune disease and/or its associated symptoms. Autoimmune diseases that can be treated or prevented with the 2,4-pyrimidinediamine compounds include those diseases that are commonly associated with nonanaphylactic hypersensitivity reactions (Type II, Type III and/or Type IV hypersensitivity reactions) and/or those diseases that are mediated, at least in part, by activation of the FcγR signaling cascade in monocyte cells. Such autoimmune disease include, but are not limited to, those autoimmune diseases that are frequently designated as single organ or single cell-type autoimmune disorders and those autoimmune disease that are frequently designated as involving systemic autoimmune disorder. Non-limiting examples of diseases frequently designated as single organ or single cell-type autoimmune

disorders include: Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune atrophic gastritis of pernicious anemia, autoimmune encephalomyelitis, autoimmune orchitis, Goodpasture's disease, autoimmune thrombocytopenia, sympathetic ophthalmia, myasthenia gravis, Graves' disease, primary biliary cirrhosis, chronic aggressive hepatitis, ulcerative colitis and membranous glomerulopathy. Non-limiting examples of diseases often designated as involving systemic autoimmune disorder include: systemic lupus erythematosis, rheumatoid arthritis, Sjogren's syndrome, Reiter's syndrome, polymyositis-dermatomyositis, systemic sclerosis, polyarteritis nodosa, multiple sclerosis and bullous pemphigoid.

5. BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 provides a cartoon illustrating allergen-induced production of IgE and consequent release of preformed and other chemical mediators from mast cells;

FIG. 2 provides a cartoon illustrating the FcεR1 signal transduction cascade leading to degranulation of mast and/or basophil cells;

FIG. 3 provides a cartoon illustrating the putative points of action of compounds that selectively inhibit upstream FcεRI-mediated degranulation and compounds that inhibit both FcεRI-mediated and ionomycin-induced degranulation;

FIG. 4 provides graphs illustrating the effects of certain 2,4-pyrimidinediamine compounds, DMSO (control) and ionomycin on Ca^{2+} flux in CHMC cells;

FIG. 5 provides graphs illustrating the immediacy of the inhibitory activity of compounds R921218 and R926495;

FIG. 6 provides a graph illustrating the effect of washout on the inhibitory activity of compounds R921218 and R921302;

FIG. 7 provides data showing that varying concentrations of compounds R921218 (A) and R921219 (B) inhibit phosporylation of various proteins downstream of Syk kinase in the IgE receptor signal transduction cascade in activated BMMC cells;

FIG. 8 provides data showing dose responsive inhibition of Syk kinase phosphorylation of an endogenous substrate (LAT) and a peptide substrate in the presence of increasing concentrations of compounds R921218 (X), R921219 (Y) and R921304 (Z);

FIG. 9 provides data showing that the inhibition of Syk kinase by compound R921219 is ATP competitive;

FIG. 10 provides data showing that varying concentrations of compounds R921219 (A) and R218218 (B) inhibit phosphorylation of proteins downstream of Syk kinase, but not

LYN kinase, in the FcεRI signal transduction cascade in activated CHMC cells; also shown is inhibition of phosphorylation of proteins downstream of LYN kinase but not Syk kinase, in the presence of a known LYN kinase inhibitor (PP2);

FIGS. 11A-D provide data showing inhibition of phosphorylation of proteins downstream of Syk kinase in the FcεRI signal transduction cascade in BMMC cells;

FIG. 12 is a graph illustrating the efficacy of compound R921302 in a mouse model of collagen antibody-induced arthritis ("CAIA");

FIG. 13 is a graph illustrating the efficacy of compound R921302 in the CAIA model as compared to other agents and control agents;

FIG. 14 is a graph illustrating the efficacy of compound R921302 in a rat model of collagen-induced arthritis ("CIA");

FIG. 15 is a graph illustrating the efficacy of compound R921302 in inhibiting experimental autoimmune encephalomyelitis ("EAE") in mice, a clinical model for multiple sclerosis; and

FIG. 16 is a graph illustrating the efficacy compound R921302 on SJL mice treated on the starting day of immunization with 150 μg PLP 139-151/200 μg MTB (CFA).

6. DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

6.1 Definitions

As used herein, the following terms are intended to have the following meanings:

"Alkyl" by itself or as part of another substituent refers to a saturated or unsaturated branched, straight-chain or cyclic monovalent hydrocarbon radical having the stated number of carbon atoms (*i.e.*, C1-C6 means one to six carbon atoms) that is derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane, alkene or alkyne. Typical alkyl groups include, but are not limited to, methyl; ethyls such as ethanyl, ethenyl, ethynyl; propyls such as propan-1-yl, propan-2-yl, cyclopropan-1-yl, prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl, prop-1-yn-1-yl , prop-2-yn-1-yl, etc.; butyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, cyclobutan-1-yl, but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl , but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, etc.; and the like. Where specific levels of

saturation are intended, the nomenclature "alkanyl," "alkenyl" and/or "alkynyl" is used, as defined below. In preferred embodiments, the alkyl groups are (C1-C6) alkyl.

"Alkanyl" by itself or as part of another substituent refers to a saturated branched, straight-chain or cyclic alkyl derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Typical alkanyl groups include, but are not limited to, methanyl; ethanyl; propanyls such as propan-1-yl, propan-2-yl (isopropyl), cyclopropan-1-yl, etc.; butanyls such as butan-1-yl, butan-2-yl (*sec*-butyl), 2-methyl-propan-1-yl (isobutyl), 2-methyl-propan-2-yl (*t*-butyl), cyclobutan-1-yl, etc.; and the like. In preferred embodiments, the alkanyl groups are (C1-C6) alkanyl.

"Alkenyl" by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The group may be in either the *cis* or *trans* conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl , prop-1-en-2-yl, prop-2-en-1-yl, prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl ; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, etc.; and the like. In preferred embodiments, the alkenyl group is (C2-C6) alkenyl.

"Alkynyl" by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl , prop-2-yn-1-yl, etc.; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl , etc.; and the like. In preferred embodiments, the alkynyl group is (C2-C6) alkynyl.

"Alkyldiyl" by itself or as part of another substituent refers to a saturated or unsaturated, branched, straight-chain or cyclic divalent hydrocarbon group having the stated number of carbon atoms (*i.e.*, C1-C6 means from one to six carbon atoms) derived by the removal of one hydrogen atom from each of two different carbon atoms of a parent alkane, alkene or alkyne, or by the removal of two hydrogen atoms from a single carbon atom of a parent alkane, alkene or alkyne. The two monovalent radical centers or each valency of the divalent radical center can form bonds with the same or different atoms. Typical alkyldiyl

groups include, but are not limited to, methandiyl; ethyldiyls such as ethan-1,1-diyl, ethan-1,2-diyl, ethen-1,1-diyl, ethen-1,2-diyl; propyldiyls such as propan-1,1-diyl, propan-1,2-diyl, propan-2,2-diyl, propan-1,3-diyl, cyclopropan-1,1-diyl, cyclopropan-1,2-diyl, prop-1-en-1,1-diyl, prop-1-en-1,2-diyl, prop-2-en-1,2-diyl, prop-1-en-1,3-diyl, cycloprop-1-en-1,2-diyl, cycloprop-2-en-1,2-diyl, cycloprop-2-en-1,1-diyl, prop-1-yn-1,3-diyl, etc.; butyldiyls such as, butan-1,1-diyl, butan-1,2-diyl, butan-1,3-diyl, butan-1,4-diyl, butan-2,2-diyl, 2-methyl-propan-1,1-diyl, 2-methyl-propan-1,2-diyl, cyclobutan-1,1-diyl; cyclobutan-1,2-diyl, cyclobutan-1,3-diyl, but-1-en-1,1-diyl, but-1-en-1,2-diyl, but-1-en-1,3-diyl, but-1-en-1,4-diyl, 2-methyl-prop-1-en-1,1-diyl, 2-methanylidene-propan-1,1-diyl, buta-1,3-dien-1,1-diyl, buta-1,3-dien-1,2-diyl, buta-1,3-dien-1,3-diyl, buta-1,3-dien-1,4-diyl, cyclobut-1-en-1,2-diyl, cyclobut-1-en-1,3-diyl, cyclobut-2-en-1,2-diyl, cyclobuta-1,3-dien-1,2-diyl, cyclobuta-1,3-dien-1,3-diyl, but-1-yn-1,3-diyl, but-1-yn-1,4-diyl, buta-1,3-diyn-1,4-diyl, etc.; and the like. Where specific levels of saturation are intended, the nomenclature alkanyldiyl, alkenyldiyl and/or alkynyldiyl is used. Where it is specifically intended that the two valencies are on the same carbon atom, the nomenclature "alkylidene" is used. In preferred embodiments, the alkyldiyl group is (C1-C6) alkyldiyl. Also preferred are saturated acyclic alkanyldiyl groups in which the radical centers are at the terminal carbons, *e.g.*, methandiyl (methano); ethan-1,2-diyl (ethano); propan-1,3-diyl (propano); butan-1,4-diyl (butano); and the like (also referred to as alkylenos, defined *infra*).

"Alkyleno" by itself or as part of another substituent refers to a straight-chain saturated or unsaturated alkyldiyl group having two terminal monovalent radical centers derived by the removal of one hydrogen atom from each of the two terminal carbon atoms of straight-chain parent alkane, alkene or alkyne. The locant of a double bond or triple bond, if present, in a particular alkyleno is indicated in square brackets. Typical alkyleno groups include, but are not limited to, methano; ethylenos such as ethano, etheno, ethyno; propylenos such as propano, prop[1]eno, propa[1,2]dieno, prop[1]yno, etc.; butylenos such as butano, but[1]eno, but[2]eno, buta[1,3]dieno, but[1]yno, but[2]yno, buta[1,3]diyno, etc.; and the like. Where specific levels of saturation are intended, the nomenclature alkano, alkeno and/or alkyno is used. In preferred embodiments, the alkyleno group is (C1-C6) or (C1-C3) alkyleno. Also preferred are straight-chain saturated alkano groups, *e.g.*, methano, ethano, propano, butano, and the like.

"Heteroalkyl," Heteroalkanyl," Heteroalkenyl," Heteroalkynyl," Heteroalkyldiyl" and "Heteroalkyleno" by themselves or as part of another substituent refer to alkyl, alkanyl, alkenyl, alkynyl, alkyldiyl and alkyleno groups, respectively, in which one or more of the carbon atoms are each independently replaced with the same or different heteratoms or heteroatomic groups. Typical heteroatoms and/or heteroatomic groups which can replace the carbon atoms include, but are not limited to, -O-, -S-, -S-O-, -NR'-, -PH-, -S(O)-, $-S(O)_2-$, -S(O) NR'-, $-S(O)_2NR'-$, and the like, including combinations thereof, where each R' is independently hydrogen or (C1-C6) alkyl.

"Cycloalkyl" and "Heterocycloalkyl" by themselves or as part of another substituent refer to cyclic versions of "alkyl" and "heteroalkyl" groups, respectively. For heteroalkyl groups, a heteroatom can occupy the position that is attached to the remainder of the molecule. Typical cycloalkyl groups include, but are not limited to, cyclopropyl; cyclobutyls such as cyclobutanyl and cyclobutenyl; cyclopentyls such as cyclopentanyl and cyclopentenyl; cyclohexyls such as cyclohexanyl and cyclohexenyl; and the like. Typical heterocycloalkyl groups include, but are not limited to, tetrahydrofuranyl (*e.g.*, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, etc.), piperidinyl (*e.g.*, piperidin-1-yl, piperidin-2-yl, etc.), morpholinyl (*e.g.*, morpholin-3-yl, morpholin-4-yl, etc.), piperazinyl (*e.g.*, piperazin-1-yl, piperazin-2-yl, etc.), and the like.

"Acyclic Heteroatomic Bridge" refers to a divalent bridge in which the backbone atoms are exclusively heteroatoms and/or heteroatomic groups. Typical acyclic heteroatomic bridges include, but are not limited to, -O-, -S-, -S-O-, -NR'-, -PH-, -S(O)-, $-S(O)_2-$, -S(O) NR'-, $-S(O)_2NR'-$, and the like, including combinations thereof, where each R' is independently hydrogen or (C1-C6) alkyl.

"Parent Aromatic Ring System" refers to an unsaturated cyclic or polycyclic ring system having a conjugated π electron system. Specifically included within the definition of "parent aromatic ring system" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, fluorene, indane, indene, phenalene, tetrahydronaphthalene, etc. Typical parent aromatic ring systems include, but are not limited to, aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene,

rubicene, tetrahydronaphthalene, triphenylene, trinaphthalene, and the like, as well as the various hydro isomers thereof.

"Aryl" by itself or as part of another substituent refers to a monovalent aromatic hydrocarbon group having the stated number of carbon atoms (*i.e.*, C5-C15 means from 5 to 15 carbon atoms) derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene, and the like, as well as the various hydro isomers thereof. In preferred embodiments, the aryl group is (C5-C15) aryl, with (C5-C10) being even more preferred. Particularly preferred aryls are cyclopentadienyl, phenyl and naphthyl.

"Arylaryl" by itself or as part of another substituent refers to a monovalent hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a ring system in which two or more identical or non-identical parent aromatic ring systems are joined directly together by a single bond, where the number of such direct ring junctions is one less than the number of parent aromatic ring systems involved. Typical arylaryl groups include, but are not limited to, biphenyl, triphenyl, phenyl-naphthyl, binaphthyl, biphenyl-naphthyl, and the like. Where the number of carbon atoms in an arylaryl group are specified, the numbers refer to the carbon atoms comprising each parent aromatic ring. For example, (C5-C15) arylaryl is an arylaryl group in which each aromatic ring comprises from 5 to 15 carbons, *e.g.*, biphenyl, triphenyl, binaphthyl, phenylnaphthyl, etc. Preferably, each parent aromatic ring system of an arylaryl group is independently a (C5-C15) aromatic, more preferably a (C5-C10) aromatic. Also preferred are arylaryl groups in which all of the parent aromatic ring systems are identical, *e.g.*, biphenyl, triphenyl, binaphthyl, trinaphthyl, etc.

"Biaryl" by itself or as part of another substituent refers to an arylaryl group having two identical parent aromatic systems joined directly together by a single bond. Typical biaryl groups include, but are not limited to, biphenyl, binaphthyl, bianthracyl, and the like. Preferably, the aromatic ring systems are (C5-C15) aromatic rings, more preferably (C5-C10) aromatic rings. A particularly preferred biaryl group is biphenyl.

"Arylalkyl" by itself or as part of another substituent refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl group. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. Where specific alkyl moieties are intended, the nomenclature arylalkanyl, arylakenyl and/or arylalkynyl is used. In preferred embodiments, the arylalkyl group is (C6-C21) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C1-C6) and the aryl moiety is (C5-C15). In particularly preferred embodiments the arylalkyl group is (C6-C13), *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C1-C3) and the aryl moiety is (C5-C10).

"Parent Heteroaromatic Ring System" refers to a parent aromatic ring system in which one or more carbon atoms are each independently replaced with the same or different heteroatoms or heteroatomic groups. Typical heteroatoms or heteroatomic groups to replace the carbon atoms include, but are not limited to, N, NH, P, O, S, S(O), $S(O)_2$, Si, etc. Specifically included within the definition of "parent heteroaromatic ring systems" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, benzodioxan, benzofuran, chromane, chromene, indole, indoline, xanthene, etc. Also included in the definition of "parent heteroaromatic ring system" are those recognized rings that include common substituents, such as, for example, benzopyrone and 1-methyl-1,2,3,4-tetrazole. Specifically excluded from the definition of "parent heteroaromatic ring system" are benzene rings fused to cyclic polyalkylene glycols such as cyclic polyethylene glycols. Typical parent heteroaromatic ring systems include, but are not limited to, acridine, benzimidazole, benzisoxazole, benzodioxan, benzodioxole, benzofuran, benzopyrone, benzothiadiazole, benzothiazole, benzotriazole, benzoxaxine, benzoxazole, benzoxazoline, carbazole, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like.

"Heteroaryl" by itself or as part of another substituent refers to a monovalent heteroaromatic group having the stated number of ring atoms (*e.g.*, "5-14 membered" means from 5 to 14 ring atoms) derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring system. Typical heteroaryl groups include, but are not limited to, groups derived from acridine, benzimidazole, benzisoxazole, benzodioxan, benzodiaxole, benzofuran, benzopyrone, benzothiadiazole, benzothiazole, benzotriazole, benzoxazine, benzoxazole, benzoxazoline, carbazole, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like, as well as the various hydro isomers thereof. In preferred embodiments, the heteroaryl group is a 5-14 membered heteroaryl, with 5-10 membered heteroaryl being particularly preferred.

"Heteroaryl-Heteroaryl" by itself or as part of another substituent refers to a monovalent heteroaromatic group derived by the removal of one hydrogen atom from a single atom of a ring system in which two or more identical or non-identical parent heteroaromatic ring systems are joined directly together by a single bond, where the number of such direct ring junctions is one less than the number of parent heteroaromatic ring systems involved. Typical heteroaryl-heteroaryl groups include, but are not limited to, bipyridyl, tripyridyl, pyridylpurinyl, bipurinyl, etc. Where the number of atoms are specified, the numbers refer to the number of atoms comprising each parent heteroaromatic ring systems. For example, 5-15 membered heteroaryl-heteroaryl is a heteroaryl-heteroaryl group in which each parent heteroaromatic ring system comprises from 5 to 15 atoms, *e.g.*, bipyridyl, tripuridyl, etc. Preferably, each parent heteroaromatic ring system is independently a 5-15 membered heteroaromatic, more preferably a 5-10 membered heteroaromatic. Also preferred are heteroaryl-heteroaryl groups in which all of the parent heteroaromatic ring systems are identical.

"Biheteroaryl" by itself or as part of another substituent refers to a heteroaryl-heteroaryl group having two identical parent heteroaromatic ring systems joined directly together by a single bond. Typical biheteroaryl groups include, but are not limited to, bipyridyl, bipurinyl, biquinolinyl, and the like. Preferably, the heteroaromatic ring

systems are 5-15 membered heteroaromatic rings, more preferably 5-10 membered heteroaromatic rings.

"Heteroarylalkyl" by itself or as part of another substituent refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heteroaryl group. Where specific alkyl moieties are intended, the nomenclature heteroarylalkanyl, heteroarylakenyl and/or heteroarylalkynyl is used. In preferred embodiments, the heteroarylalkyl group is a 6-21 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the heteroarylalkyl is (C1-C6) alkyl and the heteroaryl moiety is a 5-15-membered heteroaryl. In particularly preferred embodiments, the heteroarylalkyl is a 6-13 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety is (C1-C3) alkyl and the heteroaryl moiety is a 5-10 membered heteroaryl.

"Halogen" or "Halo" by themselves or as part of another substituent, unless otherwise stated, refer to fluoro, chloro, bromo and iodo.

"Haloalkyl" by itself or as part of another substituent refers to an alkyl group in which one or more of the hydrogen atoms is replaced with a halogen. Thus, the term "haloalkyl" is meant to include monohaloalkyls, dihaloalkyls, trihaloalkyls, etc. up to perhaloalkyls. For example, the expression "(C1-C2) haloalkyl" includes fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl, 1,2-difluoroethyl, 1,1,1-trifluoroethyl, perfluoroethyl, etc.

The above-defined groups may include prefixes and/or suffixes that are commonly used in the art to create additional well-recognized substituent groups. As examples, "alkyloxy" or "alkoxy" refers to a group of the formula -OR", "alkylamine" refers to a group of the formula –NHR" and "dialkylamine" refers to a group of the formula –NR"R", where each R" is independently an alkyl. As another example, "haloalkoxy" or "haloalkyloxy" refers to a group of the formula –OR"', where R"' is a haloalkyl.

"Protecting group" refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, *Protective Groups in Organic Chemistry*, 3rd Ed., 1999, John Wiley & Sons, NY and Harrison *et al.*, *Compendium of Synthetic Organic Methods*, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative amino protecting groups include, but are not limited to,

formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), *tert*-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("TES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxyl protecting groups include, but are not limited to, those where the hydroxyl group is either acylated or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (*e.g.*, TMS or TIPPS groups) and allyl ethers.

"Prodrug" refers to a derivative of an active 2,4-pyrimidinediamine compound (drug) that requires a transformation under the conditions of use, such as within the body, to release the active 2,4-pyrimidinediamine drug. Prodrugs are frequently, but not necessarily, pharmacologically inactive until converted into the active drug. Prodrugs are typically obtained by masking a functional group in the 2,4-pyrimidinediamine drug believed to be in part required for activity with a progroup (defined below) to form a promoiety which undergoes a transformation, such as cleavage, under the specified conditions of use to release the functional group, and hence the active 2,4-pyrimidinediamine drug. The cleavage of the promoiety may proceed spontaneously, such as by way of a hydrolysis reaction, or it may be catalyzed or induced by another agent, such as by an enzyme, by light, by acid or base, or by a change of or exposure to a physical or environmental parameter, such as a change of temperature. The agent may be endogenous to the conditions of use, such as an enzyme present in the cells to which the prodrug is administered or the acidic conditions of the stomach, or it may be supplied exogenously.

A wide variety of progroups, as well as the resultant promoieties, suitable for masking functional groups in the active 2,4-pyrimidinediamines compounds to yield prodrugs are well-known in the art. For example, a hydroxyl functional group may be masked as a sulfonate, ester or carbonate promoiety, which may be hydrolyzed *in vivo* to provide the hydroxyl group. An amino functional group may be masked as an amide, carbamate, imine, urea, phosphenyl, phosphoryl or sulfenyl promoiety, which may be hydrolyzed *in vivo* to provide the amino group. A carboxyl group may be masked as an ester (including silyl esters and thioesters), amide or hydrazide promoiety, which may be hydrolyzed *in vivo* to provide the carboxyl group. Other specific examples of suitable progroups and their respective promoieties will be apparent to those of skill in the art.

"Progroup" refers to a type of protecting group that, when used to mask a functional group within an active 2,4-pyrimidinediamine drug to form a promoiety, converts the drug

into a prodrug. Progroups are typically attached to the functional group of the drug *via* bonds that are cleavable under specified conditions of use. Thus, a progroup is that portion of a promoiety that cleaves to release the functional group under the specified conditions of use. As a specific example, an amide promoiety of the formula –NH-C(O)CH_3 comprises the progroup –C(O)CH_3.

"Fc Receptor" refers to a member of the family of cell surface molecules that binds the Fc portion (containing the specific constant region) of an immunoglobulin. Each Fc receptor binds immunoglobulins of a specific type. For example the Fcα receptor ("FcαR") binds IgA, the FcϵR binds IgE and the FcγR binds IgG.

The FcαR family includes the polymeric Ig receptor involved in epithelial transport of IgA/IgM, the mycloid specific receptor RcαRI (also called CD89), the Fcα/μR and at least two alternative IgA receptors (for a recent review see Monteiro & van de Winkel, 2003, Annu. Rev. Immunol, advanced e-publication. The FcαRI is expressed on neutrophils, eosinophils, moncytes/macrophages, dendritic cells and kupfer cells. The FcαRI inclues one alpha chain and the FcR gamma homodimer that bears an activation motif (ITAM) in the cytoplasmic domain and phosphorylates Syk kinase.

The FcϵR family includes two types, designated FcϵRI and FcϵRII (also known as CD23). FcϵRI is a high affinity receptor (binds IgE with an affinity of about $10^{10}M^{-1}$) found on mast, basophil and eosinophil cells that anchors monomeric IgE to the cell surface. The FcϵRI possesses one alpha chain, one beta chain and the gamma chain homodimer discussed above. The FcϵRII is a low affinity receptor expressed on mononuclear phagocytes, B lymphocytes, eosinophils and platelets. The FcϵRII comprises a single polypeptide chain and does not include the gamma chain homodimer.

The FcγR family includes three types, designated FcγRI (also known as CD64), FcγRII (also known as CD32) and FcγRIII (also known as CD16). FcγRI is a high affinity receptor (binds IgG1 with an affinity of $10^{8}M^{-1}$) found on mast, basophil, mononuclear, neutrophil, eosinophil, deudritic and phagocyte cells that anchors nomomeric IgG to the cell surface. The FcγRI includes one alpha chain and the gamma chain dimer shared by FcαRI and FcϵRI.

The FcγRII is a low affinity receptor expressed on neutrophils, monocytes, eosinophils, platelets and B lymphocytes. The FcγRII includes one alpha chain, and does not include the gamma chain homodimer discussed above.

The FcγRIII is a low affinity (bindes IgG1 with an affinity of $5x10^5M^{-1}$) expressed on NK, eosinophil, macrophage, neutrophil and mast cells. It comprises one alpha chain and the gamma homodimer shared by FcαRI, FcεRI and FcγRI.

Skilled artisans will recognize that the subunit structure and binding properties of these various Fc receptors, cell types expressing them, are not completely characterized. The above discussion merely reflects the current state-of-the-art regarding these receptors (*see, e.g.,* Immunobiology: The Immune System in Health & Disease, 5th Edition, Janeway et al., Eds, 2001, ISBN 0-8153-3642-x, Figure 9.30 at pp. 371), and is not intended to be limiting with respect to the myriad receptor signaling cascades that can be regulated with the compounds described herein.

"Fc Receptor-Mediated Degranulation" or "Fc Receptor-Induced Degranulation" refers to degranulation that proceeds *via* an Fc receptor signal transduction cascade initiated by crosslinking of an Fc receptor.

"IgE-Induced Degranulation" or "FcεRI-Mediated Degranulation" refers to degranulation that proceeds *via* the IgE receptor signal transduction cascade initiated by crosslinking of FcεR1-bound IgE. The crosslinking may be induced by an IgE-specific allergen or other multivalent binding agent, such as an anti-IgE antibody. Referring to FIG. 2, in mast and/or basophil cells, the FcεRI signaling cascade leading to degranulation may be broken into two stages: upstream and downstream. The upstream stage includes all of the processes that occur prior to calcium ion mobilization (illustrated as "Ca^{2+}" in FIG. 2; see also FIG. 3). The downstream stage includes calcium ion mobilization and all processes downstream thereof. Compounds that inhibit FcεRI-mediated degranulation may act at any point along the FcεRI-mediated signal transduction cascade. Compounds that selectively inhibit upstream FcεRI-mediated degranulation act to inhibit that portion of the FcεRI signaling cascade upstream of the point at which calcium ion mobilization is induced. In cell-based assays, compounds that selectively inhibit upstream FcεRI-mediated degranulation inhibit degranulation of cells such as mast or basophil cells that are activated or stimulated with an IgE-specific allergen or binding agent (such as an anti-IgE antibody) but do not appreciably inhibit degranulation of cells that are activated or stimulated with degranulating agents that bypass the FcεRI signaling pathway, such as, for example the calcium ionophores ionomycin and A23187.

"IgG-Induced Degranulation" or "FcγRI-Mediated Degranulation" refers to degranulation that proceeds *via* the FcγRI signal transduction cascade initiated by

crosslinking of FcγRI-bound IgG. The crosslinking may be induced by an IgG-specific allergen or another multivalent binding agent, such as an anti-IgG or fragment antibody. Like the FcεRI signaling cascade, in mast and basophil cells the FcγRI signaling cascade also leads to degranulation which may be broken into the same two stages: upstream and downstream. Similar to FcεRI-mediated degranulation, compounds that selectively inhibit upstream FcγRI-mediated degranulation act upstream of the point at which calcium ion mobilization is induced. In cell-based assays, compounds that selectively inhibit upstream FcγRI-mediated degranulation inhibit degranulation of cells such as mast or basophil cells that are activated or stimulated with an IgG-specific allergen or binding agent (such as an anti-IgG antibody or fragment) but do not appreciably inhibit degranulation of cells that are activated or stimulated with degranulating agents that bypass the FcγRI signaling pathway, such as, for example the calcium ionophores ionomycin and A23187.

"Ionophore-Induced Degranulation" or "Ionophore-Mediated Degranulation" refers to degranulation of a cell, such as a mast or basophil cell, that occurs upon exposure to a calcium ionophore such as, for example, ionomycin or A23187.

"Syk Kinsase" refers to the well-known 72kDa non-receptor (cytoplasmic) spleen protein tyrosine kinase expressed in B-cells and other hematopoetic cells. Syk kinase includes two consensus Src-homology 2 (SH2) domains in tandem that bind to phosphorylated immunoreceptor tyrosine-based activation motifs ("ITAMs"), a "linker" domain and a catalytic domain (for a review of the structure and function of Syk kinase see Sada *et al.*, 2001, J. Biochem. (Tokyo) 130:177-186); see also Turner *et al.*, 2000, Immunology Today 21:148-154). Syk kinase has been extensively studied as an effector of B-cell receptor (BCR) signaling (Turner *et al.*, 2000, *supra*). Syk kinase is also critical for tyrosine phosphorylation of multiple proteins which regulate important pathways leading from immunoreceptors, such as Ca^{2+} mobilization and mitogen-activated protein kinase (MAPK) cascades (see, e.g., FIG. 2) and degranulation. Syk kinase also plays a critical role in integrin signaling in neutrophils (*see, e.g.,* Mocsai *et al.* 2002, Immunity 16:547-558).

As used herein, Syk kinase includes kinases from any species of animal, including but not limited to, homosapiens, simian, bovine, porcine, rodent, etc., recognized as belonging to the Syk family. Specifically included are isoforms, splice variants, allelic variants, mutants, both naturally occuring and man-made. The amino acid sequences of such Syk kinases are well known and available from GENBANK. Specific examples of mRNAs encoding different isoforms of human Syk kinase can be found at GENBANK

accession no. gi|21361552|ref|NM__003177.2|, gi|496899|emb|Z29630.1|HSSYKPTK[496899] and gi|15030258|gb|BC011399.1|BC011399[15030258], which are incorporated herein by reference.

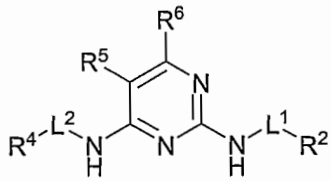
Skilled artisans will appreciate that tyrosine kinases belonging to other families may have active sites or binding pockets that are similar in three-dimensional structure to that of Syk. As a consequence of this structural similarity, such kinases, referred to herein as "Syk mimics," are expected to catalyze phosphorylation of substrates phosphorylated by Syk. Thus, it will be appreciated that such Syk mimics, signal transduction cascades in which such Syk mimics play a role and biological responses effected by such Syk mimics and Syk mimic-dependent signaling cascades may be regulated, and in particular inhibited, with the 2,4-pyrimidinediamine compounds described herein.

"Syk-Dependent Signaling Cascade" refers to a signal transduction cascade in which Syk kinase plays a role. Non-limiting examples of such Syk-dependent signaling cascades include the FcαRI, FcεRI, FcγRI, FcγRIII, BCR and integrin signaling cascades.

"Autoimmune Disease" refers to those diseases which are commonly associated with the nonanaphylactic hypersensitivity reactions (Type II, Type III and/or Type IV hypersensitivity reactions) that generally result as a consequence of the subject's own humoral and/or cell-mediated immune response to one or more immunogenic substances of endogenous and/or exogenous origin. Such autoimmune diseases are distinguished from diseases associated with the anaphylactic (Type I or IgE-mediated) hypersensitivity reactions.

6.2 The 2,4-Pyrimidinediamine Compounds

The compounds of the invention are generally 2,4-pyrimidinediamine compounds according to structural formula (I):



including salts, hydrates, solvates and N-oxides thereof, wherein:

L^1 and L^2 are each, independently of one another, selected from the group consisting of a direct bond and a linker;

R^2 is selected from the group consisting of (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^4 is selected from the group consisting of hydrogen, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^5 is selected from the group consisting of R^6, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C1-C4) alkanyl optionally substituted with one or more of the same or different R^8 groups, (C2-C4) alkenyl optionally substituted with one or more of the same or different R^8 groups and (C2-C4) alkynyl optionally substituted with one or more of the same or different R^8 groups;

each R^6 is independently selected from the group consisting of hydrogen, an electronegative group, $-OR^d$, $-SR^d$, (C1-C3) haloalkyloxy, (C1-C3) perhaloalkyloxy, $-NR^cR^c$, halogen, (C1-C3) haloalkyl,(C1-C3) perhaloalkyl, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)NR^cR^c$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-OC(O)R^d$, $-SC(O)R^d$, $-OC(O)OR^d$, $-SC(O)OR^d$, $-OC(O)NR^cR^c$, $-SC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-SC(NH)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$ and $-[NHC(NH)]_nNR^cR^c$, (C5-C10) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups, (C6-C16) arylalkyl optionally substituted with one or more of the same or different R^8 groups, 5-10 membered

heteroaryl optionally substituted with one or more of the same or different R^8 groups and 6-16 membered heteroarylalkyl optionally substituted with one or more of the same or different R^8 groups;

R^8 is selected from the group consisting of R^a, R^b, R^a substituted with one or more of the same or different R^a or R^b, $-OR^a$ substituted with one or more of the same or different R^a or R^b, $-B(OR^a)_2$, $-B(NR^cR^c)_2$, $-(CH_2)_m-R^b$, $-(CHR^a)_m-R^b$, $-O-(CH_2)_m-R^b$, $-S-(CH_2)_m-R^b$, $-O-CHR^aR^b$, $-O-CR^a(R^b)_2$, $-O-(CHR^a)_m-R^b$, $-O-(CH_2)_m-CH[(CH_2)_mR^b]R^b$, $-S-(CHR^a)_m-R^b$, $-C(O)NH-(CH_2)_m-R^b$, $-C(O)NH-(CHR^a)_m-R^b$, $-O-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-S-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-O-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-S-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-NH-(CH_2)_m-R^b$, $-NH-(CHR^a)_m-R^b$, $-NH[(CH_2)_mR^b]$, $-N[(CH_2)_mR^b]_2$, $-NH-C(O)-NH-(CH_2)_m-R^b$, $-NH-C(O)-(CH_2)_m-CHR^bR^b$ and $-NH-(CH_2)_m-C(O)-NH-(CH_2)_m-R^b$;

each R^a is independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C3-C8) cycloalkyl, cyclohexyl, (C4-C11) cycloalkylalkyl, (C5-C10) aryl, phenyl, (C6-C16) arylalkyl, benzyl, 2-6 membered heteroalkyl, 3-8 membered cycloheteroalkyl, morpholinyl, piperazinyl, homopiperazinyl, piperidinyl, 4-11 membered cycloheteroalkylalkyl, 5-10 membered heteroaryl and 6-16 membered heteroarylalkyl;

each R^b is a suitable group independently selected from the group consisting of =O, $-OR^d$, (C1-C3) haloalkyloxy, $-OCF_3$, =S, $-SR^d$, $=NR^d$, $=NOR^d$, $-NR^cR^c$, halogen, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-C(NR^a)NR^cR^c$, $-C(NOH)R^a$, $-C(NOH)NR^cR^c$, $-OC(O)R^d$, $-OC(O)OR^d$, $-OC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-OC(NR^a)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NR^aC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NR^aC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$, $-[NR^aC(O)]_nNR^cR^c$, $-[NHC(NH)]_nNR^cR^c$ and $-[NR^aC(NR^a)]_nNR^cR^c$;

each R^c is independently R^a, or, alternatively, each R^c is taken together with the nitrogen atom to which it is bonded to form a 5 to 8-membered cycloheteroalkyl or heteroaryl which may optionally include one or more of the same or different additional heteroatoms and which is optionally substituted with one or more of the same or different R^a or suitable R^b groups;

each R^d is independently R^a;

each *m* is independently an integer from 1 to 3; and

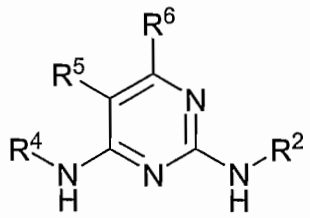
each *n* is independently an integer from 0 to 3.

In the compounds of structural formula (I), L^1 and L^2 represent, independently of one another, a direct bond or a linker. Thus, as will be appreciated by skilled artisans, the substituents R^2 and/or R^4 may be bonded either directly to their respective nitrogen atoms or, alternatively, spaced away from their respective nitrogen atoms by way of a linker. The identity of the linker is not critical and typical suitable linkers include, but are not limited to, (C1-C6) alkyldiyls, (C1-C6) alkanos and (C1-C6) heteroalkyldiyls, each of which may be optionally substituted with one or more of the same or different R^8 groups, where R^8 is as previously defined for structural formula (I). In a specific embodiment, L^1 and L^2 are each, independently of one another, selected from the group consisting of a direct bond, (C1-C3) alkyldiyl optionally substituted with one or more of the same or different R^a, suitable R^b or R^9 groups and 1-3 membered heteroalkyldiyl optionally substituted with one or more of the same or different R^a, suitable R^b or R^9 groups, wherein R^9 is selected from the group consisting of (C1-C3) alkyl, $-OR^a$, $-C(O)OR^a$, (C5-C10) aryl optionally substituted with one or more of the same or different halogens, phenyl optionally substituted with one or more of the same or different halogens, 5-10 membered heteroaryl optionally substituted with one or more of the same or different halogens and 6 membered heteroaryl optionally substituted with one or more of the same or different halogens; and R^a and R^b are as previously defined for structural formula (I). Specific R^9 groups that may be used to substitute L^1 and L^2 include $-OR^a$, $-C(O)OR^a$, phenyl, halophenyl and 4-halophenyl, wherein R^a is as previously defined for structural formula (I).

In another specific embodiment, L^1 and L^2 are each, independently of one another, selected from the group consisting of methano, ethano and propano, each of which may be optionally monosubstituted with an R^9 group, where R^9 is as previously defined above.

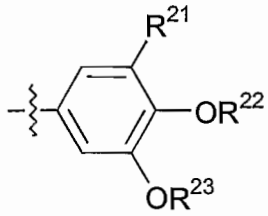
In all of the above embodiments, specific R^a groups that may be included in R^9 groups are selected from the group consisting of hydrogen, (C1-C6) alkyl, phenyl and benzyl.

In still another specific embodiment, L^1 and L^2 are each a direct bond such that the 2,4-pyrimidinediamine compounds of the invention are compounds according to structural formula (Ia):



including salts, hydrates, solvates and N-oxides thereof, wherein R^2, R^4, R^5 and R^6 are as previously defined for structural formula (I). Additional specific embodiments of the 2,4-pyrimidinediamine compounds of the invention are described below.

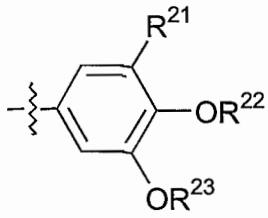
In a first embodiment of the compounds of structural formulae (I) and (Ia), R^2, R^4, R^5, R^6, L^1 and L^2 are as previously defined for their respective structures (I) and (Ia), with the proviso that R^2 is not 3,4,5-trimethoxyphenyl, 3,4,5-tri (C1-C6) alkoxyphenyl or



where R^{21}, R^{22} and R^{23} are as defined for R^1, R^2 and R^3, respectively of U.S. Patent No. 6,235,746, the disclosure of which is incorporated by reference. In a specific embodiment of this first embodiment, R^{21} is hydrogen, halo, straight-chain or branched (C1-C6) alkyl optionally substituted with one or more of the same or different R^{25} groups, hydroxyl, (C1-C6) alkoxy optionally substituted with one or more of the same or different phenyl or R^{25} groups, thiol (-SH), (C1-C6) alkylthio optionally substituted with one or more of the same or different phenyl or R^{25} groups, amino ($-NH_2$), $-NHR^{26}$ or $-NR^{26}R^{26}$; R^{22} and R^{23} are each, independently of one another, a (C1-C6) straight-chain or branched alkyl optionally substituted with one or more of the same or different R^{25} groups; R^{25} is selected from the group consisting of halo, hydroxyl, (C1-C6) alkoxy, thiol, (C1-C6) alkylthio, (C1-C6) alkylamino and (C1-C6) dialkylamino; and each R^{26} is independently a (C1-C6) alkyl optionally substituted with one or more of the same or different phenyl or R^{25} groups or a $-C(O)R^{27}$, where R^{27} is a (C1-C6) alkyl optionally substituted with one or more of the same or different phenyl or R^{25} groups.

In another specific embodiment of this first embodiment, R^{21} is methoxy optionally substituted with one or more of the same or different halo groups and/or R^{22} and R^{23} are each, independently of one another, a methyl or ethyl optionally substituted with one or more of the same or different halo groups.

In a second embodiment of the compounds of structural formulae (I) and (Ia), R^2, R^4, R^5 and L^2 are as previously described for their respective structures (I) and (Ia), L^1 is a direct bond and R^6 is hydrogen, with the proviso that R^2 is not 3,4,5-trimethoxyphenyl, 3,4,5-tri (C1-C6) alkoxyphenyl or



where R^{21}, R^{22} and R^{23} are as defined above, in connection with the first embodiment.

In a third embodiment, the 2,4-pyrimidinediamine compounds of structural formulae (I) and (Ia) exclude one or more of the following compounds:

N2,N4-bis(4-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R070790);

N2,N4-bis(2-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R081166);

N2,N4-bis(4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R088814);

N2,N4-bis(2-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R088815);

N2,N4-bisphenyl-5-fluoro-2,4-pyrimidinediamine (R091880);

N2,N4-bis(3-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R092788);

N2,N4-bis(3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R067962);

N2,N4-bis(2,5-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067963);

N2,N4-bis(3,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067964);

N2,N4-bis(4-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R0707153);

N2,N4-bis(2,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R070791);

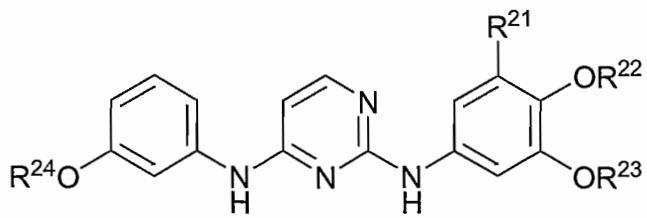
N2,N4-bis(3-bromophenyl)-5-fluoro-2,4-pyrimidinediamine (R008958);

N2,N4-bis(phenyl)-5-fluoro-2,4-pyrimidinediamine;

N2,N4-bis(morpholino)-5-fluoro-2,4-pyrimidinediamine; and

N2,N4-bis[(3-chloro-4-methoxyphenyl)]-5-fluoro-2,4-pyrimidinediamine.

In a fourth embodiment, the compounds of structural formulae (I) and (Ia) exclude compounds according to the following structural formula (Ib):



wherein R^{24} is (C1-C6) alkyl; and R^{21}, R^{22} and R^{23} are as previously defined in connection with the first embodiment.

In a fifth embodiment, the compounds of structural formulae (I) and (Ia) exclude the compounds described in Examples 1-141 of U.S. Patent No. 6,235,746, the disclosure of which is incorporated herein by reference.

In a sixth embodiment, the compounds of structural formulae (I) and (Ia) exclude compounds defined by formula (1) or formula 1(a) of this U.S. Patent No. 6,235,746 (see, e.g., the disclosure at Col. 1, line 48 through Col. 7, line 49 and Col. 8, lines 9-36, which is incorporated by reference).

In a seventh embodiment, the compounds of structural formulae (I) and (Ia) exclude compounds in which R^5 is cyano or –C(O)NHR, where R is hydrogen or (C1-C6) alkyl, when R^2 is a substituted phenyl; R4 is a substituted or unsubstituted (C1-C6) alkyl, (C_3-C_8) cycloalkyl, 3-8 membered cycloheteralkyl or 5-15 membered heteroaryl; and R^6 is hydrogen.

In an eighth embodiment, the compounds of structural formulae (I) and (Ia) exclude the compounds defined by formulae (I) and (X) of WO 02/04429 or any compound disclosed in WO 02/04429, the disclosure of which is incorporated herein by reference.

In a ninth embodiment of the compounds of structural formulae (I) and (Ia), when R^5 is cyano or –C(O)NHR, where R is hydrogen or (C1-C6) alkyl; and R^6 is hydrogen, then R^2 is other than a substituted phenyl group.

In a tenth embodiment, the compounds of structural formulae (I) and (Ia) exclude compounds in which R^2 and R^4 are each independently a substituted or unsubstituted pyrrole or indole ring which is attached to the remainder of the molecule *via* its ring nitrogen atom.

In an eleventh embodiment, the compounds of structural formulae (I) and (Ia) exclude compounds defined by formulae (I) and (IV) of U.S. Patent No. 4,983,608 or any compound disclosed in U.S. Patent No. 4,983,608, the disclosure of which is incorporated herein by reference.

Those of skill in the art will appreciate that in the compounds of formulae (I) and (Ia), R^2 and R^4 may be the same or different, and may vary broadly. When R^2 and/or R^4 are optionally substituted rings, such as optionally substituted cycloalkyls, cycloheteroalkyls, aryls and heteroaryls, the ring may be attached to the remainder of the molecule through any available carbon or heteroatom. The optional substituents may be attached to any available carbon atoms and/or heteroatoms.

In a twelfth embodiment of the compounds of structural formulae (I) and (Ia), R^2 and/or R^4 is an optionally substituted phenyl or an optionally substituted (C5-C15) aryl, subject to the provisos that (1) when R^6 is hydrogen, then R^2 is not 3,4,5-trimethoxyphenyl or 3,4,5-tri (C1-C6) alkoxyphenyl; (2) when R^2 is a 3,4,5-trisubstituted phenyl, then the substituents at the 3- and 4-positions are not simultaneously methoxy or (C1-C6) alkoxy; or (3) when R^6 is hydrogen and R^4 is (C1-C6) alkyl, (C_3-C_8) cycloalkyl, 3-8 membered cycloheteroalkyl or 5-15 membered heteroaryl, then R^5 is other than cyano. Alternatively, R^2 is subject to the provisos described in connection with the first or second embodiments. The optionally substituted aryl or phenyl group may be attached to the remainder of the molecule through any available carbon atom. Specific examples of optionally substituted phenyls include phenyls that are optionally mono-, di- or tri-substituted with the same or different R^8 groups, where R^8 is as previously defined for structural formula (I) and subject to the above provisos. When the phenyl is mono-substituted, the R^8 substituent may be positioned at either the *ortho, meta* or *para* position. When positioned at the *ortho, meta* or *para* position, R^8 is preferably selected from the group consisting of (C1-C10) alkyl, (C1-C10) branched alkyl, $-OR^a$ optionally substituted with one or more of the same or different R^b groups, $-O-C(O)OR^a$, $-O-(CH_2)_m-C(O)OR^a$, $-C(O)OR^a$, $-O-(CH_2)_m-NR^cR^c$, $-O-C(O)NR^cR^c$, $-O-(CH_2)_m-C(O)NR^cR^c$, $-O-C(NH)NR^cR^c$, $-O-(CH_2)_m-C(NH)NR^cR^c$ and $-NH-(CH_2)_m-NR^cR^c$, where *m*, R^a and R^c are as previously defined for structural formula (I). In one embodiment of these compounds, $-NR^cR^c$ is a 5-6 membered heteroaryl which optionally includes one or more of the same or different additional heteroatoms. Specific examples of such 5-6 membered heteroaryls include, but are not limited to, oxadiazolyl, triazolyl, thiazolyl, oxazolyl, tetrazolyl and isoxazolyl.

In another embodiment of these compounds, $-NR^cR^c$ is a 5-6 membered saturated cycloheteroalkyl ring which optionally includes one or more of the same or different heteroatoms. Specific examples of such cycloheteroalkyls include, but are not limited to, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl and morpholinyl.

In still another embodiment of these compounds, each R^a is independently a (C1-C6) alkyl and/or each $-NR^cR^c$ is $-NHR^a$, where R^a is a (C1-C6) alkyl. In one specific embodiment, R^8 is $-O-CH_2-C(O)NHCH_3$. In another specific embodiment R^8 is –OH.

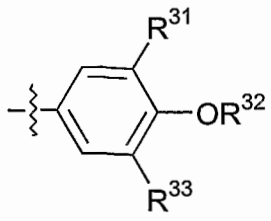
When the phenyl is di-substituted or tri-substituted, the R^8 substituents may be positioned at any combination of positions. For example, the R^8 substituents may be positioned at the 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, 3,5-, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, 2,5,6- or

3,4,5-positions. In one embodiment of compounds including a disubstituted phenyl, the substituents are positioned other than 3,4. In another embodiment they are positioned 3,4. In one embodiment of compounds including a trisubstituted phenyl, the substituents are positioned other than 3,4,5 or, alternatively, no two of the substituents are positioned 3,4. In another embodiment, the substituents are positioned 3,4,5.

Specific examples of R^8 substituents in such di- and trisubstituted phenyls include the various R^8 substituents described above in connection with the *ortho, meta* and *para* substituted phenyls.

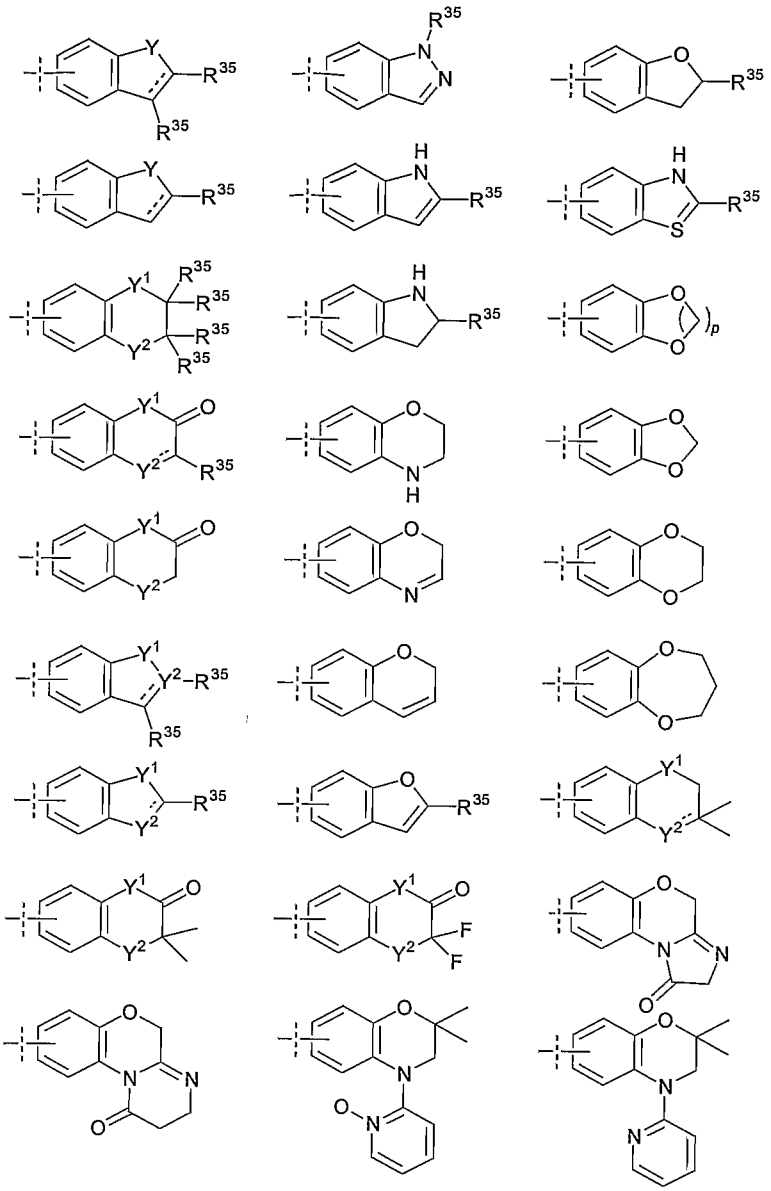
In another specific embodiment, R^8 substituents useful for substitituting such di-and trisubstituted phenyls include (C1-C6) alkyl, (C1-C6) alkoxy, methoxy, halo, chloro, (C1-C6) perhaloalkyl, $-CF_3$, (C1-C6) perhaloalkoxy and $-OCF_3$. In a preferred embodiment, such R^8 substituents are positioned 3,4 or 3,5. Specific examples of preferred di-substituted phenyl rings include 3-chloro-4-methoxy-phenyl, 3-methoxy-4-chlorophenyl, 3-chloro-4-trifluoromethoxy-phenyl, 3-trifluoromethoxy-4-chloro-phenyl, 3,4-dichloro-phenyl, 3,4-dimethoxyphenyl and 3,5-dimethoxyphenyl, with the provisos that: (1) when R^4 is one of the above-identified phenyls, and R^5 and R^6 are each hydrogen, then R^2 is not 3,4,5-tri(C1-C6)alkoxyphenyl or 3,4,5-trimethoxyphenyl; (2) when R^2 is 3,4-dimethoxyphenyl and R^5 and R^6 are each hydrogen, then R4 is not 3-(C1-C6)alkoxyphenyl, 3-methoxyphenyl, 3,4-di-(C1-C6) alkoxyphenyl or 3,4-dimethoxyphenyl; (3) when R^4 is 3-chloro-4-methoxyphenyl and R^5 is halo or fluoro, and optionally R^6 is hydrogen, then R^2 is not 3-chloro-4-(C1-C6)alkoxyphenyl or 3-chloro-4-methoxyphenyl; (4) when R^4 is 3,4-dichlorophenyl, R^5 is hydrogen, (C1-C6) alkyl, methyl, halo or chloro and optionally R^6 is hydrogen, then R^2 is not a phenyl mono substituted at the *para* position with a (C1-C6) alkoxy group which is optionally substituted with one or more of the same or different R^b, -OH or $-NR^cR^c$ groups, where R^b and R^c are as previously described for structural formula (I); and/or (5) R^2 and/or R^4 is not 3,4,5-tri(C1-C6)alkoxyphenyl or 3,4,5-trimethoxyphenyl, especially when R^5 and R^6 are each hydrogen..

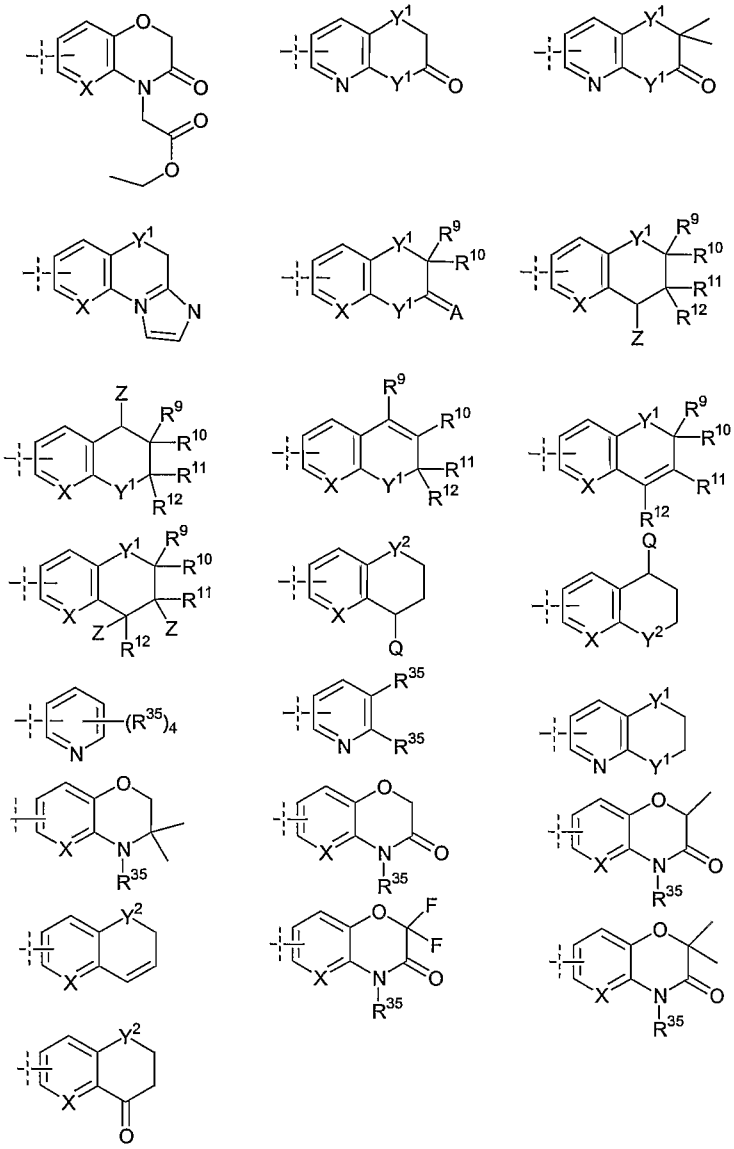
In another embodiment of compounds including a trisubstituted phenyl, the trisubstituted phenyl has the formula:

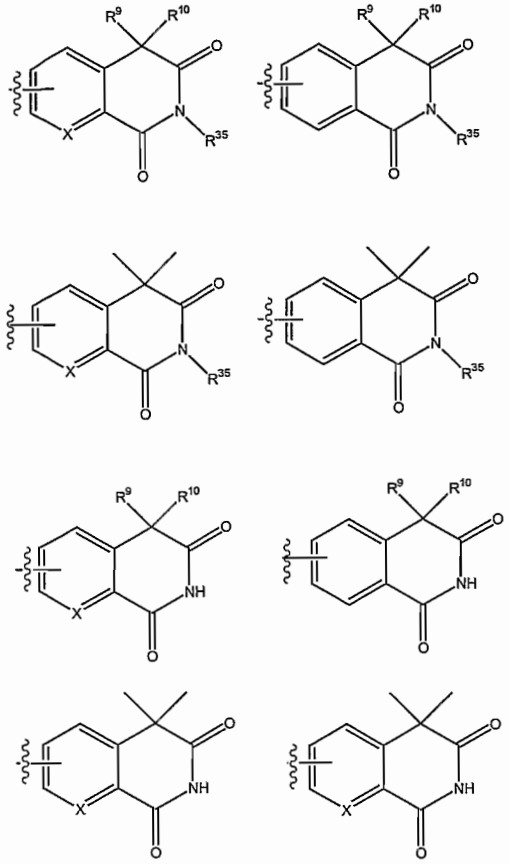


wherein: R^{31} is methyl or (C1-C6) alkyl; R^{32} is hydrogen, methyl or (C1-C6) alkyl; and R^{33} is a halo group.

In a thirteenth embodiment of the compounds of structural formulae (I) and (Ia), R^2 and/or R^4 is an optionally substituted heteroaryl. Typical heteroaryl groups according to this thirteenth embodiment comprise from 5 to 15, and more typically from 5 to 11 ring atoms, and include one, two, three or four of the same or different heteratoms or heteroatomic groups selected from the group consisting of N, NH, O, S, S(O) and $S(O)_2$. The optionally substituted heteroaryl may be attached to its respective C2 or C4 nitrogen atom or linker L^1 or L^2 through any available carbon atom or heteroatom, but is typically attached *via* a carbon atom. The optional substituents may be the same or different, and may be attached to any available carbon atom or heteroatom. In one embodiment of these compounds, R^5 is other than bromo, nitro, trifluoromethyl, cyano or –C(O)NHR, where R is hydrogen or (C1-C6) alkyl. In another embodiment of these compounds, when R^2 and R^4 are each a substituted or unsubstituted pyrrole or indole, then the ring is attached to the remainder of the molecule *via* a ring carbon atom. In still another embodiment of compounds including an optionally substituted heteroaryl group, the heteroaryl is unsubstituted or substituted with from one to four of the same or different R^8 groups, where R^8 is as previously defined for structural formula (I). Specific examples of such optionally substituted heteroaryls include, but are not limited to, the following heteroaryl groups:







wherein:

p is an integer from one to three;

each - - - independently represents a single bond or a double bond;

R^{35} is hydrogen or R^8, where R^8 is as previously defined for structural formula (I);

X is selected from the group consisting of CH, N and N-O;

each Y is independently selected from the group consisting of O, S and NH;

each Y^1 is independently selected from the group consisting of O, S, SO, SO_2, $SONR^{36}$, NH and NR^{37};

each Y^2 is independently selected from the group consisting of CH, CH_2, O, S, N, NH and NR^{37};

R^{36} is hydrogen or alkyl;

R^{37} is selected from the group consisting of hydrogen and a progroup, preferably hydrogen or a progroup selected from the group consisting of aryl, arylalkyl, heteroaryl, R^a, R^b–CR^aR^b-O-C(O)R^8, -CR^aR^b-O-$PO(OR^8)_2$, -CH_2-O-$PO(OR^8)_2$,

$-CH_2-PO(OR^8)_2$, $-C(O)-CR^aR^b-N(CH_3)_2$, $-CR^aR^b-O-C(O)-CR^aR^b-N(CH_3)_2$, $-C(O)R^8$, $-C(O)CF_3$ and $-C(O)-NR^8-C(O)R^8$;

A is selected from the group consisting of O, NH and NR^{38};

R^{38} is selected from the group consisting of alkyl and aryl;

R^9, R^{10}, R^{11} and R^{12} are each, independently of one another, selected from the group consisting of alkyl, alkoxy, halogen, haloalkoxy, aminoalkyl and hydroxyalkyl, or, alternatively, $R^9$and R^{10} and/or R^{11} and R^{12} are taken together form a ketal;

each Z is selected from the group consisting of hydroxyl, alkoxy, aryloxy, ester, carbamate and sulfonyl;

Q is selected from the group consisting of -OH, OR^8, $-NR^cR^c$, $-NHR^{39}-C(O)R^8$, $-NHR^{39}-C(O)OR^8$, $-NR^{39}-CHR^{40}-R^b$, $-NR^{39}-(CH_2)_m-R^b$ and $-NR^{39}-C(O)-CHR^{40}-NR^cR^c$;

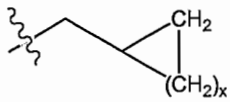
R^{39} and R^{40} are each, independently of one another, selected from the group consisting of hydrogen, alkyl, aryl, alkylaryl;arylalkyl and NHR^8; and

R^a, R^b and R^c are as previously defined for structural formula (I). Preferred R^b substitutents for Q are selected from $-C(O)OR^8$, $-O-C(O)R^8$, $-O-P(O)(OR^8)_2$ and $-P(O)(OR^8)_2$.

In one embodiment of the above-depicted heteroaryls, as well as other 5-15 membered heteroaryls according to this embodiment of the invention, each R^8 is independently selected from the group consisting of R^d, $-NR^cR^c$, $-(CH_2)_m-NR^cR^c$, $-C(O)NR^cR^c$, $-(CH_2)_m-C(O)NR^cR^c$, $-C(O)OR^d$, $-(CH_2)_m-C(O)OR^d$ and $-(CH_2)_m-OR^d$, where m, R^c and R^d are as previously defined for structural formula (I).

In a specific embodiment, R^d and/or R^c is selected from the group consisting of R^a and (C3-C8) cycloalkyl optionally substituted with one or more of the same or different hydroxyl, amino or carboxyl groups.

In another embodiment of the above-depicted heteroaryls, each R^{35} is a hydrogen atom, a (C1-C6) carbon chain, including methyl, ethyl, isopropyl, a cycloalkyl group, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, a



, wherein x = 1-8, $-CH_2CONHMe$, $-CH_2CH_2NHMe$, $-CH_2CH_2CONHMe$, $-CH_2CH_2CH_2NHMe$ or $-CH_2CH_2CH_2OCH_3$.

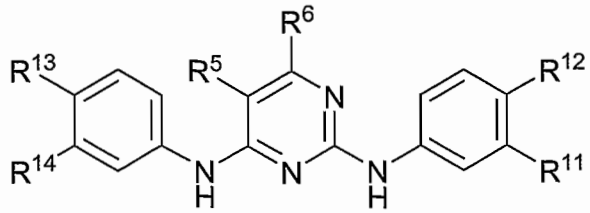
In still another embodiment of the above-depicted heteroaryls, the aromatic ring connectivity is either at the 5 or 6 position. It should be understood that either R^2 or R^4 can utilize the heteroaryl groups discussed throughout this specification.

In a fourteenth embodiment of the compounds of structural formulae (I) and (Ia), R^2 and R^4 are each, independently of one another, an optionally substituted phenyl, aryl or heteroaryl, with the provisos that: (1) when L^1 is a direct bond and R^6 and optionally R^5 is hydrogen, then R^2 is other than 3,4,5-trimethoxyphenyl or 3,4,5-tri(C1-C6) alkoxyphenyl; (2) when L^1 and L^2 are each a direct bond, R^6 is hydrogen and R^5 is halo, then R^2 and R^4 are not each simultaneously 3,4,5-trimethoxyphenyl or 3,4,5-tri(C1-C6) alkoxyphenyl; (3) when R^4 is 3-methoxyphenyl or 3-(C1-C6) alkoxyphenyl and R^2 is a 3,4,5-trisubstituted phenyl, the substituents positioned at the 3 and 4 positions are not both simultaneously methoxy or (C1-C6) alkoxy; (4) when R^2 is a substituted phenyl and R^6 is hydrogen, then R^5 is other than cyano or –C(O)NHR, where R is hydrogen or (C1-C6) alkyl; and/or (5) when R^2 and R^4 are each independently a substituted or unsubstituted pyrrole or indole, then the pyrrole or indole is attached to the remainder of the molecule *via* a ring carbon atom. Alternatively, R^2 is subject to the provisos described in connection with the first or second embodiment.

In this fourteenth embodiment of the invention, the R^2 and R^4 substituents may be the same or different. Specific optionally substituted phenyl, aryl and/or heteroaryls include those illustrated above in connection with the twelfth and thirteenth embodiments.

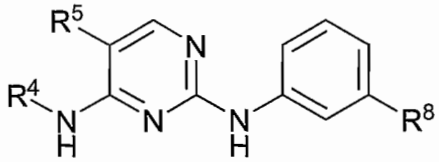
In a fifteenth embodiment of the compounds of structural formulae (I) and (Ia), including the above-described first through fourteenth embodiments thereof, R^6 is hydrogen and R^5 is an electronegative group. As will be recognized by skilled artisans, electronegative groups are atoms or groups of atoms that have a relatively great tendency to attract electrons to themselves. Specific examples of electronegative groups according to this fourteenth embodiment include, but are not limited to, -CN, -NC, $-NO_2$, halo, bromo, chloro, fluoro, (C1-C3) haloalkyl, (C1-C3) perhaloalkyl, (C1-C3) fluoroalkyl, (C1-C3) perfluoroalkyl, $-CF_3$, (C1-C3) haloalkoxy, (C1-C3) perhaloalkoxy, (C1-C3) fluoroalkoxy, (C1-C3) perfluoroalkoxy, $-OCF_3$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)CF_3$ and $-C(O)OCF_3$. In a specific embodiment, the electronegative group is a halogen-containing electronegative group, such as $–OCF_3$, $–CF_3$, bromo, chloro or fluoro. In another specific embodiment, R^5 is fluoro, subject to the proviso that the the compound is not any compound according to the third embodiment.

In a sixteenth embodiment, the compounds of structural formulae (I) and (Ia) are compounds according to structural formula (Ib):



and salts, hydrates, solvates and N-oxides thereof, wherein R^{11}, R^{12}, R^{13} and R^{14} are each, independently of one another, selected from the group consisting of hydrogen, hydroxy, (C1-C6) alkoxy and $-NR^cR^c$; and R^5, R^6 and R^c are as previously defined for structural formula (I), with the proviso that when R^{13}, R^5 and R^6 are each hydrogen, then R^{11} and R^{12} are not simultaneously methoxy, (C1-C6) alkoxy or (C1-C6) haloalkoxy

In a seventeenth embodiment, the compounds of structural formulae (I) and (Ia) are compounds according to structural formula (Ic):



and salts, hydrates, solvates and N-oxides thereof, wherein:

R^4 is selected from the group consisting of 5-10 membered heteroaryl and 3-hydroxyphenyl;

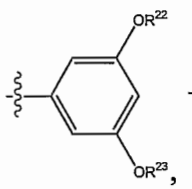
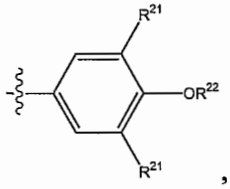
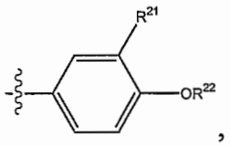
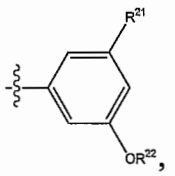
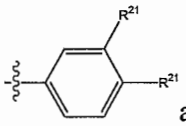
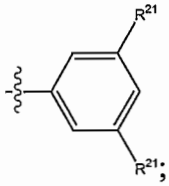
R^5 is F or $-CF_3$; and

R^8 is $-O(CH_2)_m-R^b$, where *m* and R^b are as previously defined for structural formula (I). In a specific embodiment, R^8 is $-O-CH_2-C(O)NH-CH_3$ and/or R^4 is a heteroaryl according to the thirteenth embodiment.

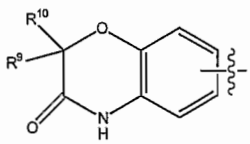
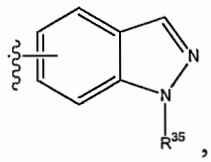
In an eighteenth embodiment, the compounds of structural formulae (I) and (Ia) include any compound selected from TABLE 1 that inhibits an Fc receptor signal transduction cascade, a Syk kinase activity, a Syk-kinase dependent receptor signal transduction cascade orcell degranulation as measured in an *in vitro* assay, optionally subject to the proviso that the compound is not a compound excluded by the above-described third embodiment and/or other embodiments. In a specific embodiment, such

compounds have an IC_{50} of about 20 μM or less as measured in an *in vitro* degranulation assay, such as one of the degranulation assays described in the Examples section.

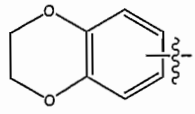
In a nineteenth embodiment, the compounds of structural formulae (I) and (Ia) include any compound selected from TABLE 1 that inhibits the FcγR1 or FcεR1 receptor cascade with an IC_{50} of about 20 μM or less as measured in an *in vitro* assay, such as one of the *in vitro* assays provided in the Examples section, optionally subject to the proviso that the compound is not a compound excluded by the above-described third embodiment and/or other embodiments.

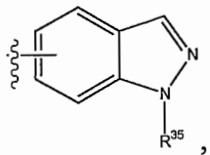
In a twentieth embodiment, the compounds of structural formulae (Ia) are those wherein R^2 is selected from the group consisting of , , , ,  and ;

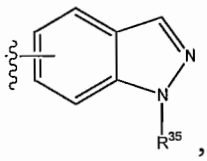
R^4, R^8, R^a, R^b, R^c, R^d are as described above, R^5 is a fluorine atom; R^6 is a hydrogen atom and each R^{21} is independently a halogen atoms or an alkyl optionally substituted with one or more of the same or different halo groups, R^{22} and R^{23} are each, independently of one another, a hydrogen atom, methyl or ethyl optionally substituted with one or more of the same or different halo groups, each *m* is independently an integer from 1 to 3, and each *n* is independently an integer from 0 to 3.

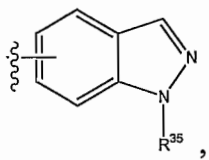
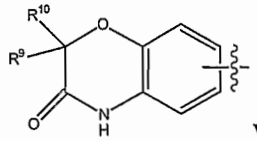
In a twenty first embodiment, the compounds of structural formulae (Ia) are those wherein R^4 is , wherein R^9 and R^{10} are as defined above and further include, each independently a hydrogen atom, and R^2 is a phenyl group, substituted with one or more of the same R^8 groups, or , wherein R^{35} is as defined above. In one particular aspect, when R^2 is a phenyl group, one or more of R^8 is selected from a

halogen and an alkoxy group. In one aspect, the phenyl group is di or tri substituted with one or more of the same R^8 groups.

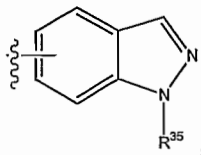
In a twenty second embodiment, the compounds of structural formulae (Ia) are those wherein R^4 is  and R^2 is a phenyl group, substituted with one or more of the same R^8 groups. In one particular aspect, one or more of R^8 is selected from a halogen and an alkoxy group. In one aspect, the phenyl group is di or tri substituted with one or more of the same R^8 groups.

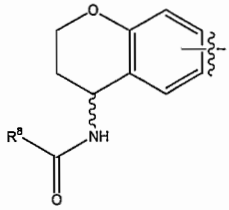
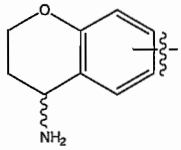
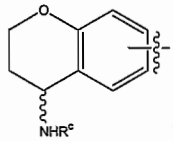
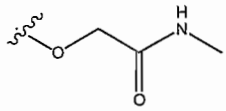
In a twenty third embodiment, the compounds of structural formulae (Ia) are those wherein R^4 is a phenyl group substituted with one or more of the same R^8 groups, wherein R^2 is , wherein R^{35} is as defined above. In particular embodiments, the R^4 phenyl group is di or tri substituted with the the same or different halgoen atoms. In another embodiment, R^4 is a monosubstituted phenyl group with a halogen atom. In one aspect, R^{35} is a hydroxyalkyl group. In certain aspects, the hydroxyalkyl group can be further functionalized into an ester group, carbamate, etc.

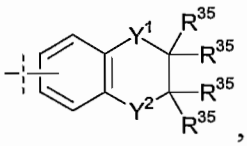
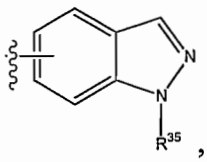
In a twenty fourth embodiment, the compounds of structural formulae (Ia) are those wherein R^4 is , wherein R^{35} is as defined above and R^2 is a phenyl group substituted with one or more of the same R^8 groups. In one particular aspect, R^{35} is a hydrogen atom or an alkyl group. In another aspect, the R^2 phenyl group is di or tri substituted with the same or different R^8 groups, and in particular, halogen atoms.

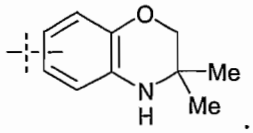
In a twenty fifth embodiment, the compounds of structural formulae (Ia) are those wherein R^4 is , wherein R^{35} is as defined above and R^2 is  wherein R^9 and R^{10} are defined as above and further include, each

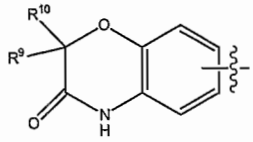
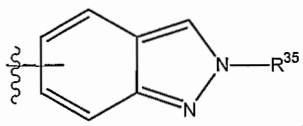
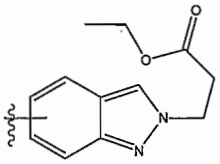
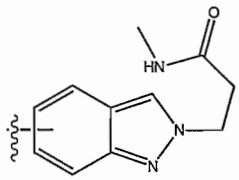
independently a hydrogen atom. In one aspect, R^{35} is a hydrogen atom or an alkyl group, e.g., methyl and R^9 and R^{10} are alkyl groups, e.g., methyl groups.

In a twenty sixth embodiment, the compounds of structural formulae (Ia) are those wherein R^4 is a disubstituted phenyl group, substituted with the same or different R^8 groups and R^2 is , wherein R^{35} is as defined above. In certain aspects, the phenyl group is substituted with a halogen atom and an alkyoxy group, e.g. a methoxy group. In certain embodiments, R^{35} is a hydrogen atom, an alkyl group, e.g., a methyl group, or a hydroxyalkyl group. In certain aspects, the hydroxyalkyl group can be further functionalized into an ester group, carbamate, etc.

In a twenty seventh embodiment, the compounds of structural formulae (Ia) are those wherein R^4 is ,  or  wherein R^8 and R^c are as defined above and R^2 is a phenyl group that is substituted with one or more of the same R^8 groups. In one particular aspect, R^c is a hydrogen atom or an alkyl group. In another aspect, the R^2 phenyl group is di or tri substituted with the same or different R^8 groups, and in particular, halogen atoms or .

In a twenty eighth embodiment, the compounds of structural formulae (Ia) are those wherein R^4 is , wherein Y^1, Y^2 and each R^{35} independently, are defined as above and R^2 is , wherein R^{35} is as defined above. In one aspect of the twenty eighth embodiment with regard to R^4, Y^1 is oxygen, Y^2 is NH and one or more of R^{35} or the R^4 moiety is an alkyl group, and in particular, a methyl group. In certain aspects of the twenty eighth embodiment, two R^{35}'s of the R^4 moiety form a gem dialkyl moiety, in

particular, a gem dimethyl moiety adjacent to the NH depicted as  . In certain aspects of the twenty eighth embodiment, with regard to R^2, R^{35} is a hydrogen atom or an alkyl group, and in particular, a methyl group.

In a twenty nineth embodiment, the compounds of structural formulae (Ia) are those wherein R^4 is  , wherein R^9 and R^{10} are as defined above or a substituted phenyl group. In one aspect the phenyl group is di or tri substituted with one or more of the same R^8 groups. In particular, the phenyl group can be di or tri substituted with one or more halogen atoms that can be the same or different. R^2 in the twenty nineth embodiment is  , wherein R^{35} is as defined above. In one aspect of the twenty nineth embodiment, R^{35} of R^2 is not a methyl group. In another still another aspect of the twenty nineth embodiment, R^2 is  or  .

In a thirtieth embodiment, applicable to the first through twenty nineth embodiments, R^5 is a halogen atom, such as fluorine, and R^6 is a hydrogen atom.

Also specifically described are combinations of the above first through thirtieth embodiments.

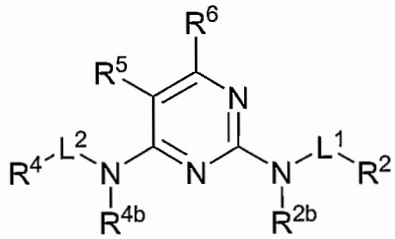
Those of skill in the art will appreciate that the 2,4-pyrimidinediamine compounds described herein may include functional groups that can be masked with progroups to create prodrugs. Such prodrugs are usually, but need not be, pharmacologically inactive until converted into their active drug form. Indeed, many of the active 2,4-pyrimidinediamine compounds described in TABLE 1, *infra*, include promoieties that are hydrolyzable or otherwise cleavable under conditions of use. For example, ester groups commonly undergo acid-catalyzed hydrolysis to yield the parent carboxylic acid when exposed to the acidic conditions of the stomach, or base-catalyzed hydrolysis when exposed to the basic conditions of the intestine or blood. Thus, when administered to a subject orally, 2,4-

pyrimidinediamines that include ester moieties may be considered prodrugs of their corresponding carboxylic acid, regardless of whether the ester form is pharmacologically active. Referring to TABLE 1, numerous ester-containing 2,4-pyrimidinediamines of the invention are active in their ester, "prodrug" form.

In the prodrugs of the invention, any available functional moiety may be masked with a progroup to yield a prodrug. Functional groups within the 2,4-pyrimidinediamine compounds that may be masked with progroups for inclusion in a promoiety include, but are not limited to, amines (primary and secondary), hydroxyls, sulfanyls (thiols), carboxyls, etc. Myriad progroups suitable for masking such functional groups to yield promoieties that are cleavable under the desired conditions of use are known in the art. All of these progroups, alone or in combinations, may be included in the prodrugs of the invention.

In one illustrative embodiment, the prodrugs of the invention are compounds according to structural formula (I) in which R^c and R^d may be, in addition to their previously-defined alternatives, a progroup.

Replacing the hydrogens attached to N2 and N4 in the 2,4-pyrimidinediamines of structural formula (I) with substituents adversely effects the activity of the compounds. However, as will be appreciated by skilled artisans, these nitrogens may be included in promoieties that, under conditions of use, cleave to yield 2,4-pyrimidinediamines according to structural formula (I). Thus, in another embodiment, the prodrugs of the invention are compounds according to structural formula (II):



including salts, hydrates, solvates and N-oxides thereof, wherein:

R^2, R^4, R^5, R^6, L^1 and L^2 are as previously defined for structural formula (I); and

R^{2b} and R^{4b} are each, independently of one another, a progroup. Specific examples of progroups according to this embodiment of the invention include, but are not limited to, (C1-C6) alkyl, $-C(O)CH_3$, $-C(O)NHR^{36}$ and $-S(O)_2R^{36}$, where R^{36} is (C1-C6) alkyl, (C5-C15) aryl and (C3-C8) cycloalkyl.

In the prodrugs of structural formula (II), the various substituents may be as described for the various first through twentieth embodiments previously described for the compounds of structural formulae (I) and (Ia), or combinations of such embodiments.

Those of skill in the art will appreciate that many of the compounds and prodrugs of the invention, as well as the various compound species specifically described and/or illustrated herein, may exhibit the phenomena of tautomerism, conformational isomerism, geometric isomerism and/or optical isomerism. For example, the compounds and prodrugs of the invention may include one or more chiral centers and/or double bonds and as a consequence may exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers and diasteromers and mixtures thereof, such as racemic mixtures. As another example, the compounds and prodrugs of the invention may exist in several tautomeric forms, including the enol form, the keto form and mixtures thereof. As the various compound names, formulae and compound drawings within the specification and claims can represent only one of the possible tautomeric, conformational isomeric, optical isomeric or geometric isomeric forms, it should be understood that the invention encompasses any tautomeric, conformational isomeric, optical isomeric and/or geometric isomeric forms of the compounds or prodrugs having one or more of the utilities described herein, as well as mixtures of these various different isomeric forms. In cases of limited rotation around the 2,4-pryimidinediamine core structure, atrop isomers are also possible and are also specifically included in the compounds of the invention.

Moreover, skilled artisans will appreciate that when lists of alternative substituents include members which, owing to valency requirements or other reasons, cannot be used to substitute a particular group, the list is intended to be read in context to include those members of the list that are suitable for substituting the particular group. For example, skilled artisans will appreciate that while all of the listed alternatives for R^b can be used to substitute an alkyl group, certain of the alternatives, such as =O, cannot be used to substitute a phenyl group. It is to be understood that only possible combinations of substituent-group pairs are intended.

The compounds and/or prodrugs of the invention may be identified by either their chemical structure or their chemical name. When the chemical structure and the chemical name conflict, the chemical structure is determinative of the identity of the specific compound.

Depending upon the nature of the various substituents, the 2,4-pyrimidinediamine compounds and prodrugs of the invention may be in the form of salts. Such salts include salts suitable for pharmaceutical uses ("pharmaceutically-acceptable salts"), salts suitable for veterinary uses, etc. Such salts may be derived from acids or bases, as is well-known in the art.

In one embodiment, the salt is a pharmaceutically acceptable salt. Generally, pharmaceutically acceptable salts are those salts that retain substantially one or more of the desired pharmacological activities of the parent compound and which are suitable for administration to humans. Pharmaceutically acceptable salts include acid addition salts formed with inorganic acids or organic acids. Inorganic acids suitable for forming pharmaceutically acceptable acid addition salts include, by way of example and not limitation, hydrohalide acids (*e.g.,* hydrochloric acid, hydrobromic acid, hydriodic, etc.), sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids suitable for forming pharmaceutically acceptable acid addition salts include, by way of example and not limitation, acetic acid, trifluoroacetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, oxalic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, palmitic acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, alkylsulfonic acids (*e.g.*, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, etc.), arylsulfonic acids (*e.g.*, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, cycloalkylsulfonic acids (*e.g.*, camphorsulfonic acid), 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

Pharmaceutically acceptable salts also include salts formed when an acidic proton present in the parent compound is either replaced by a metal ion (*e.g.*, an alkali metal ion, an alkaline earth metal ion or an aluminum ion), an ammonium ion or coordinates with an organic base (*e.g.*, ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, morpholine, piperidine, dimethylamine, diethylamine, etc.).

The 2,4-pyrimidinediamine compounds and of the invention, as well as the salts thereof, may also be in the form of hydrates, solvates and N-oxides, as are well-known in the art.

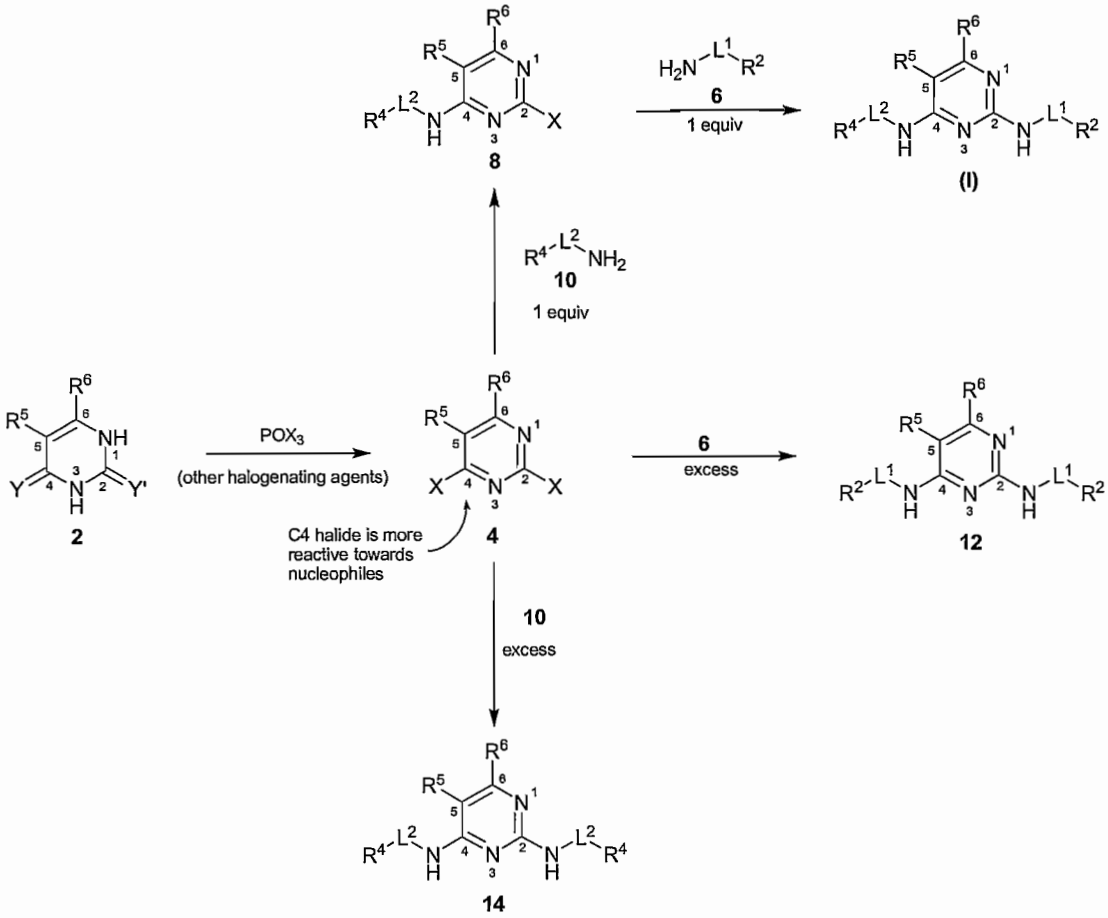
6.3 Methods of Synthesis

The compounds and prodrugs of the invention may be synthesized *via* a variety of different synthetic routes using commercially available starting materials and/or starting materials prepared by conventional synthetic methods. Suitable exemplary methods that may be routinely adapted to synthesize the 2,4-pyrimidinediamine compounds and prodrugs of the invention are found in U.S. Patent No. 5,958,935, the disclosure of which is incorporated herein by reference. Specific examples describing the synthesis of numerous compounds and prodrugs of the invention, as well as intermediates therefor, are provided in the Examples section. All of the compounds of structural formulae (I), (Ia) and (II) may be prepared by routine adaptation of these methods.

A variety of exemplary synthetic routes that can be used to synthesize the 2,4-pyrimidinediamine compounds of the invention are described in Schemes (I)-(XI), below. In Schemes (I)-(XI), like-numbered compounds have similar structures. These methods may be routinely adapted to synthesize the prodrugs according to structural formula (II).

In one exemplary embodiment, the compounds can be synthesized from substituted or unsubstituted uracils or thiouracils as illustrated in Scheme (I), below:

Scheme (I)



In Scheme (I), R^2, R^4, R^5, R^6, L^1 and L^2 are as previously defined for structural formula (I), X is a halogen (*e.g.*, F, Cl, Br or I) and Y and Y' are each, independently of one another, selected from the group consisting of O and S. Referring to Scheme (I), uracil or thiouracil **2** is dihalogenated at the 2- and 4-positions using standard halogenating agent POX_3 (or other standard halogenating agent) under standard conditions to yield 2,4-bishalo pyrimidine **4**. Depending upon the R^5 substituent, in pyrimidine **4**, the halide at the C4 position is more reactive towards nucleophiles than the halide at the C2 position. This differential reactivity can be exploited to synthesize 2,4-pyrimidinediamines according structural formula (I) by first reacting 2,4-bishalopyrimidine **4** with one equivalent of amine **10**, yielding 4N-substituted-2-halo-4-pyrimidineamine **8**, followed by amine **6** to yield a 2,4-pyrimidinediamine according structural formula **(I)**. 2N,4N-bis(substituted)-2,4-

pyrimidinediamines **12** and **14** can be obtained by reacting 2,4-bishalopyrimidine **4** with excess **6** or **10**, respectively.

In most situations, the C4 halide is more reactive towards nucleophiles, as illustrated in the Scheme. However, as will be recognized by skilled artisans, the identity of the R^5 substituent may alter this reactivity. For example, when R^5 is trifluoromethyl, a 50:50 mixture of 4N-substituted-4-pyrimidineamine **8** and the corresponding 2N-substituted-2-pyrimidineamine is obtained. Regardless of the identity of the R^5 substituent, the regioselectivity of the reaction can be controlled by adjusting the solvent and other synthetic conditions (such as temperature), as is well-known in the art.

The reactions depicted in Scheme (I) may proceed more quickly when the reaction mixtures are heated *via* microwave. When heating in this fashion, the following conditions may be used: heat to 175°C in ethanol for 5-20 min. in a Smith Reactor (Personal Chemistry) in a sealed tube (at 20 bar pressure).

The uracil or thiouracil **2** starting materials may be purchased from commercial sources or prepared using standard techniques of organic chemistry. Commercially available uracils and thiouracils that can be used as starting materials in Scheme (I) include, by way of example and not limitation, uracil (Aldrich #13,078-8; CAS Registry 66-22-8); 2-thio-uracil (Aldrich #11,558-4; CAS Registry 141-90-2); 2,4-dithiouracil (Aldrich #15,846-1; CAS Registry 2001-93-6); 5-acetouracil (Chem. Sources Int'l 2000; CAS Registry 6214-65-9); 5-azidouracil; 5-aminouracil (Aldrich #85,528-6; CAS Registry 932-52-5); 5-bromouracil (Aldrich #85,247-3; CAS Registry 51-20-7); 5-(trans-2-bromovinyl)-uracil (Aldrich #45,744-2; CAS Registry 69304-49-0); 5-(trans-2-chlorovinyl)-uracil (CAS Registry 81751-48-2); 5-(trans-2-carboxyvinyl)-uracil; uracil-5-carboxylic acid (2,4-dihydroxypyrimidine-5-carboxylic acid hydrate; Aldrich #27,770-3; CAS Registry 23945-44-0); 5-chlorouracil (Aldrich #22,458-8; CAS Registry 1820-81-1); 5-cyanouracil (Chem. Sources Int'l 2000; CAS Registry 4425-56-3); 5-ethyluracil (Aldrich #23,044-8; CAS Registry 4212-49-1); 5-ethenyluracil (CAS Registry 37107-81-6); 5-fluorouracil (Aldrich #85,847-1; CAS Registry 51-21-8); 5-iodouracil (Aldrich #85,785-8; CAS Registry 696-07-1); 5-methyluracil (thymine; Aldrich #13,199-7; CAS Registry 65-71-4); 5-nitrouracil (Aldrich #85,276-7; CAS Registry 611-08-5); uracil-5-sulfamic acid (Chem. Sources Int'l 2000; CAS Registry 5435-16-5); 5-(trifluoromethyl)-uracil (Aldrich #22,327-1; CAS Registry 54-20-6); 5-(2,2,2-trifluoroethyl)-uracil (CAS Registry 155143-31-6); 5-(pentafluoroethyl)-uracil (CAS Registry 60007-38-3); 6-aminouracil (Aldrich #A5060-6;

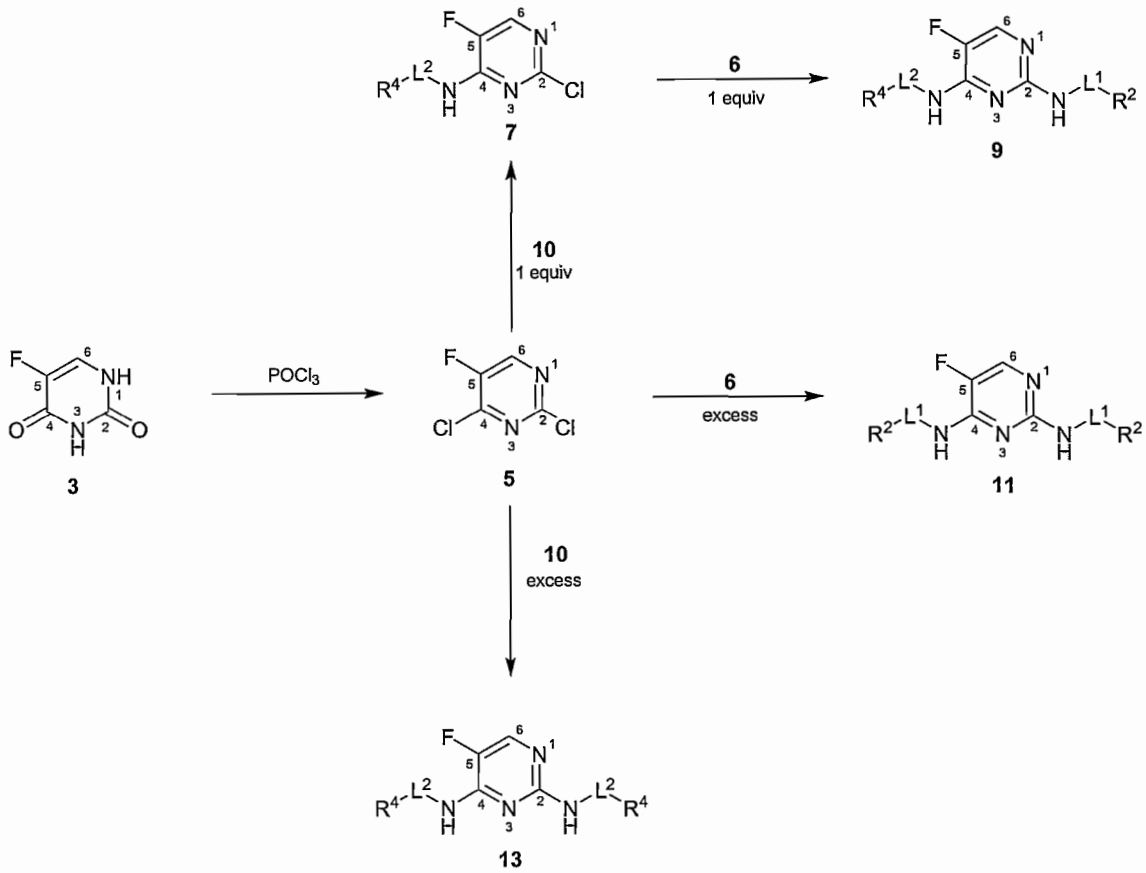
CAS Registry 873-83-6) uracil-6-carboxylic acid (orotic acid; Aldrich #0-840-2; CAS Registry 50887-69-9); 6-methyluracil (Aldrich #D11,520-7; CAS Registry 626-48-2); uracil-5-amino-6-carboxylic acid (5-aminoorotic acid; Aldrich #19,121-3; CAS Registry #7164-43-4); 6-amino-5-nitrosouracil (6-amino-2,4-dihydroxy-5-nitrosopyrimidine; Aldrich #27,689-8; CAS Registry 5442-24-0); uracil-5-fluoro-6-carboxylic acid (5-fluoroorotic acid; Aldrich #42,513-3; CAS Registry 00000-00-0); and uracil-5-nitro-6-carboxylic acid (5-nitroorotic acid; Aldrich #18,528-0; CAS Registry 600779-49-9). Additional 5-, 6- and 5,6-substituted uracils and/or thiouracils are available from General Intermediates of Canada, Inc., Edmonton, Alberta, CA (www.generalintermediates.com) and/or Interchim, France (www.interchim.com), or may be prepared using standard techniques. Myriad textbook references teaching suitable synthetic methods are provided *infra*.

Amines **6** and **10** may be purchased from commercial sources or, alternatively, may be synthesized utilizing standard techniques. For example, suitable amines may be synthesized from nitro precursors using standard chemistry. Specific exemplary reactions are provided in the Examples section. See also Vogel, 1989, *Practical Organic Chemistry*, Addison Wesley Longman, Ltd. and John Wiley & Sons, Inc.

Skilled artisans will recognize that in some instances, amines **6** and **10** and/or substituents R^5 and/or R^6 on uracil or thiouracil **2** may include functional groups that require protection during synthesis. The exact identity of any protecting group(s) used will depend upon the identity of the functional group being protected, and will be apparent to these of skill in the art. Guidance for selecting appropriate protecting groups, as well as synthetic strategies for their attachment and removal, may be found, for example, in Greene & Wuts, *Protective Groups in Organic Synthesis*, 3d Edition, John Wiley & Sons, Inc., New York (1999) and the references cited therein (hereinafter "Greene & Wuts").

A specific embodiment of Scheme (I) utilizing 5-fluorouracil (Aldrich #32,937-1) as a starting material is illustrated in Scheme (Ia), below:

Scheme (Ia)

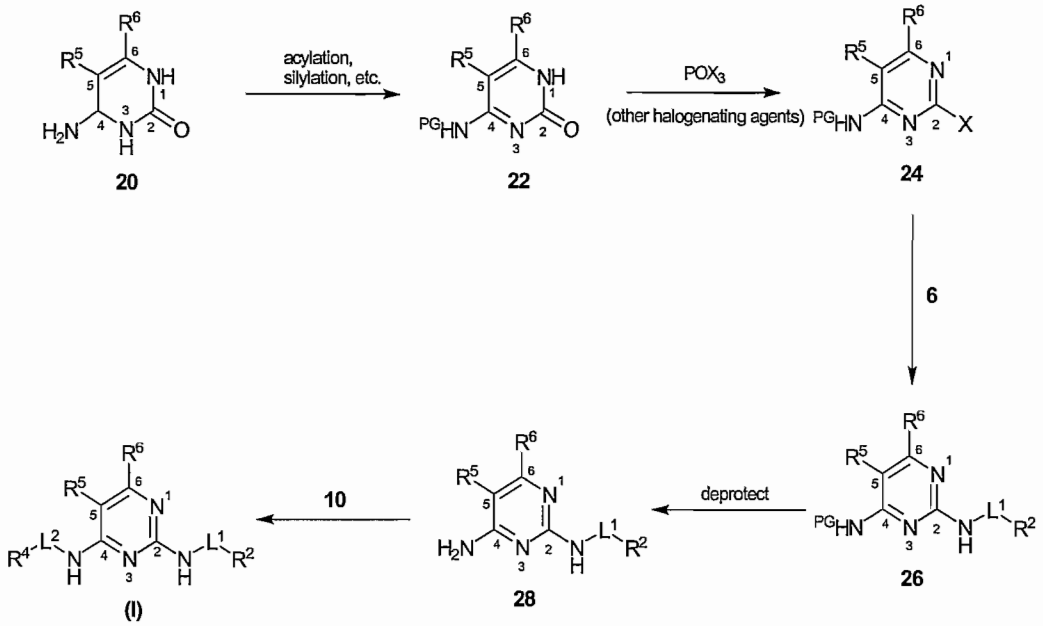


In Scheme (Ia), R^2, R^4, L^1 and L^2 are as previously defined for Scheme (I).

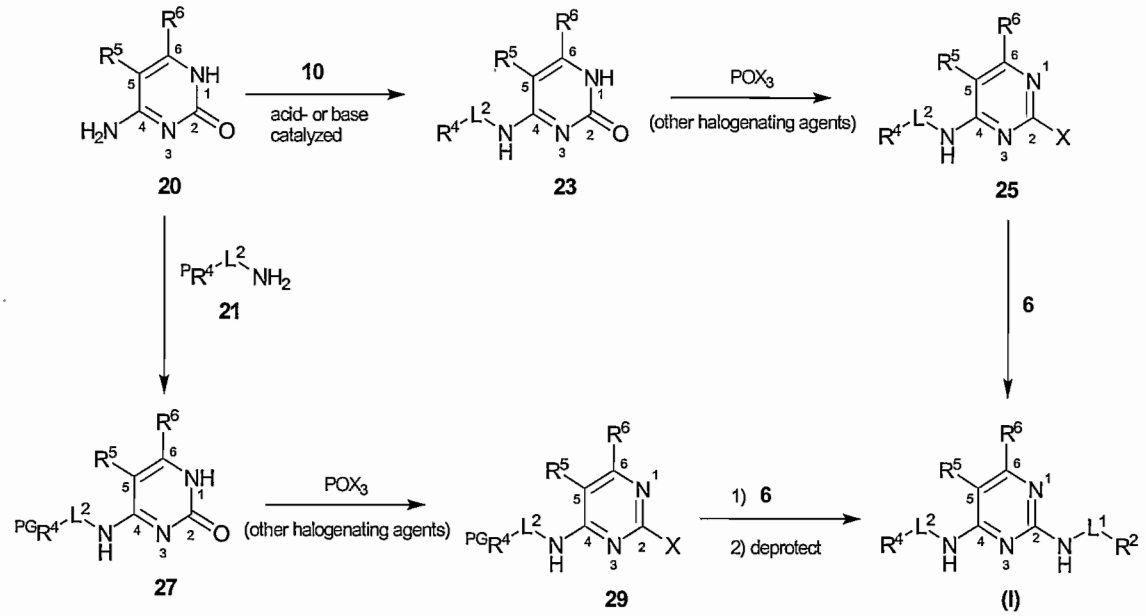
According to Scheme (Ia), 5-fluorouracil **3** is halogenated with $POCl_3$ to yield 2,4-dichloro-5-fluoropyrimidine **5**, which is then reacted with excess amine **6** or **10** to yield N2,N4-bis substituted 5-fluoro-2,4-pyrimidinediamine **11** or **13**, respectively. Alternatively, asymmetric 2N,4N-disubstituted-5-fluoro-2,4-pyrimidinediamine **9** may be obtained by reacting 2,4-dichloro-5-fluoropyrimidine **5** with one equivalent of amine **10** (to yield 2-chloro-N4-substituted-5-fluoro-4-pyrimidineamine **7**) followed by one or more equivalents of amine **6**.

In another exemplary embodiment, the 2,4-pyrimidinediamine compounds of the invention may be synthesized from substituted or unsubstituted cytosines as illustrated in Schemes (IIa) and (IIb), below:

Scheme (IIa)



Scheme (IIb)



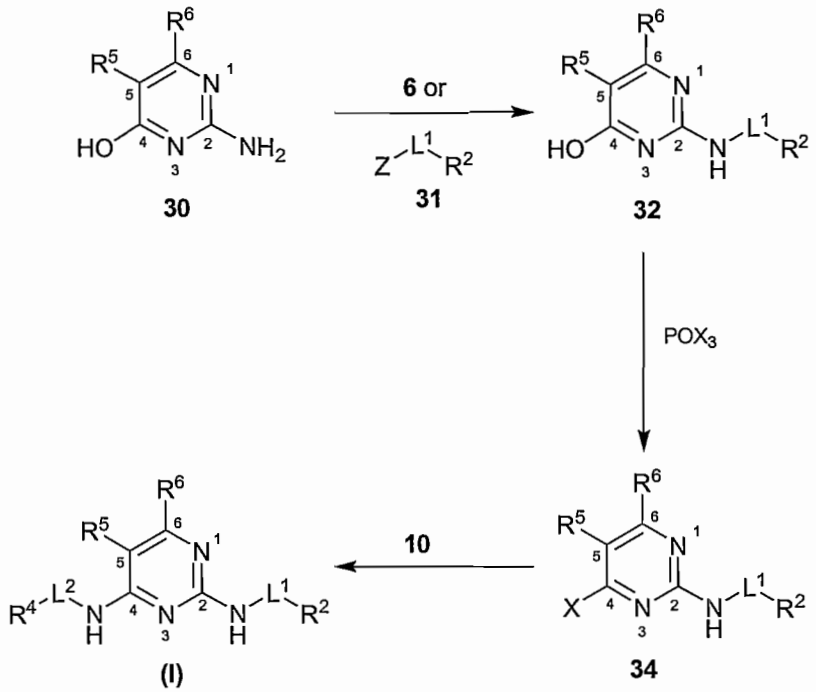
In Schemes (IIa) and (IIb), R^2, R^4, R^5, R^6, L^1, L^2 and X are as previously defined for Scheme (I) and PG represents a protecting group. Referring to Scheme (IIa), the C4 exocyclic amine of cytosine **20** is first protected with a suitable protecting group PG to yield N4-protected cytosine **22**. For specific guidance regarding protecting groups useful in this context, *see* Vorbrüggen and Ruh-Pohlenz, 2001, *Handbook of Nucleoside Synthesis*, John Wiley & Sons, NY, pp. 1-631 ("Vorbrüggen"). Protected cytosine **22** is halogenated at the C2 position using a standard halogenation reagent under standard conditions to yield 2-chloro-4N-protected-4-pyrimidineamine **24**. Reaction with amine **6** followed by deprotection of the C4 exocyclic amine and reaction with amine **10** yields a 2,4-pyrimidinediamine according to structural formula **(I)**.

Alternatively, referring to Scheme (IIb), cytosine **20** may be reacted with amine **10** or protected amine **21** to yield N4-substituted cytosine **23** or **27**, respectively. These substituted cytosines may then be halogenated as previously described, deprotected (in the case of N4-substituted cytosine **27**) and reacted with amine **6** to yield a 2,4-pyrimidinediamine according to structural formula **(I)**.

Commercially-available cytosines that may be used as starting materials in Schemes (IIa) and (IIb) include, but are not limited to, cytosine (Aldrich #14,201-8; CAS Registry 71-30-7); N^4-acetylcytosine (Aldrich #37,791-0; CAS Registry 14631-20-0); 5-fluorocytosine (Aldrich #27,159-4; CAS Registry 2022-85-7); and 5-(trifluoromethyl)-cytosine. Other suitable cytosines useful as starting materials in Schemes (IIa) are available from General Intermediates of Canada, Inc., Edmonton, Alberta, CA (www.generalintermediates.com) and/or Interchim, France (www.interchim.com), or may be prepared using standard techniques. Myriad textbook references teaching suitable synthetic methods are provided *infra.*

In still another exemplary embodiment, the 2,4-pyrimidinediamine compounds of the invention may be synthesized from substituted or unsubstituted 2-amino-4-pyrimidinols as illustrated in Scheme (III), below:

Scheme (III)

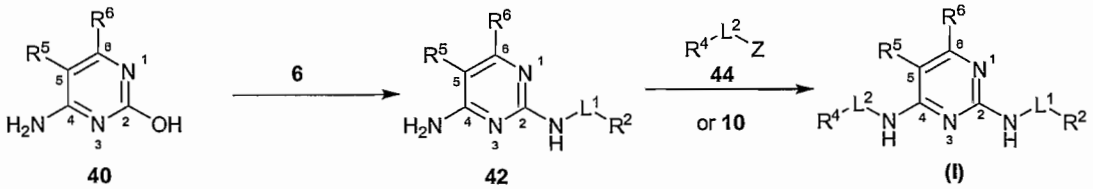


In Scheme (III), R^2, R^4, R^5, R^6, L^1, L^2 and X are as previously defined for Scheme (I) and Z is a leaving group as discussed in more detail in connection with Scheme IV, *infra*. Referring to Scheme (III), 2-amino-4-pyrimidinol **30** is reacted with amine **6** (or optionally protected amine **21**) to yield N2-substituted-4-pyrimidinol **32**, which is then halogenated as previously described to yield N2-substituted-4-halo-2-pyrimidineamine **34**. Optional deprotection (for example if protected amine **21** was used in the first step) followed by reaction with amine **10** affords a 2,4-pyrimidinediamine according to structural formula **(I)**. Alternatively, pyrimidinol **30** can be reacted with acylating agent **31**.

Suitable commercially-available 2-amino-4-pyrimidinols **30** that can be used as starting materials in Scheme (III) include, but are not limited to, 2-amino-6-chloro-4-pyrimidinol hydrate (Aldrich #A4702-8; CAS Registry 00000-00-0) and 2-amino-6-hydroxy-4-pyrimidinol (Aldrich #A5040-1; CAS Registry 56-09-7). Other 2-amino-4-pyrimidinols **30** useful as starting materials in Scheme (III) are available from General Intermediates of Canada, Inc., Edmonton, Alberta, CA (www.generalintermediates.com) and/or Interchim, France (www.interchim.com), or may be prepared using standard techniques. Myriad textbook references teaching suitable synthetic methods are provided *infra*.

Alternatively, the 2,4-pyrimidinediamine compounds of the invention may be prepared from substituted or unsubstituted 4-amino-2-pyrimidinols as illustrated in Scheme (IV), below:

Scheme (IV)

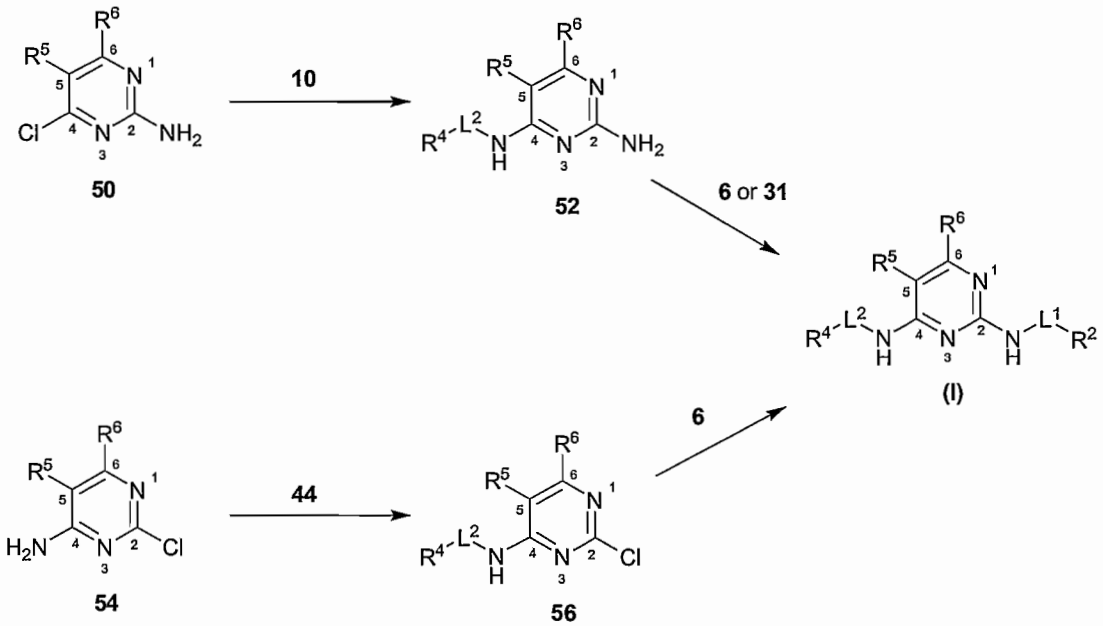


In Scheme (IV), R^2, R^4, R^5, R^6, L^1 and L^2 are as previously defined for Scheme (I) and Z represents a leaving group. Referring to Scheme (IV), the C2-hydroxyl of 4-amino-2-pyrimidinol **40** is more reactive towards nucleophiles than the C4-amino such that reaction with amine **6** yields N2-substituted-2,4-pyrimidinediamine **42**. Subsequent reaction with compound **44**, which includes a good leaving group Z, or amine **10** yields a 2,4-pyrimidinediamine according to structural formula **(I)**. Compound **44** may include virtually any leaving group that can be displaced by the C4-amino of N2-substituted-2,4-pyrimidinediamine **42**. Suitable leaving groups Z include, but are not limited to, halogens, methanesulfonyloxy (mesyloxy; "OMs"), trifluoromethanesulfonyloxy ("OTf") and *p*-toluenesulfonyloxy (tosyloxy; "OTs"), benzene sulfonyloxy ("besylate") and metanitro benzene sulfonyloxy ("nosylate"). Other suitable leaving groups will be apparent to those of skill in the art.

Substituted 4-amino-2-pyrimidinol starting materials may be obtained commercially or synthesized using standard techniques. Myriad textbook references teaching suitable synthetic methods are provided *infra*.

In still another exemplary embodiment, the 2,4-pyrimidinediamine compounds of the invention can be prepared from 2-chloro-4-aminopyrimidines or 2-amino-4-chloropyrimidines as illustrated in Scheme (V), below:

Scheme (V)

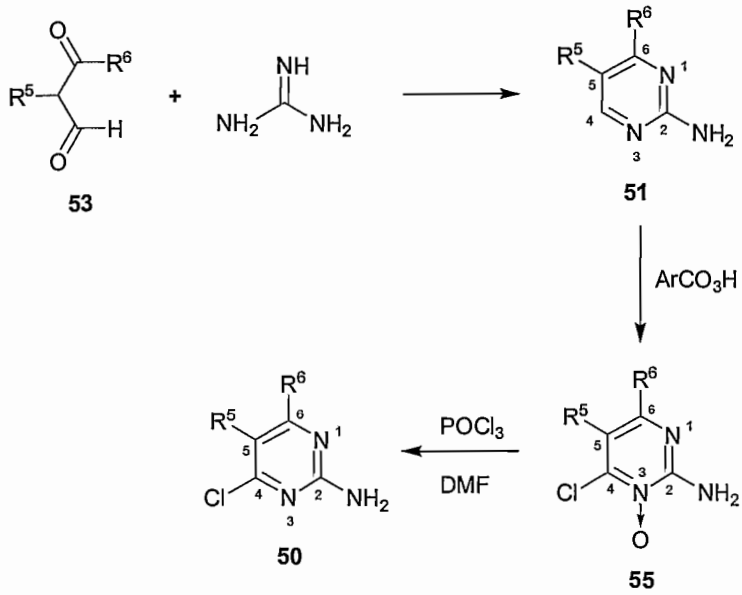


In Scheme (V), R^2, R^4, R^5, R^6, L^1, L^2 and X are as defined for Scheme (I) and Z is as defined for Scheme (IV). Referring to Scheme (V), 2-amino-4-chloropyrimidine **50** is reacted with amino **10** to yield 4N-substituted-2-pyrimidineamine **52** which, following reaction with compound **31** or amine **6**, yields a 2,4-pyrimidinediamine according to structural formula **(I)**. Alternatively, 2-chloro-4-amino-pyrimidine **54** may be reacted with compound **44** followed by amine **6** to yield a compound according to structural formula **(I)**.

A variety of pyrimidines **50** and **54** suitable for use as starting materials in Scheme (V) are commercially available, including by way of example and not limitation, 2-amino-4,6-dichloropyrimidine (Aldrich #A4860-1; CAS Registry 56-05-3); 2-amino-4-chloro-6-methoxy-pyrimidine (Aldrich #51,864-6; CAS Registry 5734-64-5); 2-amino-4-chloro-6-methylpyrimidine (Aldrich #12,288-2; CAS Registry 5600-21-5); and 2-amino-4-chloro-6-methylthiopyrimidine (Aldrich #A4600-5; CAS Registry 1005-38-5). Additional pyrimidine starting materials are available from General Intermediates of Canada, Inc., Edmonton, Alberta, CA (www.generalintermediates.com) and/or Interchim, France (www.interchim.com), or may be prepared using standard techniques. Myriad textbook references teaching suitable synthetic methods are provided *infra*.

Alternatively, 4-chloro-2-pyrimidineamines **50** may be prepared as illustrated in Scheme (Va):

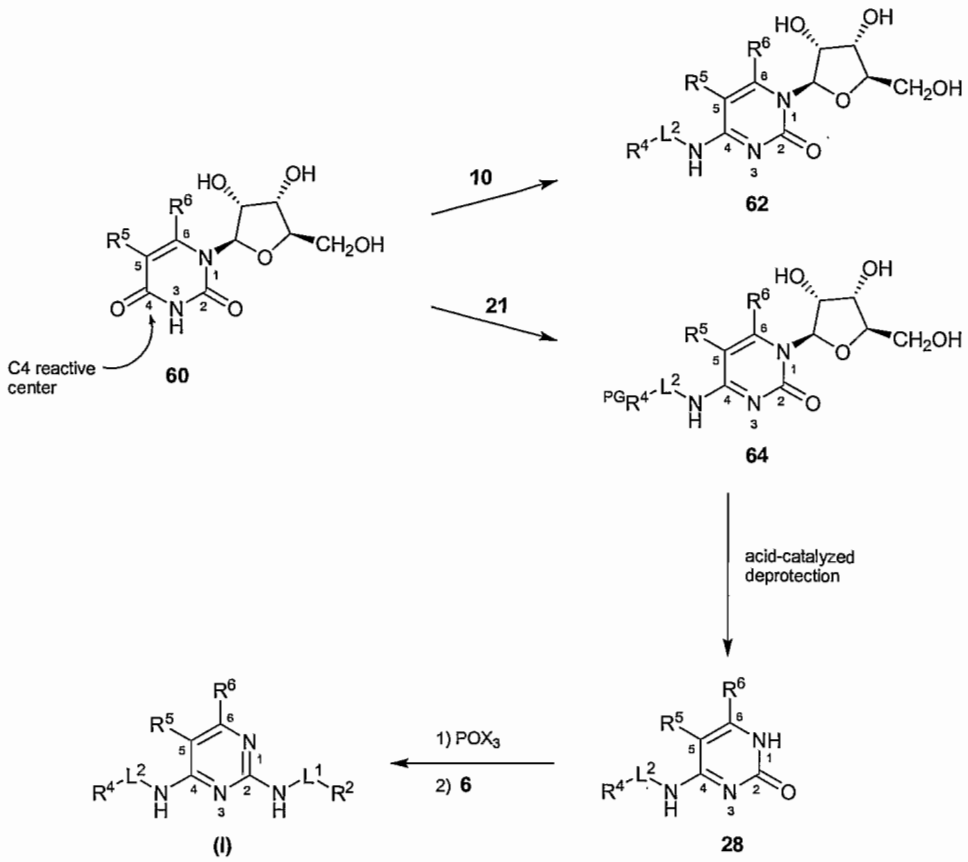
Scheme (Va)



In Scheme (Va), R^5 and R^6 are as previously defined for structural formula (I). In Scheme (Va), dicarbonyl **53** is reacted with guanidine to yield 2-pyrimidineamine **51**. Reaction with peracids like m-chloroperbenzoic acid, trifluoroperacetic acid or urea hydrogen peroxide complex yields N-oxide **55,** which is then halogenated to give 4-chloro-2-pyrimidineamine **50**. The corresponding 4-halo-2-pyrimidineamines may be obtained by using suitable halogenation reagents.

In yet another exemplary embodiment, the 2,4-pyrimidinediamine compounds of the invention can be prepared from substituted or unsubstituted uridines as illustrated in Scheme (VI), below:

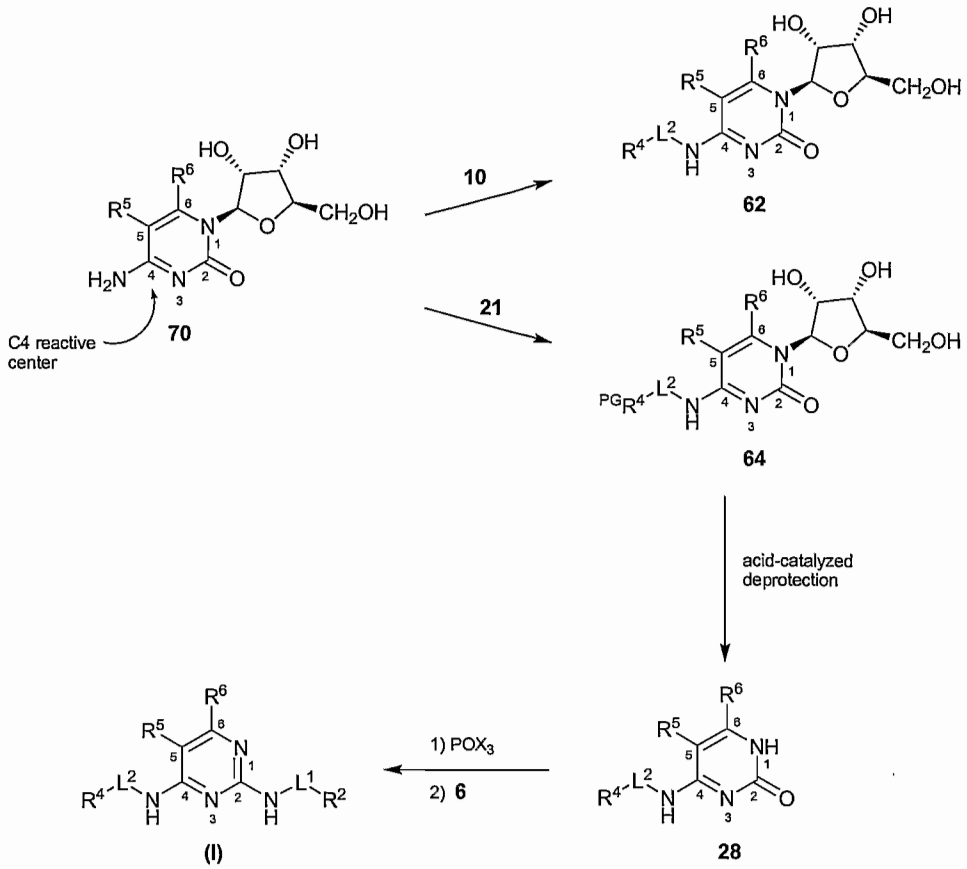
Scheme (VI)



In Scheme (VI), R^2, R^4, R^5, R^6, L^1, L^2 and X are as previously defined for Scheme (I) and the superscript PG represents a protecting group, as discussed in connection with Scheme (IIb). According to Scheme (VI), uridine **60** has a C4 reactive center such that reaction with amine **10** or protected amine **21** yields N4-substituted cytidine **62** or **64**, respectively. Acid-catalyzed deprotection of N4-substituted **62** or **64** (when "PG" represents an acid-labile protecting group) yields N4-substituted cytosine **28**, which may be subsequently halogenated at the C2-position and reacted with amine **6** to yield a 2,4-pyrimidinediamine according to structural formula **(I)**.

Cytidines may also be used as starting materials in an analogous manner, as illustrated in Scheme (VII), below:

Scheme (VII)



In Scheme (VII), R^2, R^4, R^5, R^6, L^1, L^2 and X are as previously defined in Scheme (I) and the superscript PG represents a protecting group as discussed above. Referring to Scheme (VII), like uridine **60**, cytidine **70** has a C4 reactive center such that reaction with amine **10** or protected amine **21** yields N4-substituted cytidine **62** or **64**, respectively. These cytidines **62** and **64** are then treated as previously described for Scheme (VI) to yield a 2,4-pyrimidinediamine according to structural formula **(I)**.

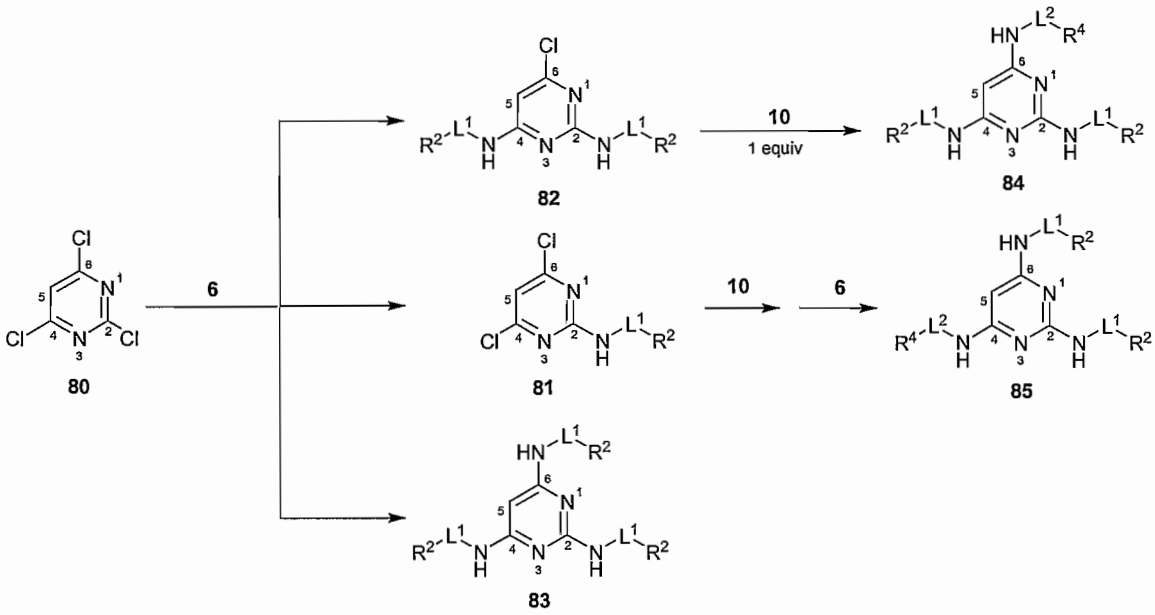
Although Schemes (VI) and (VII) are exemplified with ribosylnucleosides, skilled artisans will appreciate that the corresponding 2'-deoxyribo and 2',3'-dideoxyribo nucleosides, as well as nucleosides including sugars or sugar analogs other than ribose, would also work.

Numerous uridines and cytidines useful as starting materials in Schemes (VI) and (VII) are known in the art, and include, by way of example and not limitation, 5-trifluoromethyl-2'-deoxycytidine (Chem. Sources #ABCR F07669; CAS Registry 66,384-66-5); 5-bromouridine (Chem. Sources Int'l 2000; CAS Registry 957-75-5); 5-iodo-2'-deoxyuridine (Aldrich #1-775-6; CAS Registry 54-42-2); 5-fluorouridine

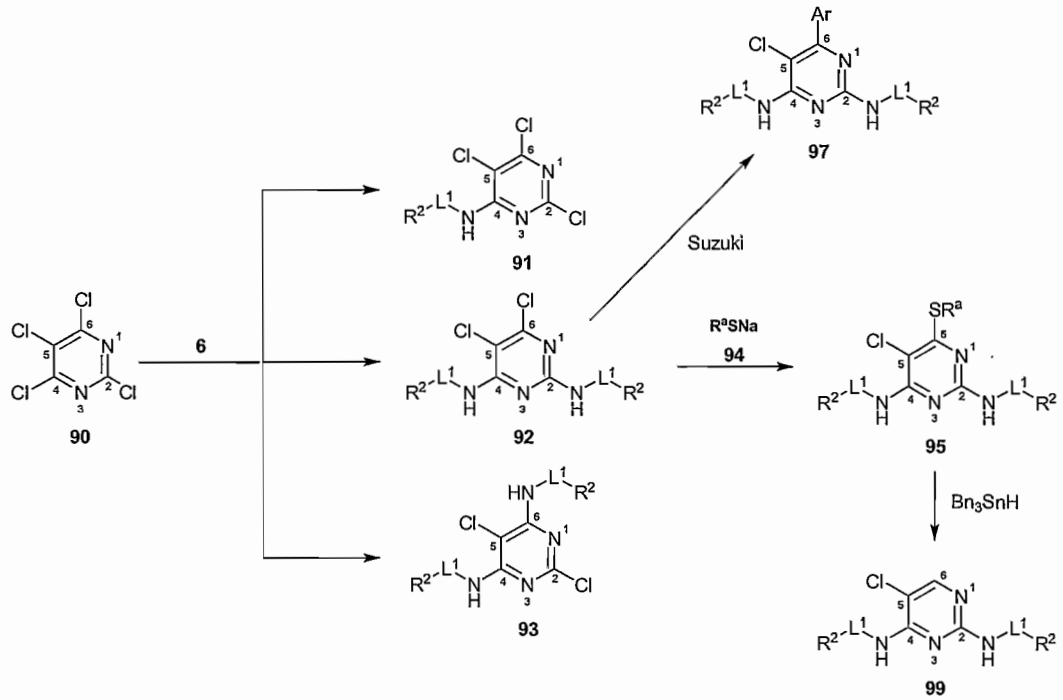
(Aldrich #32,937-1; CAS Registry 316-46-1); 5-iodouridine (Aldrich #85,259-7; CAS Registry 1024-99-3); 5-(trifluoromethyl)uridine (Chem. Sources Int'l 2000; CAS Registry 70-00-8); 5-trifluoromethyl-2'-deoxyuridine (Chem. Sources Int'l 2000; CAS Registry 70-00-8). Additional uridines and cytidines that can be used as starting materials in Schemes (VI) and (VII) are available from General Intermediates of Canada, Inc., Edmonton, Alberta, CA (www.generalintermediates.com) and/or Interchim, France (www.interchim.com), or may be prepared using standard techniques. Myriad textbook references teaching suitable synthetic methods are provided *infra*.

The 2,4-pyrimidinediamine compounds of the invention can also be synthesized from substituted pyrimidines, such as chloro-substituted pyrimidines, as illustrated in Schemes (VIII) and (IX), below:

Scheme (VIII)



Scheme (IX)



In Schemes (VIII) and (IX), R^2, R^4, L^1, L^2 and R^a are as previously defined for structural formula (I) and "Ar" represents an aryl group. Referring to Scheme (VIII), reaction of 2,4,6-trichloropyrimidine **80** (Aldrich #T5,620-0; CAS#3764-01-0) with amine **6** yields a mixture of three compounds: substituted pyrimidine mono-, di- and triamines **81, 82** and **83**, which can be separated and isolated using HPLC or other conventional techniques. Mono- and diamines **81** and **82** may be further reacted with amines **6** and/or **10** to yield N2,N4,N6-trisubstituted-2,4,6-pyrimidinetriamines **84** and **85**, respectively.

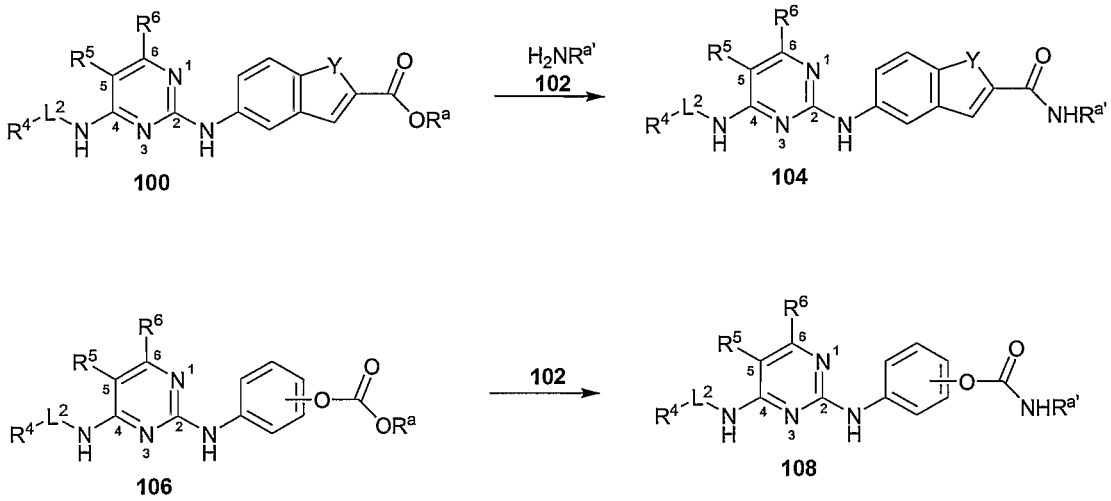
N2,N4-bis-substituted-2,4-pyrimidinediamines can be prepared in a manner analogous to Scheme (VIII) by employing 2,4-dichloro-5-methylpyrimidine or 2,4-dichloro-pyrimidine as starting materials. In this instance, the mono-substituted pyrimidineamine corresponding to compound **81** is not obtained. Instead, the reaction proceeds to yield the N2,N4-bis-substituted-2,4-pyrimidinediamine directly.

Referring to Scheme (IX), 2,4,5,6-tetrachloropyrimidine **90** (Aldrich #24,671-9; CAS#1780-40-1) is reacted with excess amine **6** to yield a mixture of three compounds: **91, 92,** and **93**, which can be separated and isolated using HPLC or other conventional techniques. As illustrated, N2,N4-bis-substituted-5,6,-dichloro-2,4-pyrimidinediamine **92** may be further reacted at the C6 halide with, for example a nucleophilic agent **94** to yield compound **95**. Alternatively, compound **92** can be converted into N2,N4-bis-subsituted-5-

chloro-6-aryl-2,4-pyrimidinediamine **97** *via* a Suzuki reaction. 2,4-Pyrimidinediamine **95** may be converted to 2,4-pyrimidinediamine **99** by reaction with Bn_3SnH.

As will be recognized by skilled artisans, 2,4-pyrimidinediamines according to the invention, synthesized *via* the exemplary methods described above or by other well-known means, may also be utilized as starting materials and/or intermediates to synthesize additional 2,4-pyrimidinediamine compounds of the invention. A specific example is illustrated in Scheme (X), below:

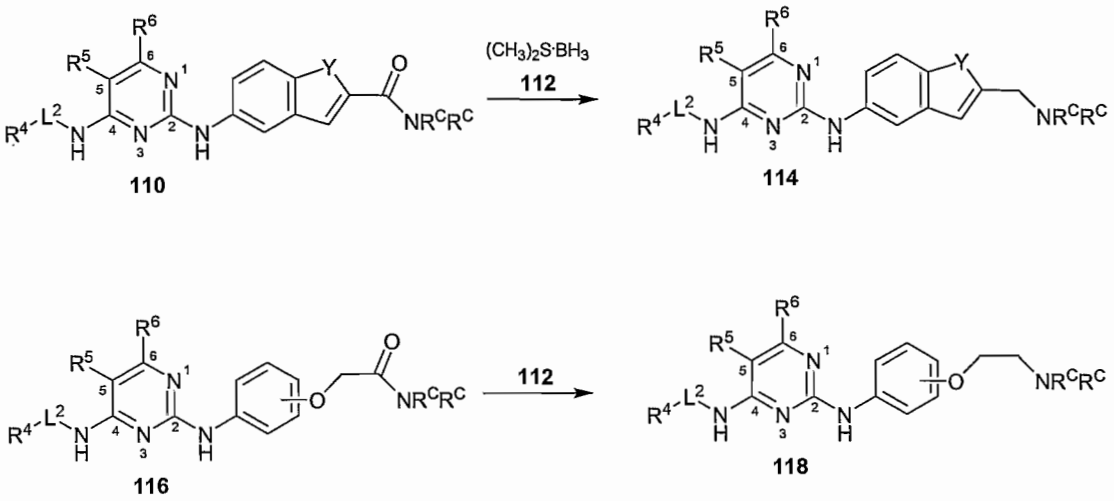
Scheme (X)



In Scheme (X), R^4, R^5, R^6, L^2 and R^a are as previously defined for structural formula (I). Each $R^{a'}$ is independently an R^a, and may be the same or different from the illustrated R^a. Referring to Scheme (X), carboxylic acid or ester **100** may be converted to amide **104** by reaction with amine **102**. In amine **102**, $R^{a'}$ may be the same or different than R^a of acid or ester **100**. Similarly, carbonate ester **106** may be converted to carbamate **108**.

A second specific example is illustrated in Scheme (XI), below:

Scheme (XI)



In Scheme (XI), R^4, R^5, R^6, L^2 and R^c are as previously defined for structural formula (I). Referring to Scheme (XI), amide **110** or **116** may be converted to amine **114** or **118**, respectively, by borane reduction with borane methylsulfide complex **112**. Other suitable reactions for synthesizing 2,4-pyrimidinediamine compounds from 2,4-pyrimidinediamine starting materials will be apparent to those of skill in the art.

Although many of the synthetic schemes discussed above do not illustrate the use of protecting groups, skilled artisans will recognize that in some instances substituents R^2, R^4, R^5, R^6, L^1 and/or L^2 may include functional groups requiring protection. The exact identity of the protecting group used will depend upon, among other things, the identity of the functional group being protected and the reaction conditions used in the particular synthetic scheme, and will be apparent to those of skill in the art. Guidance for selecting protecting groups and chemistries for their attachment and removal suitable for a particular application can be found, for example, in Greene & Wuts, *supra*.

Prodrugs according to structural formula (II) may be prepared by routine modification of the above-described methods. Alternatively, such prodrugs may be prepared by reacting a suitably protected 2,4-pyrimidinediamine of structural formula (I) with a suitable progroup. Conditions for carrying out such reactions and for deprotecting the product to yield a prodrug of formula (II) are well-known.

Myriad references teaching methods useful for synthesizing pyrimidines generally, as well as starting materials described in Schemes (I)-(IX), are known in the art. For

specific guidance, the reader is referred to Brown, D. J., "The Pyrimidines", in *The Chemistry of Heterocyclic Compounds, Volume 16* (Weissberger, A., Ed.), 1962, Interscience Publishers, (A Division of John Wiley & Sons), New York ("Brown I"); Brown, D. J., "The Pyrimidines", in *The Chemistry of Heterocyclic Compounds, Volume 16, Supplement I* (Weissberger, A. and Taylor, E. C., Ed.), 1970, Wiley-Interscience, (A Division of John Wiley & Sons), New York (Brown II"); Brown, D. J., "The Pyrimidines", in *The Chemistry of Heterocyclic Compounds, Volume 16, Supplement II* (Weissberger, A. and Taylor, E. C., Ed.), 1985, An Interscience Publication (John Wiley & Sons), New York ("Brown III"); Brown, D. J., "The Pyrimidines" in *The Chemistry of Heterocyclic Compounds, Volume 52* (Weissberger, A. and Taylor, E. C., Ed.), 1994, John Wiley & Sons, Inc., New York, pp. 1-1509 (Brown IV"); Kenner, G. W. and Todd, A., in *Heterocyclic Compounds*, Volume 6, (Elderfield, R. C., Ed.), 1957, John Wiley, New York, Chapter 7 (pyrimidines); Paquette, L. A., *Principles of Modern Heterocyclic Chemistry*, 1968, W. A. Benjamin, Inc., New York, pp. 1 – 401 (uracil synthesis pp. 313, 315; pyrimidine synthesis pp. 313-316; amino pyrimidine synthesis pp. 315); Joule, J. A., Mills, K. and Smith, G. F., *Heterocyclic Chemistry*, 3rd Edition, 1995, Chapman and Hall, London, UK, pp. 1 – 516; Vorbrüggen, H. and Ruh-Pohlenz, C., *Handbook of Nucleoside Synthesis*, John Wiley & Sons, New York, 2001, pp. 1-631 (protection of pyrimidines by acylation pp. 90-91; silylation of pyrimidines pp. 91-93); Joule, J. A., Mills, K. and Smith, G. F., *Heterocyclic Chemistry*, 4th Edition, 2000, Blackwell Science, Ltd, Oxford, UK, pp. 1 – 589; and *Comprehensive Organic Synthesis*, Volumes 1-9 (Trost, B. M. and Fleming, I., Ed.), 1991, Pergamon Press, Oxford, UK.

6.4 Inhibition of Fc Receptor Signal Cascades

Active 2,4-pyrimidinediamine compounds of the invention inhibit Fc receptor signalling cascades that lead to, among other things, degranulation of cells. As a specific example, the compounds inhibit the FcεRI and/or FcγRI signal cascades that lead to degranulation of immune cells such as neutrophil, eosinophil, mast and/or basophil cells. Both mast and basophil cells play a central role in allergen-induced disorders, including, for example, allergic rhinitis and asthma. Referring to FIG. 1, upon exposure allergens, which may be, among other things, pollen or parasites, allergen-specific IgE antibodies are synthesized by B-cells activated by IL-4 (or IL-13) and other messengers to switch to IgE class specific antibody synthesis. These allergen-specific IgEs bind to the high affinity

FcεRI. Upon binding of antigen, the FcεR1-bound IgEs are cross-linked and the IgE receptor signal transduction pathway is activated, which leads to degranulation of the cells and consequent release and/or synthesis of a host of chemical mediators, including histamine, proteases (e.g., tryptase and chymase), lipid mediators such as leukotrienes (e.g., LTC4), platelet-activating factor (PAF) and prostaglandins (e.g., PGD2) and a series of cytokines, including TNF-α, IL-4, IL-13, IL-5, IL-6, IL-8, GMCSF, VEGF and TGF-β. The release and/or synthesis of these mediators from mast and/or basophil cells accounts for the early and late stage responses induced by allergens, and is directly linked to downstream events that lead to a sustained inflammatory state.

The molecular events in the FcεRI signal transduction pathway that lead to release of preformed mediators *via* degranulation and release and/or synthesis of other chemical mediators are well-known and are illustrated in FIG. 2. Referring to FIG. 2, the FcεRI is a heterotetrameric receptor composed of an IgE-binding alpha-subunit, a beta subunit, and two gamma subunits (gamma homodimer). Cross-linking of FcεRI-bound IgE by multivalent binding agents (including, for example IgE-specific allergens or anti-IgE antibodies or fragments) induces the rapid association and activation of the Src-related kinase Lyn. Lyn phosphorylates immunoreceptor tyrosine-based activation motifs (ITAMS) on the intracellular beta and gamma subunits, which leads to the recruitment of additional Lyn to the beta subunit and Syk kinase to the gamma homodimer. These receptor-associated kinases, which are activated by intra- and intermolecular phosphorylation, phosphorylate other components of the pathway, such as the Btk kinase, LAT, and phospholipase C-gamma PLC-gamma). Activated PLC-gamma initiates pathways that lead to protein kinase C activation and Ca^{2+} mobilization, both of which are required for degranulation. FcεR1 cross-linking also activates the three major classes of mitogen activated protein (MAP) kinases, *i.e.* ERK1/2, JNK1/2, and p38. Activation of these pathways is important in the transcriptional regulation of proinflammatory mediators, such as TNF-α and IL-6, as well as the lipid mediator leukotriene CA (LTC4).

Although not illustrated, the FcγRI signaling cascade is believed to share some common elements with the FceRI signaling cascade. Importantly, like FcεRI, the FcγRI includes a gamma homodimer that is phosphorylated and recruits Syk, and like FcεRI, activation of the FcγRI signaling cascade leads to, among other things, degranulation. Other Fc receptors that share the gamma homodimer, and which can be regulated by the

active 2,4-pyrimidinediamine compounds include, but are not limited to, FcαRI and FcγRIII.

The ability of the 2,4-pyrimidinediamine compounds of the invention to inhibit Fc receptor signaling cascades may be simply determined or confirmed in *in vitro* assays. Suitable assays for confirming inhition of FcεRI-mediated degranulation are provided in the Examples section. In one typical assay, cells capable of undergoing FcεRI-mediated degranulation, such as mast or basophil cells, are first grown in the presence of IL-4, Stem Cell Factor (SCF), IL-6 and IgE to increase expression of the FcεRI, exposed to a 2,4-pyrimidinediamine test compound of the invention and stimulated with anti-IgE antibodies (or, alternatively, an IgE-specific allergen). Following incubation, the amount of a chemical mediator or other chemical agent released and/or synthesized as a consequence of activating the FcεRI signaling cascade may be quantified using standard techniques and compared to the amount of the mediator or agent released from control cells (*i.e.,* cells that are stimulated but that are not exposed to test compound). The concentration of test compound that yields a 50% reduction in the quantity of the mediator or agent measured as compared to control cells is the IC_{50} of the test compound. The origin of the mast or basophil cells used in the assay will depend, in part, on the desired use for the compounds and will be apparent to those of skill in the art. For example, if the compounds will be used to treat or prevent a particular disease in humans, a convenient source of mast or basophil cells is a human or other animal which constitutes an accepted or known clinical model for the particular disease. Thus, depending upon the particular application, the mast or basophil cells may be derived from a wide variety of animal sources, ranging from, for example, lower mammals such as mice and rats, to dogs, sheep and other mammals commonly employed in clinical testing, to higher mammals such as monkeys, chimpanzees and apes, to humans. Specific examples of cells suitable for carrying out the *in vitro* assays include, but are not limited to, rodent or human basophil cells, rat basophil leukemia cell lines, primary mouse mast cells (such as bone marrow-derived mouse mast cells "BMMC") and primary human mast cells isolated from cord blood ("CHMC") or other tissues such as lung. Methods for isolating and culturing these cell types are well-known or are provided in the Examples section (*see, e.g.*, Demo *et al.*, 1999, Cytometry 36(4):340-348 and copending application Serial No. 10/053,355, filed November 8, 2001, the disclosures of which are incorporated herein by reference). Of course, other types of immune cells that degranulate upon activation of the FcεRI signaling cascade may also be used, including, for example, eosinophils.

As will be recognized by skilled artisans, the mediator or agent quantified is not critical. The only requirement is that it be a mediator or agent released and/or synthesized as a consequence of initiating or activating the Fc receptor signaling cascade. For example, referring to FIG. 1, activation of the FcεRI signaling cascade in mast and/or basophil cells leads to numerous downstream events. For example, activation of the FcεRI signal cascade leads to the immediate release (i.e., within 1-3 min. following receptor activation) of a variety of preformed chemical mediators and agents *via* degranulation. Thus, in one embodiment, the mediator or agent quantified may be specific to granules (*i.e.,* present in granules but not in the cell cytoplasm generally). Examples of granule-specific mediators or agents that can be quantified to determine and/or confirm the activity of a 2,4-pyrimidinediamine compound of the invention include, but are not limited to, granule-specific enzymes such as hexosaminidase and tryptase and granule-specific components such as histamine and serotonin. Assays for quantifying such factors are well-known, and in many instances are commercially available. For example, tryptase and/or hexosaminidase release may be quantified by incubating the cells with cleavable substrates that fluoresce upon cleavage and quantifying the amount of fluorescence produced using conventional techniques. Such cleavable fluorogenic substrates are commercially available. For example, the fluorogenic substrates Z-Gly-Pro-Arg-AMC (Z=benzyloxycarbonyl; AMC=7-amino-4-methylcoumarin; BIOMOL Research Laboratories, Inc., Plymouth Meeting, PA 19462, Catalog No. P-142) and Z-Ala-Lys-Arg-AMC (Enzyme Systems Products, a division of ICN Biomedicals, Inc., Livermore, CA 94550, Catalog No. AMC-246) can be used to quantify the amount of tryptase released. The fluorogenic substrate 4-methylumbelliferyl-N-acetyl-β-D-glucosaminide (Sigma, St. Louis, MO, Catalog #69585) can be used to quantify the amount of hexosaminidase released. Histamine release may be quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) such as Immunotech histamine ELISA assay #IM2015 (Beckman-Coulter, Inc.). Specific methods of quantifying the release of tryptase, hexosaminidase and histamine are provided in the Examples section. Any of these assays may be used to determine or confirm the activity of the 2,4-pyrimidinediamine compounds of the invention.

Referring again to FIG. 1, degranulation is only one of several responses initiated by the FcεRI signaling cascade. In addition, activation of this signaling pathway leads to the *de novo* synthesis and release of cytokines and chemokines such as IL-4, IL-5, IL-6, TNF-α, IL-13 and MIP1-α), and release of lipid mediators such as leukotrienes (e.g., LTC4),

platelet activating factor (PAF) and prostaglandins. Accordingly, the 2,4-pyrimidinediamine compounds of the invention may also be assessed for activity by quantifying the amount of one or more of these mediators released and/or synthesized by activated cells.

Unlike the granule-specific components discussed above, these "late stage" mediators are not released immediately following activation of the FcεRI signaling cascade. Accordingly, when quantifying these late stage mediators, care should be taken to insure that the activated cell culture is incubated for a time sufficient to result in the synthesis (if necessary) and release of the mediator being quantified. Generally, PAF and lipid mediators such as leukotriene C4 are released 3-30 min. following FcεRI activation. The cytokines and other late stage mediators are released approx. 4-8 hrs. following FcεRI activation. Incubation times suitable for a specific mediator will be apparent to those of skill in the art. Specific guidance and assays are provided in the Examples section.

The amount of a particular late stage mediator released may be quantified using any standard technique. In one embodiment, the amount(s) may be quantified using ELISA assays. ELISA assay kits suitable for quantifying the amount of TNFα, IL-4, IL-5, IL-6 and/or IL-13 released are available from, for example, Biosource International, Inc., Camarillo, CA 93012 (see, e.g., Catalog Nos. KHC3011, KHC0042, KHC0052, KHC0061 and KHC0132). ELISA assay kits suitable for quantifying the amount of leukotriene C4 (LTC4) released from cells are available from Cayman Chemical Co., Ann Arbor, MI 48108 (see, e.g., Catalog No. 520211).

Typically, active 2,4-pyrimidinediamine compounds of the invention will exhibit IC_{50}s with respect to FcεRI-mediated degranulation and/or mediator release or synthesis of about 20 μM or lower, as measured in an *in vitro* assay, such as one of the *in vitro* assays described above or in the Examples section. Of course, skilled artisans will appreciate that compounds which exhibit lower IC_{50}s, for example on the order of 10 μM, 1 μM, 100 nM, 10 nM, 1 nM, or even lower, are particularly useful.

Skilled artisans will also appreciate that the various mediators discussed above may induce different adverse effects or exhibit different potencies with respect to the same adverse effect. For example, the lipid mediator LTC4 is a potent vasoconstrictor – it is approximately 1000-fold more potent at inducing vasoconstriction than histamine. As another example, in addition to mediating atopic or Type I hypersensitivity reactions, cytokines can also cause tissue remodeling and cell proliferation. Thus, although

compounds that inhibit release and/or synthesis of any one of the previously discussed chemical mediators are useful, skilled artisans will appreciate that compounds which inhibit the release and/or synthesis of a plurality, or even all, of the previously described mediators find particular use, as such compounds are useful for ameliorating or avoiding altogether a plurality, or even all, of the adverse effects induced by the particular mediators. For example, compounds which inhibit the release of all three types of mediators—granule-specific, lipid and cytokine—are useful for treating or preventing immediate Type I hypersensitivity reactions as well as the chronic symptoms associated therewith.

Compounds of the invention capable of inhibiting the release of more than one type of mediator (*e.g.*, granule-specific or late stage) may be identified by determining the IC_{50} with respect to a mediator representative of each class using the various *in vitro* assays described above (or other equivalent *in vitro* assays). Compounds of the invention which are capable of inhibiting the release of more than one mediator type will typically exhibit an IC_{50} for each mediator type tested of less than about 20 μM. For example, a compound which exhibits an IC_{50} of 1 μM with respect to histamine release ($IC_{50}^{histamine}$) and an IC_{50} of 1 nM with respect to leukotriene LTC4 synthesis and/or release (IC_{50}^{LTC4}) inhibits both immediate (granule-specific) and late stage mediator release. As another specific example, a compound that exhibits an $IC_{50}^{tryptase}$ of 10 μM, an IC_{50}^{LTC4} of 1 μM and an IC_{50}^{IL-4} of 1 μM inhibits immediate (granule-specific), lipid and cytokine mediator release. Although the above specific examples utilize the IC_{50}s of one representative mediator of each class, skilled artisans will appreciate that the IC_{50}s of a plurality, or even all, mediators comprising one or more of the classes may be obtained. The quantity(ies) and identity(ies) of mediators for which IC_{50} data should be ascertained for a particular compound and application will be apparent to those of skill in the art.

Similar assays may be utilized to confirm inhibition of signal transduction cascades initiated by other Fc receptors, such as FcαRI, FcγRI and/or FcγRIII signaling, with routine modification. For example, the ability of the compounds to inhibit FcγRI signal transduction may be confirmed in assays similar to those described above, with the exception that the FcγRI signaling cascade is activated, for example by incubating the cells with IgG and an IgG-specific allergen or antibody, instead of IgE and an IgE-specific allergen or antibody. Suitable cell types, activating agents and agents to quantify to confirm inhibition of other Fc receptors, such as Fc receptors that comprise a gamma homodimer, will be apparent to those of skill in the art.

One particularly useful class of compounds includes those 2,4-pyrimidinediamine compounds that inhibit the release of immediate granule-specific mediators and late stage mediators with approximately equivalent IC_{50}s. By approximately equivalent is meant that the IC_{50}s for each mediator type are within about a 10-fold range of one another. Another particularly useful class of compounds includes those 2,4-pyrimidinediamine compounds that inhibit the release of immediate granule-specific mediators, lipid mediators and cytokine mediators with approximately equivalent IC_{50}s. In a specific embodiment, such compounds inhibit the release of the following mediators with approximately equivalent IC_{50}s: histamine, tryptase, hexosaminidase, IL-4, IL-5, IL-6, IL-13, TNFα and LTC4. Such compounds are particularly useful for, among other things, ameliorating or avoiding altogether both the early and late stage responses associated with atopic or immediate Type I hypersensitivity reactions.

Ideally, the ability to inhibit the release of all desired types of mediators will reside in a single compound. However, mixtures of compounds can also be identified that achieve the same result. For example, a first compound which inhibits the release of granule specific mediators may be used in combination with a second compound which inhibits the release and/or synthesis of cytokine mediators.

In addition to the FcεRI or FcγRI degranulation pathways discussed above, degranulation of mast and/or basophil cells can be induced by other agents. For example, ionomycin, a calcium ionophore that bypasses the early FcεRI or FcγRI signal transduction machinery of the cell, directly induces a calcium flux that triggers degranulation. Referring again to FIG. 2, activated PLCγ initiates pathways that lead to, among other things, calcium ion mobilization and subsequent degranulation. As illustrated, this Ca^{2+} mobilization is triggered late in the FcεRI signal transduction pathway. As mentioned above, and as illustrated in FIG. 3, ionomycin directly induces Ca^{2+} mobilization and a Ca^{2+} flux that leads to degranulation. Other ionophores that induce degranulation in this manner include A23187. The ability of granulation-inducing ionophores such as ionomycin to bypass the early stages of the FcεRI and/or FcγRI signaling cascades may be used as a counter screen to identify active compounds of the invention that specifically exert their degranulation-inhibitory activity by blocking or inhibiting the early FcεRI or FcγRI signaling cascades, as discussed above. Compounds which specifically inhibit such early FcεRI or FcγRI-mediated degranulation inhibit not only degranulation and subsequent rapid release of histamine, tryptase and other granule contents, but also inhibit the pro-inflammatory

activation pathways causing the release of TNFα, IL-4, IL-13 and the lipid mediators such as LTC4. Thus, compounds which specifically inhibit such early FcεRI and/or FcγRI-mediated degranulation block or inhibit not only acute atopic or Type I hypersensitivity reactions, but also late responses involving multiple inflammatory mediators.

Compounds of the invention that specifically inhibit early FcεRI and/or FcγRI-mediated degranulation are those compounds that inhibit FcεRI and/or FcγRI-mediated degranulation (for example, have an IC_{50} of less than about 20 μM with respect to the release of a granule-specific mediator or component as measured in an *in vitro* assay with cells stimulated with an IgE or IgG binding agent) but that do not appreciably inhibit ionophore-induced degranulation. In one embodiment, compounds are considered to not appreciably inhibit ionophore-induced degranulation if they exhibit an IC_{50} of ionophore-induced degranulation of greater than about 20 μM, as measured in an *in vitro* assay. Of course, active compounds that exhibit even higher IC_{50}s of ionophore-induced degranulation, or that do not inhibit ionophore-induced degranulation at all, are particularly useful. In another embodiment, compounds are considered to not appreciably inhibit ionophore-induced degranulation if they exhibit a greater than 10-fold difference in their IC_{50}s of FcεRI and/or FcγRI-mediated degranulation and ionophore-induced degranulation, as measured in an *in vitro* assay. Assays suitable for determining the IC_{50} of ionophore-induced degranulation include any of the previously-described degranulation assays, with the modification that the cells are stimulated or activated with a degranulation-inducing calcium ionophore such as ionomycin or A23187 (A.G. Scientific, San Diego, CA) instead of anti-IgE antibodies or an IgE-specific allergen. Specific assays for assessing the ability of a particular 2,4-pyrimidinediamine compound of the invention to inhibit ionophore-induced degranulation are provided in the Examples section.

As will be recognized by skilled artisans, compounds which exhibit a high degree of selectivity of FcεRI-mediated degranulation find particular use, as such compounds selectively target the FcεRI cascade and do not interfere with other degranulation mechanisms. Similarly, compounds which exhibit a high degree of selectivity of FcγRI-mediated degranulation find particular use, as such compounds selectively target the FcγRI cascade and do not interfere with other degranulation mechanisms. Compounds which exhibit a high degree of selectivity are generally 10-fold or more selective for FcεRI- or FcγRI -mediated degranulation over ionophore-induced degranulation, such as ionomycin-induced degranulation.

Biochemical and other data confirm that the 2,4-pyrimidinediamine compounds described herein are potent inhibitors of Syk kinase activity. For example, in experiments with an isolated Syk kinase, of twenty four 2,4-pyrimidinediamine compounds tested, all but two inhibited the Syk kinase catalyzed phosphorylation of a peptide substrate with IC50s in the submicromolar range. The remaining compounds inhibited phosphorylation in the micromolar range. In addition, of sixteen compounds tested in an *in vitro* assay with mast cells, all inhibited phosphorylation of Syk kinase substrates (*e.g.,* PLC-gamma1, LAT) and proteins downstream of Syk kinase (*e.g.,* JNK, p38, Erk1/2 and PKB, when tested), but not proteins upstream of Syk kinase in the cascade (*e.g.,* Lyn). Phosphorylation of Lyn substrates was not inhibited by the 2,4-pyrimidinediamine compounds tested. Moreover, for the following compounds, a high correlation was observed between their inhibition of Syk kinase activity in biochemical assays (IC_{50}s in the range of 3 to 1850 nM) and their inhibition of FcεR1-mediated degranulation in mast cells (IC_{50}s in the range of 30 to 1650 nM): R950373, R950368, R921302, R945371, R945370, R945369, R945365, R921304, R945144, R945140, R945071, R940358, R940353, R940352, R940351, R940350, R940347, R921303, R940338, R940323, R940290, R940277, R940276, R940275, R940269, R940255, R935393, R935372, R935366, R935310, R935309, R935307, R935304, R935302, R935293, R935237, R935198, R935196, R935194, R935193, R935191, R935190, R935138, R927050, R926968, R926956, R926931, R926891, R926839, R926834, R926816, R926813, R926791, R926782, R926780, R926757, R926753, R926745, R926715, R926508, R926505, R926502, R926501, R926500, R921218, R921147, R920410, R909268, R921219, R908712, R908702.

Accordingly, the activity of the 2,4-pyrimidinediamine compounds of the invention may also be confirmed in biochemical or cellular assays of Syk kinase activity. Referring again to FIG. 2, in the FcεRI signaling cascade in mast and/or basophil cells, Syk kinase phosphorylates LAT and PLC-gamma1, which leads to, among other things, degranulation. Any of these activities may be used to confirm the activity of the 2,4-pyrimidinediamine compounds of the invention. In one embodiment, the activity is confirmed by contacting an isolated Syk kinase, or an active fragment thereof with a 2,4-pyrimidinediamine compound in the presence of a Syk kinase substrate (*e.g.,* a synthetic peptide or a protein that is known to be phophorylated by Syk in a signaling cascade) and assessing whether the Syk kinase phosphorylated the substrate. Alternatively, the assay may be carried out with cells that express a Syk kinase. The cells may express the Syk kinase endogenously or they may be

engineered to express a recombinant Syk kinase. The cells may optionally also express the Syk kinase substrate. Cells suitable for performing such confirmation assays, as well as methods of engineering suitable cells will be apparent to those of skill in the art. Specific examples of biochemical and cellular assays suitable for confirming the activity of the 2,4-pyrimidinediamine compounds are provided in the Examples section.

Generally, compounds that are Syk kinase inhibitors will exhibit an IC_{50} with respect to a Syk kinase activity, such as the ability of Syk kinase to phosphorylate a synthetic or endogenous substrate, in an *in vitro* or cellular assay in the range of about 20 μM or less. Skilled artisans will appreciate that compounds that exhibit lower IC50s, such as in the range of 10 μM, 1μM, 100 nM, 10 nM, 1 nM, or even lower, are particularly useful.

6.5 Uses and Compositions

As previously discussed, the active compounds of the invention inhibit Fc receptor signaling cascades, especially those Fc receptors including a gamma homodimer, such as the FcϵRI and/or FcγRI signaling cascades, that lead to, among other things, the release and/or synthesis of chemical mediators from cells, either *via* degranulation or other processes. As also discussed, the active compounds are also potent inhibitors of Syk kinase. As a consequence of these activities, the active compounds of the invention may be used in a variety of *in vitro, in vivo* and *ex vivo* contexts to regulate or inhibit Syk kinase, signaling cascades in which Syk kinase plays a role, Fc receptor signaling cascades, and the biological responses effected by such signaling cascades. For example, in one embodiment, the compounds may be used to inhibit Syk kinase, either *in vitro* or *in vivo*, in virtually any cell type expressing Syk kinase. They may also be used to regulate signal transduction cascades in which Syk kinase plays a role. Such Syk-dependent signal transduction cascades include, but are not limited to, the FcϵRI, FcγRI, FcγRIII, BCR and integrin signal transduction cascades. The compounds may also be used *in vitro* or *in vivo* to regulate, and in particular inhibit, cellular or biological responses effected by such Syk-dependent signal transduction cascades. Such cellular or biological responses include, but are not limited to, respiratory burst, cellular adhesion, cellular degranulation, cell spreading, cell migration, cell aggregation, phagcytosis, cytokine synthesis and release, cell maturation and Ca^{2+} flux. Importantly, the compounds may be used to inhibit Syk kinase *in vivo* as a therapeutic approach towards the treatment or prevention of diseases mediated, either wholly or in part,

by a Syk kinase activity. Non-limiting examples of Syk kinase mediated diseases that may be treated or prevented with the compounds are those discussed in more detail, below.

In another embodiment, the active compounds may be used to regulate or inhibit the Fc receptor signaling cascades and/or FcεRI- and/or FcγRI-mediated degranulation as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by and/or associated with the release or synthesis of chemical mediators of such Fc receptor signaling cascades or degranulation. Such treatments may be administered to animals in veterinary contexts or to humans. Diseases that are characterized by, caused by or associated with such mediator release, synthesis or degranulation, and that can therefore be treated or prevented with the active compounds include, by way of example and not limitation, atopy or anaphylactic hypersensitivity or allergic reactions, allergies (e.g., allergic conjunctivitis, allergic rhinitis, atopic asthma, atopic dermatitis and food allergies), low grade scarring (*e.g.*, of scleroderma, increased fibrosis, keloids, post-surgical scars, pulmonary fibrosis, vascular spasms, migraine, reperfusion injury and post myocardial infarction), diseases associated with tissue destruction (*e.g.*, of COPD, cardiobronchitis and post myocardial infarction), diseases associated with tissue inflammation (*e.g.*, irritable bowel syndrome, spastic colon and inflammatory bowel disease), inflammation and scarring.

In addition to the myriad diseases discussed above, cellular and animal empirical data confirm that the 2,4-pyrimidinediamine compounds described herein are also useful for the treatment or prevention of autoimmune diseases, as well as the various symptoms associated with such diseases. The types of autoimmune diseases that may be treated or prevented with the 2,4-pyrimidinediamine compounds generally include those disorders involving tissue injury that occurs as a result of a humoral and/or cell-mediated response to immunogens or antigens of endogenous and/or exogenous origin. Such diseases are frequently referred to as diseases involving the nonanaphylactic (*i.e.*, Type II, Type III and/or Type IV) hypersensitivity reactions.

As discussed previously, Type I hypersensitivity reactions generally result from the release of pharmacologically active substances, such as histamine, from mast and/or basophil cells following contact with a specific exogenous antigen. As mentioned above, such Type I reactions play a role in numerous diseases, including allergic asthma, allergic rhinitis, etc.

Type II hypersensitivity reactions (also referred to as cytotoxic, cytolytic complement-dependent or cell-stimulating hypersensitivity reactions) result when immunoglobulins react with antigenic components of cells or tissue, or with an antigen or hapten that has become intimately coupled to cells or tissue. Diseases that are commonly associated with Type II hypersensitivity reactions include, but are not limited, to autoimmune hemolytic anemia, erythroblastosis fetalis and Goodpasture's disease.

Type III hypersensitivity reactions, (also referred to as toxic complex, soluble complex, or immune complex hypersensitivity reactions) result from the deposition of soluble circulating antigen-immunoglobulin complexes in vessels or in tissues, with accompanying acute inflammatory reactions at the site of immune complex deposition. Non-limiting examples of prototypical Type III reaction diseases include the Arthus reaction, rheumatoid arthritis, serum sickness, systemic lupus erythematosis, certain types of glomerulonephritis, multiple sclerosis and bullous pemphingoid.

Type IV hypersensitivity reactions (frequently called cellular, cell-mediated, delayed, or tuberculin-type hypersensitivity reactions) are caused by sensitized T-lymphocytes which result from contact with a specific antigen. Non-limiting examples of diseases cited as involving Type IV reactions are contact dermatitis and allograft rejection.

Autoimmune diseases associated with any of the above nonanaphylactic hypersensitivity reactions may be treated or prevented with the 2,4-pyrimidinediamine compounds of the invention. In particular, the methods may be used to treat or prevent those autoimmune diseases frequently characterized as single organ or single cell-type autoimmune disorders including, but not limited to: Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune atrophic gastritis of pernicious anemia, autoimmune encephalomyelitis, autoimmune orchitis, Goodpasture's disease, autoimmune thrombocytopenia, sympathetic ophthalmia, myasthenia gravis, Graves' disease, primary biliary cirrhosis, chronic aggressive hepatitis, ulcerative colitis and membranous glomerulopathy, as well as those autoimmune diseases frequently characterized as involving systemic autoimmune disorder, which include but are not limited to: systemic lupus erythematosis, rheumatoid arthritis, Sjogren's syndrome, Reiter's syndrome, polymyositis-dermatomyositis, systemic sclerosis, polyarteritis nodosa, multiple sclerosis and bullous pemphigoid.

It will be appreciated by skilled artisans that many of the above-listed autoimmune diseases are associated with severe symptoms, the amelioration of which provides

significant therapeutic benefit even in instances where the underlying autoimmune disease may not be ameliorated. Many of these symptoms, as well as their underlying disease states, result as a consequence of activating the FcγR signaling cascade in monocyte cells. As the 2,4-pyrimidinediamine compounds described herein are potent inhibitors of such FcγR signaling in monocytes and other cells, the methods find use in the treatment and/or prevention of myriad adverse symptoms associated with the above-listed autoimmune diseases.

As a specific example, rheumatoid arthritis (RA) typically results in swelling, pain, loss of motion and tenderness of target joints throughout the body. RA is characterized by chronically inflamed synovium that is densely crowded with lymphocytes. The synovial membrane, which is typically one cell layer thick, becomes intensely cellular and assumes a form similar to lymphoid tissue, including dentritic cells, T-, B- and NK cells, macrophages and clusters of plasma cells. This process, as well as a plethora of immunopathological mechanisms including the formation of antigen-immunoglobulin complexes, eventually result in destruction of the integrity of the joint, resulting in deformity, permanent loss of function and/or bone erosion at or near the joint. The methods may be used to treat or ameliorate any one, several or all of these symptoms of RA. Thus, in the context of RA, the methods are considered to provide therapeutic benefit (discussed more generally, *infra*) when a reduction or amelioration of any of the symptoms commonly associated with RA is achieved, regardless of whether the treatment results in a concomitant treatment of the underlying RA and/or a reduction in the amount of circulating rheumatoid factor ("RF").

As another specific example, systemic lupus erythematosis ("SLE") is typically associated with symptoms such as fever, joint pain (arthralgias), arthritis, and serositis (pleurisy or pericarditis). In the context of SLE, the methods are considered to provide therapeutic benefit when a reduction or amelioration of any of the symptoms commonly associated with SLE are achieved, regardless of whether the treatment results in a concomitant treatment of the underlying SLE.

As another specific example, multiple sclerosis ("MS") cripples the patient by disturbing visual acuity; stimulating double vision; disturbing motor functions affecting walking and use of the hands; producing bowel and bladder incontinence; spasticity; and sensory deficits (touch, pain and temperature sensitivity). In the context of MS, the methods are considered to provide therapeutic benefit when an improvement or a reduction in the progression of any one or more of the crippling effects commonly associated with MS

is achieved, regardless of whether the treatment results in a concomitant treatment of the underlying MS.

When used to treat or prevent such diseases, the active compounds may be administered singly, as mixtures of one or more active compounds or in mixture or combination with other agents useful for treating such diseases and/or the symptoms associated with such diseases. The active compounds may also be administered in mixture or in combination with agents useful to treat other disorders or maladies, such as steroids, membrane stablizers, 5LO inhibitors, leukotriene synthesis and receptor inhibitors, inhibitors of IgE isotype switching or IgE synthesis, IgG isotype switching or IgG synthesis, β-agonists, tryptase inhibitors, aspirin, COX inhibitors, methotrexate, anti-TNF drugs, retuxin, PD4 inhibitors, p38 inhibitors, PDE4 inhibitors, and antihistamines, to name a few. The active compounds may be administered *per se* in the form of prodrugs or as pharmaceutical compositions, comprising an active compound or prodrug.

Pharmaceutical compositions comprising the active compounds of the invention (or prodrugs thereof) may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making levigating, emulsifying, encapsulating, entrapping or lyophilization processes. The compositions may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically.

The active compound or prodrug may be formulated in the pharmaceutical compositions *per se*, or in the form of a hydrate, solvate, N-oxide or pharmaceutically acceptable salt, as previously described. Typically, such salts are more soluble in aqueous solutions than the corresponding free acids and bases, but salts having lower solubility than the corresponding free acids and bases may also be formed.

Pharmaceutical compositions of the invention may take a form suitable for virtually any mode of administration, including, for example, topical, ocular, oral, buccal, systemic, nasal, injection, transdermal, rectal, vaginal, etc., or a form suitable for administration by inhalation or insufflation.

For topical administration, the active compound(s) or prodrug(s) may be formulated as solutions, gels, ointments, creams, suspensions, etc. as are well-known in the art.

Systemic formulations include those designed for administration by injection, *e.g.*, subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal oral or pulmonary administration.

Useful injectable preparations include sterile suspensions, solutions or emulsions of the active compound(s) in aqueous or oily vehicles. The compositions may also contain formulating agents, such as suspending, stabilizing and/or dispersing agent. The formulations for injection may be presented in unit dosage form, *e.g.*, in ampules or in multidose containers, and may contain added preservatives.

Alternatively, the injectable formulation may be provided in powder form for reconstitution with a suitable vehicle, including but not limited to sterile pyrogen free water, buffer, dextrose solution, etc., before use. To this end, the active compound(s) may be dried by any art-known technique, such as lyophilization, and reconstituted prior to use.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are known in the art.

For oral administration, the pharmaceutical compositions may take the form of, for example, lozenges, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulfate). The tablets may be coated by methods well known in the art with, for example, sugars, films or enteric coatings. Compounds which are particularly suitable for oral administration include Compounds R940350, R935372, R935193, R927050 and R935391.

Liquid preparations for oral administration may take the form of, for example, elixirs, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol, cremophore™ or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, preservatives, flavoring, coloring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound or prodrug, as is well known.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For rectal and vaginal routes of administration, the active compound(s) may be formulated as solutions (for retention enemas) suppositories or ointments containing conventional suppository bases such as cocoa butter or other glycerides.

For nasal administration or administration by inhalation or insufflation, the active compound(s) or prodrug(s) can be conveniently delivered in the form of an aerosol spray from pressurized packs or a nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, fluorocarbons, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges for use in an inhaler or insufflator (for example capsules and cartridges comprised of gelatin) may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

A specific example of an aqueous suspension formulation suitable for nasal administration using commercially-available nasal spray devices includes the following ingredients: active compound or prodrug (0.5-20 mg/ml); benzalkonium chloride (0.1-0.2 mg/mL); polysorbate 80 (TWEEN® 80; 0.5-5 mg/ml); carboxymethylcellulose sodium or microcrystalline cellulose (1-15 mg/ml); phenylethanol (1-4 mg/ml); and dextrose (20-50 mg/ml). The pH of the final suspension can be adjusted to range from about pH5 to pH7, with a pH of about pH 5.5 being typical.

Another specific example of an aqueous suspension suitable for administration of the compounds *via* inhalation, and in particular for such administration of Compound R921218, contains 1-20 mg/mL Compound or prodrug, 0.1-1% (v/v) Polysorbate 80 (TWEEN®80), 50 mM citrate and/or 0.9% sodium chloride.

For ocular administration, the active compound(s) or prodrug(s) may be formulated as a solution, emulsion, suspension, etc. suitable for administration to the eye. A variety of vehicles suitable for administering compounds to the eye are known in the art. Specific non-limiting examples are described in U.S. Patent No. 6,261,547; U.S. Patent No. 6,197,934; U.S. Patent No. 6,056,950; U.S. Patent No. 5,800,807; U.S. Patent No. 5,776,445; U.S. Patent No. 5,698,219; U.S. Patent No. 5,521,222; U.S. Patent No.

5,403,841; U.S. Patent No. 5,077,033; U.S. Patent No. 4,882,150; and U.S. Patent No. 4,738,851.

For prolonged delivery, the active compound(s) or prodrug(s) can be formulated as a depot preparation for administration by implantation or intramuscular injection. The active ingredient may be formulated with suitable polymeric or hydrophobic materials (e.g., as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, e.g., as a sparingly soluble salt. Alternatively, transdermal delivery systems manufactured as an adhesive disc or patch which slowly releases the active compound(s) for percutaneous absorption may be used. To this end, permeation enhancers may be used to facilitate transdermal penetration of the active compound(s). Suitable transdermal patches are described in for example, U.S. Patent No. 5,407,713.; U.S. Patent No. 5,352,456; U.S. Patent No. 5,332,213; U.S. Patent No. 5,336,168; U.S. Patent No. 5,290,561; U.S. Patent No. 5,254,346; U.S. Patent No. 5,164,189; U.S. Patent No. 5,163,899; U.S. Patent No. 5,088,977; U.S. Patent No. 5,087,240; U.S. Patent No. 5,008,110; and U.S. Patent No. 4,921,475.

Alternatively, other pharmaceutical delivery systems may be employed. Liposomes and emulsions are well-known examples of delivery vehicles that may be used to deliver active compound(s) or prodrug(s). Certain organic solvents such as dimethylsulfoxide (DMSO) may also be employed, although usually at the cost of greater toxicity.

The pharmaceutical compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active compound(s). The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

6.6 Effective Dosages

The active compound(s) or prodrug(s) of the invention, or compositions thereof, will generally be used in an amount effective to achieve the intended result, for example in an amount effective to treat or prevent the particular disease being treated. The compound(s) may be administered therapeutically to achieve therapeutic benefit or prophylactically to achieve prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated and/or eradication or amelioration of one or more of the symptoms associated with the underlying disorder such that the patient reports an improvement in feeling or condition, notwithstanding that the patient may still be afflicted

with the underlying disorder. For example, administration of a compound to a patient suffering from an allergy provides therapeutic benefit not only when the underlying allergic response is eradicated or ameliorated, but also when the patient reports a decrease in the severity or duration of the symptoms associated with the allergy following exposure to the allergen. As another example, therapeutic benefit in the context of asthma includes an improvement in respiration following the onset of an asthmatic attack, or a reduction in the frequency or severity of asthmatic episodes. Therapeutic benefit also includes halting or slowing the progression of the disease, regardless of whether improvement is realized.

For prophylactic administration, the compound may be administered to a patient at risk of developing one of the previously described diseases. For example, if it is unknown whether a patient is allergic to a particular drug, the compound may be administered prior to administration of the drug to avoid or ameliorate an allergic response to the drug. Alternatively, prophylactic administration may be applied to avoid the onset of symptoms in a patient diagnosed with the underlying disorder. For example, a compound may be administered to an allergy sufferer prior to expected exposure to the allergen. Compounds may also be administered prophylactically to healthy individuals who are repeatedly exposed to agents known to one of the above-described maladies to prevent the onset of the disorder. For example, a compound may be administered to a healthy individual who is repeatedly exposed to an allergen known to induce allergies, such as latex, in an effort to prevent the individual from developing an allergy. Alternatively, a compound may be administered to a patient suffering from asthma prior to partaking in activities which trigger asthma attacks to lessen the severity of, or avoid altogether, an asthmatic episode.

The amount of compound administered will depend upon a variety of factors, including, for example, the particular indication being treated, the mode of administration, whether the desired benefit is prophylactic or therapeutic, the severity of the indication being treated and the age and weight of the patient, the bioavailability of the particular active compound, etc. Determination of an effective dosage is well within the capabilities of those skilled in the art.

Effective dosages may be estimated initially from *in vitro* assays. For example, an initial dosage for use in animals may be formulated to achieve a circulating blood or serum concentration of active compound that is at or above an IC_{50} of the particular compound as measured in as *in vitro* assay, such as the *in vitro* CHMC or BMMC and other *in vitro* assays described in the Examples section. Calculating dosages to achieve such circulating

blood or serum concentrations taking into account the bioavailability of the particular compound is well within the capabilities of skilled artisans. For guidance, the reader is referred to Fingl & Woodbury, "General Principles," *In: Goodman and Gilman's The Pharmaceutical Basis of Therapeutics*, Chapter 1, pp. 1-46, latest edition, Pagamonon Press, and the references cited therein.

Initial dosages can also be estimated from *in vivo* data, such as animal models. Animal models useful for testing the efficacy of compounds to treat or prevent the various diseases described above are well-known in the art. Suitable animal models of hypersensitivity or allergic reactions are described in Foster, 1995, Allergy 50(21Suppl):6-9, discussion 34-38 and Tumas *et al.*, 2001, J. Allergy Clin. Immunol. 107(6):1025-1033. Suitable animal models of allergic rhinitis are described in Szelenyi *et al.*, 2000, Arzneimittelforschung 50(11):1037-42; Kawaguchi *et al.*, 1994, Clin. Exp. Allergy 24(3):238-244 and Sugimoto *et al.*, 2000, Immunopharmacology 48(1):1-7. Suitable animal models of allergic conjunctivitis are described in Carreras *et al.*, 1993, Br. J. Ophthalmol. 77(8):509-514; Saiga *et al.*, 1992, Ophthalmic Res. 24(1):45-50; and Kunert *et al.*, 2001, Invest. Ophthalmol. Vis. Sci. 42(11):2483-2489. Suitable animal models of systemic mastocytosis are described in O'Keefe *et al.*, 1987, J. Vet. Intern. Med. 1(2):75-80 and Bean-Knudsen *et al.*, 1989, Vet. Pathol. 26(1):90-92. Suitable animal models of hyper IgE syndrome are described in Claman *et al.*, 1990, Clin. Immunol. Immunopathol. 56(1):46-53. Suitable animal models of B-cell lymphoma are described in Hough *et al.*, 1998, Proc. Natl. Acad. Sci. USA 95:13853-13858 and Hakim *et al.*, 1996, J. Immunol. 157(12):5503-5511. Suitable animal models of atopic disorders such as atopic dermatitis, atopic eczema and atopic asthma are described in Chan *et al.*, 2001, J. Invest. Dermatol. 117(4):977-983 and Suto *et al.*, 1999, Int. Arch. Allergy Immunol. 120(Suppl 1):70-75. Ordinarily skilled artisans can routinely adapt such information to determine dosages suitable for human administration. Additional suitable animal models are described in the Examples section.

Dosage amounts will typically be in the range of from about 0.0001 or 0.001 or 0.01 mg/kg/day to about 100 mg/kg/day, but may be higher or lower, depending upon, among other factors, the activity of the compound, its bioavailability, the mode of administration and various factors discussed above. Dosage amount and interval may be adjusted individually to provide plasma levels of the compound(s) which are sufficient to maintain therapeutic or prophylactic effect. For example, the compounds may be administered once per week, several times per week (e.g., every other day), once per day or multiple times per

day, depending upon, among other things, the mode of administration, the specific indication being treated and the judgment of the prescribing physician. In cases of local administration or selective uptake, such as local topical administration, the effective local concentration of active compound(s) may not be related to plasma concentration. Skilled artisans will be able to optimize effective local dosages without undue experimentation.

Preferably, the compound(s) will provide therapeutic or prophylactic benefit without causing substantial toxicity. Toxicity of the compound(s) may be determined using standard pharmaceutical procedures. The dose ratio between toxic and therapeutic (or prophylactic) effect is the therapeutic index. Compounds(s) that exhibit high therapeutic indices are preferred.

The invention having been described, the following examples are offered by way of illustration and not limitation.

7. EXAMPLES

7.1 Synthesis of Starting Materials and Intermediates Useful for Synthesizing The 2,4-Pyrimidinediamine Compounds According to Schemes (I)–(V)

A variety of starting materials and N4-monosubstituted-2-pyrimidineamines and N2-monosubstituted-4-pyrimidinediamines [mono Substitution Nucleophilic Aromatic Reaction (SNAR) products] useful for synthesizing the 2,4-pyrimidinediamine compounds of the invention according to Schemes (I)-(V) were prepared as described below. Conditions suitable for synthesizing the mono SNAR products are exemplified with 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (**R926087**).

Section Number	Name of compound and reference number	Experimental
7.1	Synthesis of Starting Materials and Intermediates Useful for Synthesizing The 2,4-Pyrimidinediamine Compounds According to Schemes (I)–(V)	A variety of starting materials and N4-monosubstituted-2-pyrimidineamines and N2-monosubstituted-4-pyrimidinediamines [mono Substitution Nucleophilic Aromatic Reaction (SNAR) prfoducts] useful for synthesizing the 2,4-pyrimidinediamine compounds of the invention according to Schemes (I)-(V) were prepared as described below. Conditions suitable for synthesizing the mono SNAR products are exemplified with 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (**R926087**)
7.1.1	2,4-Dichloro-5-fluoropyrimidine	To a dry reaction flask equipped with a stir bar and a reflux condenser was placed 5-fluorouracil (0.65g, 5mmol) followed by phosphorus oxychloride ($POCl_3$) (1.53g, 10mmol). The resultant mixture was heated at 110 °C for 8 hours under a nitrogen atmosphere. The reaction was cooled to room temperature, phosphorus pentachloride (PCl_5) (3.12g, 15mmol) was added and heated to 110 °C for a period of 12 hours. After cooling to room temperature, the mixture was poured into ice-water, saturated with sodium chloride and left for 1 hour at 0 °C to complete the decomposition of $POCl_3$ and PCl_5. The solid of 2,4-dichloro-5-fluoropyrimidine was collected by rapid filtration, dried using blotting paper and stored at low temperature. ^{1}H NMR ($CDCl_3$): δ 8 47 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 155.42, 151.87, 147.43 and 147.13; ^{19}F NMR ($CDCl_3$): –38149.
7.1.2	2,4-Dichloro-5-nitropyrimidine (Aldrich D6, 930-0)	A suspension of 5-nitrouracil (10g, 63 mmol) in $POCl_3$ (100 mL) was refluxed for 5h in the presence of N,N-dimethylaniline (10 mL), cooled to room temperature and poured on to crushed ice with vigorous stirring. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduce pressure. The residue was purified by chromatography on silica gel (hexane/ethyl acetate; 1/1; v/v) to give the desired 2,4-dichloro-5-nitropyrimidine. LCMS: ret. time: 23.26 min.; purity: 95%; ^{1}H NMR ($CDCl_3$): δ 9.16 (1H, s).
7.1.3	2,4-Dichloro-5-cyanopyrimidine	In like manner to the preparation of 2,4-dichloro-5-nitropyrimidine, the reaction of 5-cyanouracil with $POCl_3$ and N,N-dimethylaniline gave 2,4-dichloro-5-cyanopyrimidine. LCMS: ret. time: 13.75 min.; purity: 95%.
7.1.4	2,4-Dichloro-5-trifluoromethylpyrimidine	In like manner to the preparation of 2,4-dichloro-5-nitropyrimidine, the reaction of 5-cyanouracil with $POCl_3$ and N,N-dimethylaniline gave 2,4-dichloro-5-cyanopyrimidine. ^{1}H NMR (CD_3OD): δ 9.07; LCMS: ret. time: 16.98 min. (fast method); purity: 70%.

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Section Number	Name of compound and reference number	Experimental
7.1.5	2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (R926087)	The reaction flask equipped with a magnetic stirring bar and a rubber septum (to prevent loss of 2,4-dichloro-5-fluoropyrimidine and N_2 inlet was charged with 3,4-ethylenedioxyaniline (34 g, 225 mmol), MeOH (100 mL), H_2O (300 mL) and 2,4-dichloro-5-fluoropyrimidine (25 g, 150 mmol). The reaction mixture was stirred at room temperature for 1h, diluted with H_2O (1.5 liter), acidified with 2N HCl (200 mL) and sonicated. The solid obtained was filtered, washed with H_2O and dried to obtain 33 g (78%) of the desired product, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (**R926087**). ^{1}H NMR ($CDCl_3$): δ 8 02 (1H, d, J= 3Hz), 7 25 (d, 1H, J= 1.2 Hz), 6 98 (dd, 1H, J= 2.4 and 8.1 Hz), 6.85 (d, 1H, J= 5.7 Hz), 4.27 (m, 4H); ^{19}F NMR ($CDCl_3$): - 44570; LCMS: ret time: 26.70 min.; purity 100%; MS (m/e): 283 (MH^+).
7.1.6	2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-nitro-4-pyrimidineamine (R940094)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-nitropyrimidine and 3,4-ethylenedioxyaniline were reacted to prepare 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-nitro-4-pyrimidineamine. LCMS: ret. time: 28.79 min.; purity: 90%; MS (m/e): 308 (M^+); ^{1}HNMR ($CDCl_3$): δ 10.07 (1H, s), 9.15 (1H, s), 7.02-6.88 (3H, m), 4.29 (4H, s).
7.1.7	2-Chloro-N4-(3-hydroxyphenyl)-5-nitro-4-pyrimidineamine (R940097)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-nitropyrimidine and 3-hydroxyaniline were reacted to prepare 2-chloro-N4-(3-hydroxyphenyl)-5-nitro-4-pyrimidineamine. LCMS: ret. time: 24.21 min.; purity: 93%; MS (m/e): 267 (MH^+); ^{1}HNMR ($CDCl_3$): δ 10.20 (1H, s), 9.19 (1H, s), 7.32 (1H, t, J= 2.2 Hz), 7.28 (1H, d, J= 7.8 Hz), 7.11 (1H, dd, J= 7.8 and 1.8 Hz), 7.76 (1H, dd, J= 8.4 and 2.4 Hz), 5.20 (1H, s).
7.1.8	2-Chloro-N4-(3-hydroxyphenyl)-5-fluoro-4-pyrimidineamine (R926111)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-hydroxyaniline were reacted to prepare product 2-chloro-N4-(3-hydroxyphenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 8.06 (bd, 1H), 7.26 (bd, 1H), 7.20-7.00 (m, 2H), 6,57 (d, 1H, J= 7.2 Hz); ^{19}F NMR (CD_3OD): - 44374; LCMS: ret. time: 22.02; purity: 100%, MS (m/e): 240 (M^+).

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Section Number	Name of compound and reference number	Experimental
7.1.9	2-Chloro-N4-(3,4-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine (R926073)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3,4-dimethoxyaniline were reacted to prepare 2-chloro-N4-(3,4-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.02 (d, 1H, J= 2.7 Hz), 7.38 (d, 1H, J= 2.4 Hz), 7.05 (dd, 1H, J= 2.4 and 9.0 Hz), 6.89 (bs, 1H), 6.88 (d, 1H, J= 9 Hz), 3.91 (s, 3H), 3.89 (s, 3H); ^{19}F NMR ($CDCl_3$). - 44593; LCMS: ret. time: 24.95 min.; purity: 98%; MS (m/e): 285 (MH^+).
7.1.10	2-Chloro-N4-(4-ethoxyphenyl)-5-fluoro-4-pyrimidineamine (R926066)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-ethoxyaniline were reacted to prepare 2-chloro-N4-(4-ethoxyphenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.01 (d, 1H, J= 3Hz), 7.49 (bdd, 2H, J= 8.7 Hz), 6.92 (bdd, 2H, J= 9.6 Hz), 4.03 (q, 2H, J= 7.2 Hz), 1.42 (t, 3H, J= 7.2 Hz); ^{19}F NMR ($CDCl_3$): - 44627; LCMS: ret. time: 29.50 min.; purity· 99%, MS (m/e): 268 (MH^+).
7.1.11	2-Chloro-N4-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine (R926207)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-chloroaniline were reacted to prepare 2-chloro-N4-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.1 (bs, 1H), 8.60 (bdd, 2H), 8.36 (bdd, 2H), 6.90 (bs, 1H); ^{19}F NMR ($CDCl_3$): - 44407; LCMS: ret. time: 31.63 min.; purity: 85%; MS (m/e): 258 (MH^+).
7.1.12	2-Chloro-5-fluoro-N4-(3-hydroxy-4-methoxycarbonylmethyleneoxyphenyl)-4-pyrimidineamine (R926393)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-hydroxy-4-methoxycarbonylmethylenoxyaniline were reacted to prepare 2-chloro-5-fluoro-N4-(3-hydroxy-4-methoxycarbonylmethyleneoxyphenyl)-4-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 8.03 (d, 1H, J= 3.6 Hz), 7.35 (dd, 1H, J= 2.4 Hz), 7.12 (dd, 1H, J= 2.4 and 8.7 Hz), 6.82 (d, 1H, J= 8.1 Hz), 4.86 (s, 2H), 3.81 (s, 3H).
7.1.13	N4-(4-tert-Butoxycarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (R926573)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and tert-butyl 4-aminophenoxyacetate were reacted to prepare product N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.02 (d, 1H, J= 2.7 Hz), 7.51 (d, 1H, J= 8.7 Hz), 6.93 (d, 1H, J= 8.7 Hz), 4.52 (s, 2H)), 1.49 (s, 9H); LCMS: ret. time: 29.50 min.; purity: 97%; MS (m/e): 354 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.14	2-Chloro-5-fluoro-N4-(indol-5-yl)-4-pyrimidineamine (R926581)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-aminoindole were reacted to prepare 2-chloro-5-fluoro-N4-(indol-5-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 9.45 (bs, 1H), 8.00 (bs, 1H), 7.82 (bd, 1H), 7.75 (s, 1H), 7.38-7.10 (m, 3H), 6.40 (bs, 1H); LCMS: ret. time: 23.85 min.; purity: 100%; MS (m/e): 263 (MH^+).
7.1.15	2-Chloro-5-fluoro-N4-(4-methoxymethyl-coumarin-7-yl)-4-pyrimidineamine (R926618)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-methoxymethyl-7-aminocoumarin were reacted to prepare 2-chloro-5-fluoro-N4-(4-methoxymethyl-coumarin-7-yl)-4-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 8.05 (d, 1H), 7.90 (s, 1H), 7.70 (dd, 1H, J= 2.4 and 8.7 Hz), 7.53 (d, 1H, J= 8.7 Hz), 6.42 (s, 1H), 4.61 (s, 2H), 3.49 (s, 3H); LCMS: ret. time: 26.38 min.; purity: 87%; MS (m/e): 336 (MH^+).
7.1.16	2-Chloro-N4-(2,5-dimethyl-4-hydroxyphenyl)-5-fluoro-4-pyrimidineamine (R926619)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 2,5-dimethyl-4-hydroxyaniline were reacted to prepare 2-chloro-N4-(2,5-dimethyl-4-hydroxyphenyl)-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 23.31 min.; purity: 96%; MS (m/e): 268 (MH^+).
7.1.17	2-Chloro-N4-(5-chloropyrid-2-yl)-5-fluoro-4-pyrimidineamine (R926061)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-chloro-2-aminopyridine were reacted to prepare 2-chloro-N4-(5-chloropyrid-2-yl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.40 (d, 1H, J= 8.7 Hz), 8.28 (d, 1H, J= 1.8 Hz), 8.17 (d, 1H, J= 2.1 and 9 Hz); LCMS: ret. time: 28.58 min.; purity: 100%, MS (m/e): 259 (MH^+).
7.1.18	2-Chloro-5-fluoro-N4-(5-methylpyrid-2-yl))-4-pyrimidineamine (R926062)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-methyl-2-aminopyridine were reacted to prepare 2-chloro-5-fluoro-N4-(5-methylpyrid-2-yl)-5-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 9.20 (s, 1H), 8.51 (s, 1H), 7.63 (d, 1H, J= 5.7 Hz), 7.45 (dd, 1H, J= 1.8 and 9.3 Hz), 2.43 (s, 3H); LCMS: ret. time: 21.29 min.; purity: 97%; MS (m/e): 239 (MH^+).
7.1.19	N4-[6-(1,4-Benzoxazinyl)]-N2-chloro-5-fluoro-4-pyrimidineamine	In like manner to 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-1,4-benzoxazine were reacted (in methanol or methanol:water) to yield N4-[6-(1,4-benzoxazinyl)]-N2-chloro-5-fluoro-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 8.2 (d, 1H), 6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.05 (m, 2H), 3.2 (m, 2H); LCMS: ret. time: 20.8 min.; purity: 95 %; MS (m/e): 295 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.20	N2-Chloro-N4-(2,3-dihydrobenzofuran-5-yl)-5-fluoro-4-pyrimidinediamine	In like manner to 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-amino-2,3-dihydrobenzofuran were reacted to yield N2-chloro-N4-(2,3-dihydrobenzofuran-5-yl)-5-fluoro-4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.09 (d, 1H), 8.00 (m, 1H), 7.42 (m, 2H), 7.05 (m, 1H), 4.53 (m, 2H), 4.25 (s, 2H), 3.15 (m, 2H); LCMS: ret. time: 20.35 min.; purity: 90 %; MS (m/e): 266 (MH^+).
7.1.21	2-Chloro-N4-(2-carboxy-4-chlorophenyl)-5-fluoro-4-pyrimidineamine (R940050)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 2-carboxy-4-chloroaniline were reacted to prepare 2-chloro-N4-(2-carboxy-4-chlorophenyl)-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 20.83 min.; purity: 98%; ^{1}H NMR ($CDCl_3$): δ 8.64 (1H, d, J= 4.8 Hz), 8.24 (1H, d, J= 2.7 Hz), 7.76 (1H, dd, J= 8.7 and 2.7 Hz), 7.70 (1H, dd, J= 8.7 and J= 0.9 Hz).
7.1.22	N-(2-Chloro-5-fluoro-4-pyrimidinyl)-L-tyrosine Methyl Ester (R940108)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and L-tyrosine methyl ester were reacted to prepare N-(2-chloro-5-fluoro-4-pyrimidinyl)-L-tyrosine Methyl Ester. LCMS: ret. time: 23.32 min.; purity: 83%; MS (m/e): 325 (M+); ^{1}H NMR ($CDCl_3$): δ 7.90 (1H, d, J= 2.7 Hz), 6.95 (2H, d, J= 8.7 Hz), 6.75 (2H, d, J= 8.7 Hz), 5.95 (1H, s), 5.72 (1H, d, J= 7.5 Hz), 5.05 (1H, dt, J= 7.5 and 5.3 Hz), 3.77 (3H, s), 3.16 (2H, m).
7.1.23	2-Chloro-N4-[3-(5-cyano-2-methyl-4-thiomethyl-6-pyrimidinyl)phenyl]-5-fluoro-4-pyrimidineamine (R940141)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-(5-cyano-2-methyl-4-thiomethyl-6-pyrimidinyl)aniline were reacted to prepare 2-chloro-N4-[3-(5-cyano-2-methyl-4-thiomethyl-6-pyrimidinyl)phenyl]-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 18.23 min.; purity: 84%; MS (m/e): 386 (M^+); ^{1}H NMR ($CDCl_3$): δ 8.19 (1H, t, J= 1.9 Hz), 8.11 (1H, d, J= 3.1 Hz), 7.98 (1H, dd, J= 8.1 and J= 2.4 Hz), 7.82 (1H, dd, J=7.8 and 1.8 Hz), 7.57 (1H, t, J= 7.8 Hz), 7.11 (1H, s), 2.79 (3H, s), 2.69 (3H, s).
7.1.24	N4-[4-(N-Benzylpiperazino)phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (R945154)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 4-(N-benzylpiperazino)aniline and 2,4-dichloro-5-fluoropyrimidine gave N4-[4-(N-benzylpiperazino)phenyl]-2-chloro-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 2.81 (m, 4 H), 3.37 (m, 6 H), 6.85 (br, 1 H), 6.93 (d, J= 9.0 Hz, 2 H), 7.40 (m, 5 H), 7.50 (d, J= 9.3 Hz, 2 H), 8.02 (d, J= 2.7 Hz, 1 H); LCMS: ret. time: 20.56 min, purity: 97.75%, MS (m/e): 398.00 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.25	2-Chloro-N4-(4-cyanomethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine (R945069)	In a manner analogous to the preparation of N2,N4-bis(4-cyanomethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine, N4-(4-aminocarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (178 mg, 0.6 mmol), trifluoroacetic anhydride (0.17 mL, 1.2 mmol) and pyridine (0 15 mL, 1.84 mmol) gave 2-chloro-N4-(4-cyanomethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine (110 mg, 66%). ^{1}H NMR (acetone-d_6): δ 5.22 (s, 2 H), 7.24 (d, J= 9.3 Hz, 2 H), 7.62 (d, J= 9.0 Hz, 2 H), 8.94 (d, J= 1.8 Hz, 1 H); ^{19}F NMR (acetone-d_6): -137.60; LCMS: ret. time: 26.19 min.; purity: 89.93%; MS (m/e): 279.06 (MH^+).
7.1.26	N4-(4-Acetoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (R940210)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-acetoxyaniline were reacted to prepare N4-(4-acetoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine. LCMS: ret. time· 25.97 min.; purity: 98%; MS (m/e): 281 (M^+); ^{1}H NMR ($CDCl_3$): δ 8.07 (1H, d, J= 2.7 Hz), 7.64 (2H, d, J= 9 Hz), 7.12 (2H, d, J= 9 Hz), 7.00 (1H, s), 2.31 (3H, s).
7.1.27	2-Chloro-5-fluoro-N4-(4-hydroxyphenyl)-4-pyrimidineamine (R940211)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-hydroxyaniline were reacted to prepare 2-chloro-5-fluoro-N4-(4-hydroxyphenyl)-4-pyrimidineamine. LCMS: ret. time: 20.10 min.; purity: 98%; MS (m/e): 240 (MH^+); ^{1}H NMR ($CDCl_3$): δ 8.02 (1H, d, J= 2.7 Hz), 7.46 (2H, d, J= 8.7 Hz), 6.86 (2H, d, J= 9 Hz), 6.85 (1H, s), 4.94 (1H, s).
7.1.28	2-Chloro-N4-(2,3-dimethyl-4-hydroxyphenyl)-5-fluoro-4-pyrimidineamine (R940213)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 2,3-dimethyl-4-hydroxyaniline were reacted to prepare 2-chloro-N4-(2,3-dimethyl-4-hydroxyphenyl)-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 23.29 min.; purity: 93%; MS (m/e): 268 (MH^+); ^{1}H NMR ($CDCl_3$): δ 8.00 (1H, d, J= 2.7 Hz), 7.16 (1H, d, J= 8.7 Hz), 6.68 (1H, d, J= 8.7 Hz), 6.61 (1H, s), 4.87 (1H, s), 2.21 (3H, s), 2.16 (3H, s)
7.1.29	2-Chloro-N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-4-pyrimidineamine (R940230)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloro-4-hydroxy-5-methylaniline were reacted to prepare 2-chloro-N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 26.26 min.; purity: 90%; ^{1}H NMR (DMSO-d6): δ 9.94 (1H, s), 9 21 (1H, s), 8.37 (1H, d, 3.6 Hz), 7.68 (1H, s), 7.41 (1H, s), 2.30 (3H, s).

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Section Number	Name of compound and reference number	Experimental
7.1.30	2-Chloro-5-fluoro-N4-[4-[3-(N-morpholino)propyl]oxyphenyl]-4-pyrimidineamine (R940247)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-[3-(N-morpholino)propyl]oxyaniline were reacted to prepare 2-chloro-5-fluoro-N4-[4-[3-(N-morpholino)propyl]oxyphenyl]-4-pyrimidineamine. LCMS: ret. time: 17.15 min.; purity: 99%; MS (m/e): 367 (MH^+); ^1H NMR ($CDCl_3$): δ 8.02 (1H, d, J= 2.7 Hz), 7.49 (2H, d, J= 8.7 Hz), 6.92 (2H, d, J= 9 Hz), 6.85 (1H, s), 4.03 (2H, t, J= 6.3 Hz), 3.73 (4H, t, J= 4.6 Hz), 2.53 (2H, t, J= 6.7 Hz), 2.47 (4H, m), 1.98 (2H, m).
7.1.31	N4-[2-[4-(N-Benzylpiperazino)ethyl]]-2-chloro-5-fluoro-4-pyrimidineamine (R940259)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine 2,4-dichloro-5-fluoropyrimidine and 2-[4-(N-benzylpiperazino)ethylamine were reacted to prepare N4-[2-[4-(N-benzylpiperazino)ethyl]]-2-chloro-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 21 11 min., purity. 96%; MS (m/e)· 349 (M^+); ^1H NMR ($CDCl_3$)· δ 7 88 (1H, d, J= 2.6 Hz), 7.31-7.17 (4H, m), 7 14 (1H, d, J= 1.7 Hz), 7.10 (1H, s), 3.76 (2H, m), 3.24 (2H, m), 2.90 (2H, m), 2.59 (2H, m), 2.34 (2H, m), 1.76 (4H, m).
7.1.32	N4-(3-*tert*-Butylphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (R940268)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-*tert*-butylaniline were reacted to prepare N4-(3-*tert*-butylphenyl)-2-chloro-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 33.96 min.; purity: 98 %; MS (m/e): 279 (M^+); ^1H NMR ($CDCl_3$): δ 8.05 (1H, d, J= 3 Hz), 7.62 (1H, t, J= 1.3 Hz), 7.50 (1H, m), 7.34 (1H, t, J= 7.8 Hz), 7.22 (1H, m), 6.96 (1H, sl), 1.34 (9H, s).
7.1.33	2-Chloro-5-fluoro-N4-[3-(hydroxymethyl)phenyl]-4-pyrimidineamine (R925756)	In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-aminobenzylalcohol were reacted to yield 2-chloro-5-fluoro-N4-[3-(hydroxymethyl)phenyl]-4-pyrimidineamine. ^1H NMR ($CDCl_3$): δ 8.45 (bs, 1H), 7.96 (d, 1H, J= 2.9 Hz), 7.65 (d, 1H, J= 8.2 Hz), 7.34 (s, 1H), 7.31 (t,1H, J= 8.2 Hz), 7.07 (d, 1H, J= 8.2), 4.52 (s, 2H)); ^{19}F NMR ($CDCl_3$): -44394 (s, 1F); LCMS: ret. time: 20.29 min.; purity: 100 %; MS (m/e): 254 (MH^+).
7.1.34	2-Chloro-5-fluoro-N4-[4-(hydroxymethyl)phenyl]-4-pyrimidineamine (R925759)	In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-aminobenzylalcohol were reacted to yield 2-chloro-5-fluoro-N4-[4-(hydroxymethyl)phenyl]-4-pyrimidineamine. ^1H NMR ($CDCl_3$): δ 8.08 (d, 1H, J= 2.7 Hz), 7.62 (d, 2H, J= 9.0 Hz), 7.40 (d, 2H, J= 8.1 Hz), 6.99 (bs, 1H), 4.70 (s, 2H); ^{19}F NMR ($CDCl_3$): -44570 (s, 1F); LCMS: ret. time: 19.57 min.; purity: 99%; MS (m/e): 254 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.35	2-Chloro-N4-(3,3-dihydroisobenzofuranynl-1-one-6-yl)-5-fluoro-4-pyrimidineamine R940279	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-3,3-dihydroisobenzofuran-1-one were reacted to give 2-chloro-N4-(3,3-dihydroisobenzofuranynl-1-one-6-yl)-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 21.15 min.; purity: 94.7 %; MS (m/e): 280 (MH^+).
7.1.36	2-Chloro-5-fluoro-N4-((2R)-hydroxy-(1S)-methyl-2-phenylethyl)-4-pyrimidineamine (R925762)	In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and (1R,2S)-(-)-norephedrine were reacted to yield 2-chloro-5-fluoro-N4-(2R-hydroxy-1S-methyl-2-phenylethyl)-4-pyrimidineamine. ^1H NMR ($CDCl_3$): δ 7.85 (d, 1H, J= 3.0 Hz), 7.38 (m, 5H), 5.56 (d, 1H, J= 7.5 Hz), 5 00 (d, 1H, J= 3.0 Hz), 4.54 (m, 1H), 2.87 (bs, 1H), 1.10 (d, 1H, J= 6.9 Hz); ^{19}F NMR ($CDCl_3$)· - 44408.
7.1.37	N-(2-Chloro-6-ethoxycarbonyl-5-nitro-4-pyrimidinyl)glycine Ethyl Ester (R925850)	In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-6-ethoxycarbonyl-5-nitropyrimidine and glycine ethyl ester hydrochloride salt were reacted to yield N-(2-chloro-6-ethoxycarbonyl-5-nitro-4-pyrimidinyl)glycine Ethyl Ester. ^1H NMR ($CDCl_3$): δ 8.87 (bs, 1H), 4.48 (q, 2H, J= 7.2 Hz), 4.39 (d, 2H, J= 5.1 Hz), 1.40 (t, 3H, J= 6.9 Hz), 1.33 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 28.27 min.; purity: 97%; MS (m/e): 332 (M^+).
7.1.38	2-Chloro-5-fluoro-N4-(2-hydroxy-2-phenylethyl)-4-pyrimidineamine (R925763)	In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 2-amino-1-phenylethanol were reacted to yield 2-chloro-5-fluoro-N4-(2-hydroxy-2-phenylethyl)-4-pyrimidineamine. ^1H NMR ($CDCl_3$): δ 7.88 (d, 1H, J= 3.0 Hz), 7.41-7.32 (m, 5H), 5.71 (bs, 1H), 4.97 (d, 1H, J= 8.1 Hz), 3.98 (m, 1H), 3.56 (m, 1H), 2.57 (s, 1H); ^{19}F NMR ($CDCl_3$): - 45149; LCMS: ret. time: 22.27 min.; purity: 98%; MS (m/e): 263 (M^+).
7.1.39	2-Chloro-5-fluoro-N4-(furfuryl)-4-pyrimidineamine (R925764)	In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and furfurylamine were reacted to yield 2-chloro-5-fluoro-N4-(furfuryl)-4-pyrimidineamine. ^1H NMR ($CDCl_3$): δ 7.91 (d, 1H, J= 1.8 Hz), 7.39 (d, 1H, J= 1.2 Hz), 6.35 (m, 2H), 5.50 (bs, 1H), 4.69 (d, 2H, J= 5.1 Hz); ^{19}F NMR ($CDCl_3$): - 45163; LCMS: ret. time: 24.52 min.; purity: 97%; MS (m/e): 228 (M^+).
7.1.40	R935010: (±)-2-Chloro-5-fluoro-N4-[1-(4-hydroxyphenyl)ethyl]-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with 1-(4-hydroxyphenyl)ethylamine to provide (±)-2-chloro-5-fluoro-N4-[1-(4-hydroxyphenyl)ethyl]-4-pyrimidineamine. ^1H NMR ($CDCl_3$): δ 7.88 (d, 1H, J= 2.3 Hz), 7.50-7.47 (dd, 2H, J= 1.7 and 8.7 Hz), 7.26-7.23 (dd, J= 8.7 and 1.7 Hz), 5.35-5.28 (m, 2H), 1.59 (d, 3H, J= 7.0 Hz).

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Section Number	Name of compound and reference number	Experimental
7.1.41	R935011: (±)-N4-[1-(4-Bromophenyl)ethyl]-2-chloro-5-fluoro-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with 1-(4-bromophenyl)ethylamine to provide (±)-N4-[1-(4-bromophenyl)ethyl]-2-chloro-5-fluoro- 4-pyrimidineamine: ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1H, J= 2.3 Hz), 7.49 (d, 2H, J= 8.7 Hz), 7.25 (d, 2H, J= 8.7 Hz), 4.45-5.26 (m, 2H), 1.59 (d, 3H, J=7.0 Hz).
7.1.42	R935007: 2-chloro-5-fluoro-N4-[1-[(1*S*)-phenyl]ethyl]-4-pyrimidineamine	In like manner to the preparation of of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 1-(*1S*)-phenyl ethylamine were reacted to produce 2-chloro-5-fluoro-N4-[1-[(1*S*)-phenyl]ethyl]-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$). δ 7.86 (d, 1H, J = 2.9 Hz), 7.37 (d, 4H, J = 4.7 Hz), 7.34-7.30 (m, 1H), 5.40-5 32 (m, 2H), 1.62 (d, 3H, J = 6.4 Hz); LCMS: ret. time: 29.5 min.; purity: 98%; MS (*m/e*): 252 (MH^+).
7.1.43	R935008: 2-Chloro-5-fluoro-N4-[1-[(1*R*)-pheny]lethyl]-4-pyrimidineamine	In like manner to the preparation of of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 1-(*1R*)-phenyl ethylamine were reacted to produce 2-chloro-5-fluoro-N4-[1-[(*1R*)-phenyl]ethyl]-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 1H, J = 2.9 Hz), 7.37 (d, 4H, J = 4.1 Hz), 7.34-7.30 (m, 1H), 5.38-5.31 (m, 2H), 1.62 (d, 3H, J = 6.4 Hz).
7.1.44	R935012: 2-Chloro-N4-[[di(3,5-di(trifluoromethyl)phenyl)]methyl]-5-fluoro-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with di[3,5-di(trifluoromethyl)phenyl]methylamine to provide 2-chloro-N4-[[di(3,5-di(trifluoromethyl)phenyl)]methyl]-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$)· δ 8.06 (d, 1H, J= 2.3 Hz), 7.92 (s, 2H), 7.74 (s, 4H), 6.75 (d, 1H, J= 7.6 Hz), 5.80 (d, 1H, J= 7.0 Hz).
7.1.45	R935014: 2-Chloro-5-fluoro-N4-[1-[(1*R*)-4-methoxyphenyl]ethyl]-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with (*R*)-(+)-1-(4-methoxyphenyl)ethylamine to provide 2-chloro-5-fluoro-N4-[1-[(1*R*)-4-methoxyphenyl]ethyl]-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 7.84 (d, 1H, J= 2.3 Hz), 7.30 (d, 2H, J= 8.8 Hz), 6.89 (d, 2H, J= 8.8 Hz), 5.39-5.26 (m, 2H), 3.80 (s, 3H), 1.59 (d, 3H, J= 6.4 Hz).
7.1.46	R935015: 2-Chloro-5-fluoro-N4-[1-[(1*S*)-4-methoxyphenyl]ethyl]-4-pyrimidineamine	In like manner to the preparation of 2-chloro-5-fluoro-N4-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with (*S*)-(-)-1-(4-methoxyphenyl)ethylamine to provide 2-chloro-5-fluoro-N4-[1-[(1*S*)-4-methoxyphenyl]ethyl]-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 7.85 (d, 1H, J= 2.3 Hz), 7.31 (d, 2H, J= 8.8 Hz), 6.89 (d, 2H, J= 8.8 Hz), 5.38-5.29 (m, 2H), 3.80 (s, 3H), 1.59 (d, 3H, J= 7.7 Hz).

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Section Number	Name of compound and reference number	Experimental
7.1.47	R935013: 2-Chloro-N-(fluoren-9-yl)-5-fluoro-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro 4-pyrimidineamine, 9-aminofluorene hydrochloride and 2,4-dichloro-5-fluoropyrimidine with added diisopropylethylamine were reacted to produce 2-chloro-N-(fluoren-9-yl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 1H, J= 2.3 Hz), 7.73 (d, 2H, J= 7.6 Hz), 7.59(d, 2H, J= 7.6 Hz), 7.44 (t, 2H, J= 7.6 Hz), 7.32 (app t, 2H, J= 7.6 Hz), 6.50 (d, 1H, J= 8.8 Hz), 5.45 (d, 1H, J= 8.4 Hz).
7.1.48	R935210: 2-Chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-4-pyrimidineamine	In like manner to the prepartation of 2-chloro-N-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, experiment, 2,4-dichloro-5-fluoropyrimidine was reacted with 4-(methoxycarbonylmethyleneoxy)aniline to produce 2-chloro-5-fluoro-N-[4-(methoxycarbonylmethyleneoxy)phenyl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.17 (s, 1H), 8 33 (d, 1H, J= 3.5 Hz), 8.05 (s, 1H), 7.91 (s, 1H), 7.74 (d, 1H, J= 8.2 Hz), 7.40 (d, 1H, J= 7.6 Hz), 5.31 (s, 2H), 3.66 (s, 3H).
7.1.49	R935200: 2-Chloro-5-fluoro-N-(1-methyl-indazoline-5-yl)-4-pyrimidineamine:	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-amino-1-methyl-indazoline were reacted to provide 2-chloro-5-fluoro-N-(1-methyl-indazoline-5-yl)-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.01 (s, 1H), 8.27 (d, 1H, J= 3.5 Hz), 8.04 (d, 1H, J= 1.7 Hz), 7.98 (d, 1H, J= 1.7 Hz), 7.64 (d, 1H, J= 8.8 Hz), 7.56 (dd, 1H, J= 1.7 and 8.8 Hz), 4.02 (s, 3H). LCMS: ret. time: 21.72 min.; purity: 99%; MS (*m/e*): 278 (MH^+).
7.1.50	R935017: N-(5-Bromo-2-chloropyrimidinyl)-4-fluorophenylethylamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro 4-pyrimidineamine, 4-fluoro-α-methylbenzylamine and 5-bromo-2,4-dichloropyrimidine were reacted to produce N-(5-bromo-2-chloropyrimidinyl)-4-fluorophenylethylamine. ^{1}H NMR ($CDCl_3$): δ 8.12 (s, 1H), 7.35-7.25 (dd, 2H, J= 3.5 and 8.7 Hz), 7.05 (t, 1H, J= 8.7 Hz), 5.63 (d, 1H, J= 6.4 Hz), 5.36 (dq, 1H, 1H, J= 6.4 and 7.0 Hz), 1.60 (d, 3H, J= 7.0 Hz); LCMS: ret. time: 30.73 min.; purity: 94%; MS (*m/e*): 331 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.51	R935009: (±)-N-(2-Chloro-5-fluoropyrimidinyl)-1-(4-fluorophenyl)ethylamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro 4-pyrimidineamine, 4-fluoro-α-methylbenzylamine and 2,4-dichloro-5-fluoropyrimidine were reacted to produce (±)-N-(2-chloro-5-fluoropyrimidinyl)-1-(4-fluorophenyl)ethylamine. ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 1H, J= 2.3 Hz), 7.37-7.33 (dd, 2H, J= 5.4 and 8.4 Hz), 7.04 (t, 2H, J= 8.4 Hz), 5.35-5.31 (m, 2H), 1.60 (d, 3H, J= 6.4 Hz); LCMS: ret. time: 32.90 min.; purity: 98%; MS (*m/e*): 270 (MH^+).
7.1.52	R935022: 5-Bromo-2-chloro-N4-[4-(N-methyl-2-methoxycarbonyl)ypyrrolyl)-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro 4-pyrimidineamine, 5-bromo-2,4-dichloropyrimidine and N-methyl-2-carbomethoxy-4-aminopyrrole hydrochloride with added diisopropylethylamine were reacted to produce the desired product 5-bromo-2-chloro-N-(N-methyl-2-carbomethoxypyrrol-4-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.21 (s, 1H), 7.43 (d, 1H, J= 1.8 Hz), 7.13 (br s, 1H), 6.84 (d, 1H, J= 1.8 Hz), 3.95 (s, 3H), 3.82 (s, 3H); LCMS: ret. time: 26.96 min.; purity: 91%; MS (*m/e*): 346 (MH^+).
7.1.53	R935234: 2-Chloro-5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-(4-aminophenoxymethyl)-3-phenyl-1,2-4-oxadiazole were reacted to produce 2-chloro-5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d_6): δ 9.92 (s, 1H), 8.26 (d, 1H, J= 3.5 Hz), 8.02-7.99 (m, 2H), 7.60-7.56 (m, 5H), 7.11 (d, 2H, J= 8.8 Hz), 5.58 (s, 2H); LCMS: ret. time: 32.09 min.; purity: 96%; MS (*m/e*): 398 (MH^+).
7.1.54	R935235: 2-Chloro-5-fluoro-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-(4-aminophenoxymethyl)-3-methyl-1,2-4-oxadiazole were reacted to produce 2-chloro-5-fluoro-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d_6): δ 9.91 (s, 1H), 8.26 (d, 1H, J= 3.5 Hz), 7.56 (d, 2H, J= 8.8 Hz), 7.05 (d, 2H, J= 8.8 Hz), 5.46 (s, 2H), 2.34 (s, 3H); LCMS: ret. time: 25.05 min.; purity: 98%; MS (*m/e*): 336 (MH^+).
7.1.55	R935236: 2-Chloro-5-fluoro-N4-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethyleneioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-[1-ethoxycarbonyl-1-methyl)ethyl]aniline were reacted to produce 2-chloro-5-fluoro-N4-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d_6): δ 9.99 (s, 1H), 8.30 (d, 1H, J= 3.5 Hz), 7.60 (d, 2H, J= 8.8 Hz), 7.30 (d, 2H, J= 8.8 Hz), 4.04 (qt, 2H, J= 7.0 Hz), 1.47 (s, 6H), 1.10 (t, 3H, J= 7.0 Hz); LCMS: ret. time: 31.07 min.; purity: 97%; MS (*m/e*): 338 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.56	2,4-Dichloro-5-ethoxycarbonylpyrimidine	A dry reaction flask equipped with a stirring bar and a reflux condenser was charged with 5-ethoxycarbonyluracil (1.84g, 10 mmol), $POCl_3$ (10 mL) and N,N-dimethylaniline (1 mL) and heated at 90 °C for 2h. The excess $POCl_3$ was removed under a reduced pressure and quenched with ice-water (100 g). The aqueous solution was extracted with ethyl ether (3 x 100 mL), washed with saturated aqueous $NaHCO_3$ solution and water (100 mL, each). After drying over sodium sulfate, the ethyl ether was removed and the residue was dried under a high vacuum to afford 2,4-dichloro-5-ethoxycarbonylpyrimidine. ^{1}H NMR ($CDCl_3$): δ 9.00 (s, 1H), 4.45 (q, 2H, J= 6.9 Hz), 1.42 (t, 3H, J= 6.9 Hz).
7.1.57	N-(2-Chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester (R926518) and N-(4-Chloro-5-ethoxycarbonyl-2-pyrimidinyl)-L-phenylalanine Ethyl Ester (R926519)	A mixture of L-phenylalanine Ethyl Ester Hydrochloride (0.137g, 0.6 mmol) 2,4-dichloro5-ethoxycarbonylpyrimidine (0.112g, 0.5 mmol), triethylamine (0.7 mL, 0.6 mmol) in THF (4 mL) in a sealed tube was heated at 100 °C for 3h. The reaction was diluted with H_2O (20 ML), extracted with CH_2Cl_2 (3 x 50 mL), washed with 2N HCl (10 mL), water (10 mL) and solvent was evaporated. The residue obtained was purified by preparative TLC using 15% EtOAc in hexanes to obtain two products mainly, N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester (**R926518**). ^{1}H NMR ($CDCl_3$): δ 8.72 (d, 1H, J= 6.92 Hz), 8.66 (s, 1H), 7.32-7.17 (m, 5H), 5.05 (dq, 1H, J= 1.2 and 5.7 Hz), 4.34 (q, 2H, J= 6.9 Hz), 4.20 (q, 2H, J= 5.1 Hz), 3.24 (dd, 1H, J= 5.4 Hz), 3.16 (dd, 1H, J= 7.5 Hz), 1.35 (t, 3H, J= 7.2 Hz), 1.24 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 37.15 min.; purity: 99%; MS (m/e): 378 (MH^+) and N-(4-chloro-5-ethoxycarbonyl-2-pyrimidinyl)-L-phenylalanine Ethyl Ester (**R926519**). ^{1}H NMR ($CDCl_3$): δ 8.83 (s, 1H), 7.28 (m, 3H), 7.18 (m, 2H), 6.00 (bt, 1H), 4.99 (bdq, 1H), 4.36 (q, 2H, J= 7.8 Hz), 4.19 (q, 2H, J= 6.9 Hz), 3.20 (t, 2H, J= 6.9 Hz). 1.38 (t, 3H, J= 4.5 Hz), 1.24 (t, 3H, J= 6 Hz); LCMS: ret. time: 34.80 min.; purity: 88%; MS (m/e): 378 (M^+).

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Section Number	Name of compound and reference number	Experimental
7.1.58	N-(2-Chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-valine Ethyl Ester (R926520) and N-(4-Chloro-5-ethoxycarbonyl-2-pyrimidinyl)-L-valine Ethyl Ester (R926521)	In like manner to the preparation of N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester, 2,4-dichloro-5-ethoxycarbonylpyrimidine and L-valine Ethyl Ester were reacted to prepare N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-valine Ethyl Ester **(R926520).** ^{1}H NMR ($CDCl_3$): δ 8.80 (d, 1H, J= 8.1 Hz), 8.68 (s, 1H), 4.77 (dd, 1H, J= 4.8 Hz), 4.36 (q, 2H, J= 7.2 Hz), 4.24 (q, 2H, J= 6.6 Hz), 2.38 (m, 1H), 1.39 (t, 3H, J= 6.9 Hz), 1.29 (t, 3H, J= 7 2 Hz), 1.03 (d, 3H, J= 3 Hz), 1.00 (d, 3H, J= 2.7 Hz); LCMS: ret. time: 36.54 min.; purity: 89%; MS (m/e): 330 (MH^+) and N-(4-chloro-5-ethoxycarbonyl-2-pyrimidinyl)-L-valine Ethyl Ester **(R926521).** ^{1}H NMR ($CDCl_3$): δ 8.82 (s, 1H), 6.02 (m, 1H), 4.69 (dd, 1H, J= 4.8 and 4 5 Hz), 4.33 (q, 2H, J= 7.5 Hz), 4.23 (q, 2H, J= 7.5 Hz), 2 28 (sept, 1H) 1 34 (t, 3H, J= 6.9 Hz), 1.28 (t, 3H, J= 7 Hz), 1.00 (d, 6H, J= 7.2 Hz); LCMS· *ret. time: 33 53 min.; purity: 91%;* MS (m/e): 330 (M^+).
7.1.59	N-(2-Chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-leucine Ethyl Ester (R926522)	In like manner to the preparation of N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester, 2,4-dichloro-5-ethoxycarbonylpyrimidine and L-leucine Ethyl Ester were reacted to prepare N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-leucine Ethyl Ester. ^{1}H NMR ($CDCl_3$): δ 8.69 (s, 1H), 8.64 (d, 1H, 7.8 Hz), 4.84 (s, 1H), 4.38 (q, 2H, J= 7.2 Hz), 3.75 (s, 3H), 1.73 (m, 2H), 1.39 (t, 3H, J= 6.9 Hz), 0.97 (d, 3H, J= 4 2 Hz), 0 95 (d, 3H, J= 4.8 Hz) ; LCMS: ret. time: 36.09 min.; purity: 92%; MS (m/e): 330 (MH^+).
7.1.60	N-(2-Chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-alanine Ethyl Ester (R926523) and N-(4-Chloro-5-ethoxycarbonyl-2-pyrimidinyl)-L-alanine Ethyl Ester (R926524)	In like manner to the preparation of N-(2-chloro-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester, 2,4-dichloro-5-ethoxycarbonylpyrimidine and L-valine Ethyl Ester were reacted to prepare N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-alanine Ethyl Ester **(R926523).** ^{1}H NMR ($CDCl_3$): δ 8.80 (bd, 1H), 8.68 (s, 1H), 4.79 (q, 1H, J= 7.2 Hz), 4.35 (q, 2H, J= 7.2 Hz), 4.24 (m, 2H), 1.53 (d, 3H, J= 7.2 Hz), 1.38 (t, 3H, J= 7.2 Hz), 1.29 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 31.89 min.; purity: 94%; MS (m/e): 303 (MH^+) and N-(4-chloro-5-ethoxycarbonyl-2-pyrimidinyl)-L-alanine Ethyl Ester **(R926524).** ^{1}H NMR ($CDCl_3$): δ 8.80 (s, 1H), 6.01 (bs, 1H), 4.65 (bq, 1H), 4.35 (q, 2H), 4.20 (q, 2H), 1.55, t, 3H), 1.40 (t, 3H), 1.25 (t, 3H); LCMS: ret. time: 28.78 min ; purity: 84%; MS (m/e): 302 (M^+).

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Section Number	Name of compound and reference number	Experimental
7.1.61	2-Chloro-N4-(4-n-butyloxyphenyl)-5-fluoro-4-pyrimidineamine	To a solution of 2,4-dichloro-5-fluoropyrimidine (0.5 g, 3.0 mmol) and 4-n-butoxyaniline (0.49 g, 3 mmol) in acetone/H_2O (1:9 mL) at room temperature was added concentrated HCl (0.1 mL). The mixture was heated at reflux for 1 h, cooled to room temperature, and made basic with 2 N NaOH (2 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude black solid was purified by chromatography (4:1 hexanes/EtOAc) to afford 2-chloro-N4-(4-n-butyloxyphenyl)-5-fluoro-4-pyrimidineamine (0.71 g, 80%) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 2.7 Hz, 1H), 7.51-7.46 (m, 2H), 6.95-6 89 (m, 2H), 6.83 (bs, 1H), 3.99-3.95 (t, J = 6.5 Hz, 2H), 1.82-1.57 (m, 2H), 1.53-1.43 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H).
7.1.62	2-Chloro-N4-(4-n-hexyloxyphenyl)-5-fluoro-4-pyridineamine	In like manner to the preparartion of 2-chloro-N4-(4-n-butyloxyphenyl)-5-fluoro-4-pyrimidineamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-n-hexyloxyaniline gave 2-chloro-N4-(4-n-hexyloxyphenyl)-5-fluoro-4-pyridineamine. The crude product was purified by chromatography (4:1 $CHCl_3$/EtOAc) to afford (14) (0.74 g, 76%) as a red-brown oil that solidified upon standing: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 2.7 Hz, 1H), 7.50 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 6.84 (bs, 1H), 3.96 (t, J = 6.5 Hz, 2H), 1.83-1.74 (m, 2H), 1.48-1.41 (m, 2H), 1.36-1.34 (m, 4H), 0.93-0.89 (m, 3H).
7.1.63	N4-(3-Benzyloxyphenyl)-2-chloro-4-pyrimidineamine	A mixture of 2,6-dichloropyrimidine (2.00 g, 13.4 mmol), 3-benzyloxoaniline (2.07 g, 13.4 mmol) and triethylamine (2.72 g, 26.8 mmol) in 1-butanol (20 mL) was stirred at 50 °C for 17 h. The reaction mixture was concentrated to remove most of the 1-butanol, the crude product was preadsorbed onto silica gel using chloroform and purified by flash chromatography (95:5 chloroform/ methanol) to afford N4-(3-benzyloxyphenyl)-2-chloro-4-pyrimidineamine (1.70 g, 40%) as colorless oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.2 (s, 1H), 8.16 (d, J = 6.0 Hz, 1H), 7.48-7.24 (m, 7H), 7.12 (d, J = 9.0 Hz, 1H), 6.78 (m, 2H), 5.11 (s, 2H); ESI MS *m/z* 312 $[C_{17}H_{14}ClN_3O + H]^+$.
7.1.64	N4-[4-(tert-Butoxycarbonylmethyleneoxy)phenyl]-3-chloro-5-ethoxycarbonyl-4-pyrimidineamine (R926578)	In like manner to the preparation of N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester, 5-carboxyethoxy-2,4-dichloropyrimidine and tert-butyl 4-aminophenoxyacetatewere reacted to prepare N4-[4-(tert-butoxycarbonylmethyleneoxy)phenyl]-2-chloro-5-ethoxycarbonyl-2-chloro-4-pyrimidineamine. LCMS: MS (m/e): 407 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.65	N4-(4-Ethoxyphenyl)-5-ethoxycarbonyl-2-trifluoromethyl-4-pyrimidineamine (R926059)	In like manner to the preparation of N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester, 4-chloro-5-ethoxycarbonyl-2-trifluoromethylpyrimidine and 4-ethoxyaniline were reacted to prepare N4-(4-ethoxyphenyl)-5-ethoxycarbonyl-2-trifluoromethyl-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 10.39 (s, 1H), 9.02 (s, 1H), 7.59 (dd, 2H, J= 2.1 and 7.2 Hz), 6.91 (dd, 2H, J= 1.8 and 6.6 Hz), 4.44 (q, 2H, J= 7.5 Hz), 4.06 (q, 2H, J= 7.2 Hz), 1.44 (m, 6H); LCMS: ret. time: 38.49 min.; purity: 100%; MS (m/e): 356 (MH^+).
7.1.66	N2-(4-Ethoxyphenyl)-5-methoxycarbonyl-4-trifluoromethyl-2-pyrimidineamine (R926060)	In like manner to the preparation of N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester, 2-chloro-5-methoxycarbonyl-4-trifluoromethylpyrimidine and 4-ethoxyaniline were reacted to prepare N2-(2-ethoxyphenyl)-5-methoxycarbonyl-4-trifluoromethyl-2-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.98 (s, 1H), 7.47 (m, 3H), 6.91 (dd, 2H, J= 2.1 and 6.9 Hz), 4.05 (q, 2H, 6.9 Hz), 1.42 (t, 3H, J= 6.8 Hz); ^{19}F NMR ($CDCl_3$): -19105; LCMS: ret. time. 33.87 min; purity: 100%, MS (m/e): 342 (MH^+).
7.1.67	2-Chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine (R926853)	A reaction mixture containing 2,4-dichloro-5-fluoro-pyrimindine (1.2 equivalents) and 3-(tetrazol-5-yl)aniline (1 equivalents) in methanol:water (1:1; v/v) was heated at 60 °C for 24 h. Upon dilution with water and acidification, the solid formed was fitered, washed with water, dried and analyzed to give 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine (R926853). Alternatively this reaction can be achieved by treating 2,4-dichloro-5-fluoropyrimidine (1 equivalent) with 3-(tetrazol-5-yl)aniline (3 equivalents) in methanol:water (1:1; v/v) at 60 oC for 2-3 hours or at room temperature for 24 h to give 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.25 (s, 1H), 8.43 (s, 1H), 8.37 (d, 1H, J= 3.6 Hz), 7.90 (dd, 1H, J= 0.9 and 9 Hz), 7.75 (d, 1H, J= 7.5 Hz), 7.61 (t, 1H, J= 7.8 Hz); LCMS: purity: 90%; MS (m/e): 292 (MH^+).
7.1.68	2-Chloro-N4-(2,5-dimethoxy-4-chlorophenyl)-5-fluoro-4-pyrimidineamine (R926858)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 2,5-dimethoxy-4-chloroaniline gave 2-chloro-N4-(2,5-dimethoxy-4-chlorophenyl)-5-fluoro-4-pyrimidineamine. LCMS: purity: 97%; MS (m/e): 316 (M-2H) and 320 (M+2H).

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Section Number	Name of compound and reference number	Experimental
7.1.69	2-Chloro-5-fluoro-N4-(3-methoxycarbonyl-5-trifluoromethylphenyl)-4-pyrimidineamine (R926861)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-methoxycarbonyl-5-trifluoromethylaniline gave 2-chloro-5-fluoro-N4-(3-methoxycarbonyl-5-trifluoromethylphenyl)-4-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 8.60 (s, 1H), 8.43 (s, 1H), 8.20 (d, 1H, J= 3 Hz), 7.99 (s, 1H), 3.96 (s, 3H); ^{19}F NMR (CD_3OD): -18332, - 18374; and - 44259; LCMS: purity: 91%; MS (m/e): 350 (MH^+).
7.1.70	2-Chloro-5-fluoro-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl)-4-pyrimidineamine (R926869)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-(2-phenyl-1,3,4-oxadiazol-5-yl)aniline gave 2-chloro-5-fluoro-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl)-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.28 (s, 1H), 8.62 (s, 1H), 8.39 (d, 1H, J= 3.3 Hz), 8.11 (m, 2H), 7.98 (bd, 1H, J= 6.9 Hz), 7.88 (bd, 1H, J= 8.4 Hz), 7.65 (m, 4H); LCMS: purity: 76%; MS (m/e): 76%.
7.1.71	2-Chloro-N4-[3-(2-ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)phenyl)-5-fluoro-4-pyrimidineamine (R926873)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-(2-ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)aniline gave 2-chloro-N4-[3-(2-ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)phenyl]-5-fluoro-4-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 8.42 (t, 1H, J= 1.8 Hz), 8.19 (d, 1H, J= 3.3 Hz), 7.99 (dt, 1H, J= 1.2 and 8.1 Hz), 7.82 (dt, 1H, J= 1.2 and 8.1 Hz), 7.58 (t, 1H, J= 9 Hz), 4.24 (q, 2H, J= 3.9 Hz), 4.17 (s, 2H), 1.28 (t, 3H, J= 7.2 Hz); LCMS: purity: 85%; MS (m/e): 379 (MH^+).
7.1.72	2-Chloro-5-fluoro-N4-(4-trifluoromethoxyphenyl)-4-pyrimidineamine (R926875)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-trifluoromethoxyaniline gave 2-chloro-5-fluoro-N4-(4-trifluoromethoxyphenyl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.11 (d, 1H, J= 2.1 Hz), 7.68 (dd, 2H, J= 2.4 and 7.6 Hz), 7.26 (dd, 2H, J= 3 and 8.7 Hz), 7.0 (bs, 1H); ^{19}F NMR (CD_3OD): δ –16517 and –44523; LCMS: purity: 94%; MS (m/e): 308 (MH^+).
7.1.73	2-Chloro-5-fluoro-N4-(4-trifluoromethylphenyl)-4-pyrimidineamine (R926876)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-trifluoromethylaniline gave 2-chloro-5-fluoro-N4-(4-trifluoromethylphenyl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 2.1 Hz), 7.80 (d, 2H, J= 7.1 Hz), 7.66 (d, 2H, J= 9 Hz), 7.10 (bs, 1H); ^{19}F NMR ($CDCl_3$): -17682 and - 44362; LCMS: purity: 91% and MS (m/z): 292 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.74	2-Chloro-N4-(4-chloro-3-trifluoromethylphenyl)-5-fluoro-4-pyrimidineamine (R926877)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-chloro-3-trifluoromethylaniline gave 2-chloro-N4-(4-chloro-3-trifluoromethylphenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H, J= 2.1 Hz), 7.96 (d, 1H, J= 3 Hz), 7.91 (dd, 1H, J= 2.7 Hz and 8.7 Hz), 7.53 (d, 1H, J= 8.1 Hz), 7.06 (bs, 1H); ^{19}F NMR ($CDCl_3$): - 17892 and - 44402; LCMS: purity: 93%; MS (m/e): 326 (M^+).
7.1.75	2-Chloro-5-fluoro-N4-(6-methoxypyridin-3-yl)-4-pyrimidineamine (R926878)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-amino-6-methoxypyridine gave 2-chloro-5-fluoro-N4-(6-methoxypyridin-3-yl)-4-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 8.39 (d, 1H, J= 3.0 Hz), 8.10 (d, 1H, J= 3.6 Hz), 7.95 (dd, 1H, J= 2.4 and 9 Hz), 8.30 (d, 1H, J= 9 Hz), 3.91 (s, 3H); ^{19}F NMR (CD_3OD): - 44737; LCMS: purity: 97%; MS (m/e): 255 (M^+).
7.1.76	2-Chloro-N4-(3,4-difluorophenyl)-5-fluoro-4-pyrimidineamine (R926882)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3,4-difluoroaniline gave 2-chloro-N4-(3,4-difluorophenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.10 (d, 1H, J= 2.1 Hz), 7.72 (m, 1H), 7.22 (m, 2H), 6.95 (bs, 1H); LCMS: purity: 93%; MS (m/e): 260 (M^+).
7.1.77	2-Chloro-N4-(3,4-Dichlorophenyl)-5-fluoro-4-pyrimidineamine (R926884)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3,4-dichloroaniline gave 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine. LCMS: purity: 95%; MS (m/e): 294 (M+ 2H).
7.1.78	2-Chloro-5-fluoro-N4-(6-methylpyridin-2-yl)-4-pyrimidineamine (R926888)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 2-amino-6-methylpyridine gave 2-chloro-5-fluoro-N4-(6-methylpyridin-2-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.23 (s, 1H), 8.19 (s, 1H), 8.12 (d, 1H, J= 3 Hz), 7.55 (bs, 1H), 7.69 (t, 1H, J= 7.4 Hz), 9.35 (d, 1H, J= 7.5 Hz); 19F NMR (CDCl3): - 44073; LCMS: purity: 96%; MS (m/e): 239 (M^+).

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Section Number	Name of compound and reference number	Experimental
7.1.79	2-Chloro-N4-(2,6-Dimethoxypyridin-3-yl)-5-fluoro-4-pyrimidineamine (R926889)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-amino-2.6-dimethoxypyridine gave 2-chloro-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.57 (d, 1H, J= 8.7 Hz), 8.02 (d, 1H, J= 2.7 Hz), 6. 40 (d, 1H, J= 8.1 Hz), 4.03 (s, 3H), 3.98 (s, 3H), ^{19}F NMR ($CDCl_3$). - 44640; LCMS: purity: 90%; MS (m/e): 285 (M^+).
7.1.80	2-Chloro-N4-(6-chloropyridin-3-yl)-5-fluoro-4-pyrimidineamine (R920400)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-amino-6-chloropyridine gave 2-chloro-N4-(6-chloropyridin-3-yl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.53 (d, 1H, J= 3 Hz), 8.25 (dd, 1H, J= 3 and 9 Hz), 8.15 (d, 1H, J= 2.4 Hz), 7.39 (d, 1H, J= 8.7 Hz), 7.00 (bs, 1H); LCMS: purity: 98%; MS (m/e): 259 (M^+).
7.1.81	2-Chloro-5-fluoro-N4-(4-methylpyridin-2-yl)-4-pyrimidineamine (R920401)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 2-amino-4-methylpyridine gave 2-chloro-5-fluoro-N4-(4-methylpyridin-2-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.22 (s, 1H), 8.16 (d, 1H, J= 8.4 Hz), 8.13 (d, 1H, J= 2.4 Hz), 6.91 (d, 1H, J= 5.4 Hz), 2.42 (s, 3H); LCMS: purity: 87%; MS (m/e): 239 (MH^+).
7.1.82	2-Chloro-5-fluoro-N4-(3-trifluoromethoxyphenyl)-4-pyrimidineamine (R920402)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-trifluoromethoxyaniline gave 2-chloro-5-fluoro-N4-(3-trifluoromethoxyphenyl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.12 (d, 1H, J= 3 Hz), 7.68 (bs, 1H), 7.53 (dd, 1H, J= 1 2 and 8.4 Hz), 7.41 9t, 1H, J= 8.1 Hz), 7.04 (bdt, 2H); ^{19}F NMR ($CDCl_3$): -16430 and - 44463; LCMS: purity: 89%; MS (m/e): 308 (MH^+).
7.1.83	2-Chloro-N4-(3,4-Difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (R920403)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3,4-difluoromethylenedioxyaniline gave 2-chloro-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.09 (d, 1H, J= 3 Hz), 7.70 (d, 1H, J= 2.4 Hz), 7.10 (dd, 1H, J= 2.4 and 8.7 Hz), 7.06 (t, 1H, J= 8.1 Hz), 6.97 (bs, 1H); ^{19}F NMR ($CDCl_3$): - 14175 and - 44562; LCMS: purity: 95%; MS (m/e): 304 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.84	2-Chloro-5-fluoro-N4-(quinolin-6-yl)-4-pyrimidineamine (R920409)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 6-aminoquinoline gave 2-chloro-5-fluoro-N4-(quinolin-6-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.02 (dd, 1H, J= 2.7 Hz), 8.00 (dd, 1H, J= 2.4 Hz), 7.73 (d, 1H, J= 9 Hz), 7.68 (dd, 1H, J= 2.4 and 8.7 Hz), 7.28 (t, 1H, J= 10.5 Hz), 6.42 (d, 1H, J= 9.3 Hz); ^{19}F NMR ($CDCl_3$): - 44344; LCMS: purity: 91%; MS (m/e): 292 (M^+).
7.1.85	2-Chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-chloro-4-trifluoromethoxyaniline gave 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H, J= 3.0 Hz), 7.86 (d, 1H, J= 2.1 Hz), 7.61 (dd, 1H, J= 2.1 and 8.7 Hz), 7.35 (dd, 1H, J= 1.2 and 8.7 Hz), 6.98 (bs, 1H); LCMS: purity: 97%; MS (m/e): 342 (M+2H).
7.1.86	2-Chloro-N4-(4-chloro-3-methoxyphenyl)-5-fluoro-4-pyrimidineamine	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-chloro-3-methoxyaniline gave 2-chloro-N4-(4-chloro-3-methoxyphenyl)-5-fluoro-4-aminopyrimidine. LCMS: purity: 88%; MS (m/e): 288 (MH^+).
7.1.87	2-Chloro-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-4-pyrimidinediamine	In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 5-amino-2-(2-hydroxyethyloxy)pyridine gave 2-chloro-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.28 (d, 1H, J= 2.4 Hz), 8.08 (m, 1H), 7.99 (m, 1H), 7.00 (bs, 1H), 6.87 (bd, 1H), 4.47 (m, 2H), 3.97 (m, 2H).
7.1.88	2-Chloro-N4-[2-(2-chloro-5-fluoropyrimidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-5-fluoro-4-pyrimidineamine (R926910)	In a like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-1,2,3,4-tetrahydroisoquinoline were reacted to provide 2-chloro-N4-[2-(2-chloro-5-fluoropyrimidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.08 (d, 1H, J= 3.0 Hz), 7.95 (d, 1H, J= 6.0 Hz), 7.50-7.42 (m, 2H), 7.21 (d, 1H, J= 8.4 Hz), 6.96-6.90 (m, 1H), 4.95 (s, 2H), 4.04 (t, 2H, J= 5.7 Hz), 2.99 (t, 2H, J= 5.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): -42555, -44573; LCMS: purity: 98%; MS (m/e): 410(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.89	2-Chloro-5-fluoro-N4-[2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-4-pyrimidineamine (R926911)	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline were reacted to provide 2-chloro-5-fluoro-N4-[2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.03 (s, 1H), 7.50-7.26 (m, 2H), 7.19-7.11 (m, 2H), 4.57 (s, 2H), 3.64 (t, 2H, J= 5.7 Hz), 2.80 (t, 2H, J= 5.7 Hz), 1.48 (s, 9H); LCMS: purity: 89%; MS (m/e). 379(M^+).
7.1.90	2-Chloro-5-fluoro-N4-(1,2,3,4-tetrahydroisoquinolin-7-yl)-4-pyrimidineamine (R926912)	A solution of 2-chloro-5-fluoro-N4-[2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-4-pyrimidineamine in 40% trifluoroacetic acid/dichloromethane was stirred at rt for 30 min. Removal of the solvent left an oily residue which was suspended in water, made basic with $NaHCO_3$, and extracted with ethyl acetate. Purification by column chromatography over silica gel provided 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydroisoquinolin-7-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.04 (d, 1H, J= 3.0 Hz), 7.37 (dd, 1H, J= 2.4 and 8.4 Hz), 7.27 (d, 1H, J= 1.5 Hz), 7.11 (d, 1H, J= 8.4 Hz), 6.92 (s, 1H), 4.04 (s, 2H), 3.15 (t, 2H, J= 6.0 Hz), 2.79 (t, 2H, J= 6.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): -44648; LCMS: purity: 97%; MS (m/e): 279(MH^+).
7.1.91	2-Chloro-5-fluoro-N4-(4-methyl-3-trifluoromethylphenyl)-4-pyrimidineamine (R926920)	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-methyl-3-trifluoromethylaniline were reacted to provide 2-chloro-5-fluoro-N4-(4-methyl-3-trifluoromethylphenyl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.10 (d, 1H, J= 3.0 Hz), 7.85-7.78 (m, 2H), 7.33 (d, 1H, J= 9.3 Hz), 6.96 (bs, 1H), 2.48 (d, 3H, J= 1.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): -17641, -44541; LCMS: purity: 97%; MS (m/e): 306(MH^+).
7.1.92	2-Chloro-5-fluoro-N4-(4-fluoro-3-methylphenyl)-4-pyrimidineamine (R926921)	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-fluoro-3-methylaniline were reacted to provide 2-chloro-5-fluoro-N4-(4-fluoro-3-methylphenyl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$)· δ 8.06 (d, 1H, J= 2 4 Hz), 7.48-7 43 (m, 1H), 7.39 (dd, 1H, J= 2.7 and 6.3 Hz), 7.03 (t, 1H, J= 9.0 Hz), 6.84 (bs, 1H), 2.30 (d, 1H, J= 1 8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): -34285, -44676; LCMS: purity: 95%; MS (m/e): 257(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.93	N4-[3-[(N-t-butoxycarbonyl)aminomethyl]-4-methylphenyl]-2-chloro-5-fluoro-4-pyrimidineamine (R926924)	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-[(N-t-butoxycarbonyl)aminomethyl]-4-methylaniline were reacted to provide N4-[3-[(N-t-butoxycarbonyl)aminomethyl]-4-methylphenyl]-2-chloro-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.05 (d, 1H, J= 3.0 Hz), 7.52 (d, 1H, J= 9.3 Hz), 7.45 (s, 1H), 7.19 (d, 1H, J= 8.1 Hz), 6.96-6.89 (m, 1H), 4.80 (bs, 1H), 2.31 (s, 2H), 1.46 (s, 9H); LCMS: purity: 97%; MS (m/e): 311 ($M-(t$-butyl)$^+$).
7.1.94	2-Chloro-N4-[3-[[4-(ethoxycarbonyl)piperidino] methyl]phenyl]-5-fluoro-4-pyrimidineamine	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and ethyl 1-(3-aminobenzyl)piperidine-4-carboxylate were reacted to provide 2-chloro-N4-[3-[[4-(ethoxycarbonyl)piperidino]methyl]phenyl]-5-fluoro-4-pyrimidineamine. LCMS: purity: 97%; MS (m/e): 394(MH^+).
7.1.95	2-Chloro-N4-[3-[4-(ethoxycarbonyl)piperidino carbonyl]phenyl]-5-fluoro-4-pyrimidineamine	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-[[4-(ethoxycarbonyl)piperidino]carbonyl]aniline were reacted to provide 2-chloro-N4-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-4-pyrimidineamine. LCMS: purity: 96%; MS (m/e): 407(M^+).
7.1.96	2-Chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-4-pyrimidineamine	In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxonaphthalen-7-yl)-4-pyrimidineamine was reduced with Dibal-H to yield 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.05 (d, 1H, J= 3.0 Hz), 7 59 (d, 1H, J= 2.4 Hz), 7.14 (d, 1H, J= 8.1 Hz), 6.93 (bs, 1H), 4.82-4.78 (m, 1H), 2.82-2.71 (m, 2H), 2.08-1.74 (m, 5H) ; ^{19}F NMR (282 MHz, $CDCl_3$): -44661; LCMS: purity: 94%; MS (m/e): 294(MH^+).
7.1.97	2-Chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxonaphthalen-7-yl)-4-pyrimidineamine.	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-1-tetralone were reacted to provide 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxonaphthalen-7-yl)-4-pyrimidineamine. ^{1}H NMR (DMSO-d_6): δ 10.08 (s, 1H), 8.31 (d, 1H, J= 3.3 Hz), 8.15 (d, 1H, J= 2.4 Hz), 7.82 (dd, 1H, J= 2.4 and 8.1 Hz), 7.36 (d, 1H, J= 8.1 Hz), 2.91 (t, 2H, J= 6.0 Hz), 2.59 (t, 2H, J= 6.0 Hz), 2.07-1.98 (m, 2H); LCMS: purity: 93%; MS (m/e): 294(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.98	2-Chloro-5-fluoro-N4-[3-(trifluoromethylthio)phenyl]-4-pyrimidineamine	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-(trifluoromethylthio)aniline were reacted to provide 2-chloro-5-fluoro-N4-[3-(trifluoromethylthio)phenyl]-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.13 (bs, 1H), 7.92 (bs, 1H), 7.89-7.84 (m, 1H), 7.48-7.45 (m, 2H), 7.04 (bs, 1H); LCMS: purity: 97%; MS (m/e): 325(MH^+).
7.1.99	2-Chloro-5-fluoro-N4-[(3-dihydroxyboryl)phenyl)]-4-pyrimidineamine	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-aminobenzeneboronic acid were reacted to provide 2-chloro-5-fluoro-N4-[(3-dihydroxyboryl)phenyl)]-4-pyrimidineamine.
7.1.100	2-Chloro-5-fluoro-N4-[(1H)-indol-6-yl]-4-pyrimidineamine	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-aminoindole were reacted to provide 2-chloro-5-fluoro-N4-[(1H)- indol-6-yl]-4-pyrimidineamine. LCMS: purity: 92%; MS (m/e): 263(MH^+).
7.1.101	2-Chloro-5-fluoro-N4-(2-hydroxy-4-methylphenyl)-4-pyrimidineamine	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-hydroxy-4-methylaniline were reacted to provide 2-chloro-5-fluoro-N4-(2-hydroxy-4-methylphenyl)-4-pyrimidineamine. LCMS: purity: 97%; MS (m/e): 255(MH^+).
7.1.102	2-Chloro-5-fluoro-N4-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-4-pyrimidineamine	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-2-(methoxycarbonyl)-(1H)-indole were reacted to provide 2-chloro-5-fluoro-N4-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-4-pyrimidineamine which was used without further purification. LCMS: purity: 65%; MS (m/e): 322(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.103	N4-[3-(4-(2-Chloro-5-fluoropyrimidine)-N-aminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (R940298)	The reaction flask equipped with a magnetic stirring bar and a rubber septum (to prevent loss of 2,4-dichloro-5-fluoropyrimidine and N_2 inlet was charged 3-aminobenzylamine (0.22 g, 1.79 mmol), MeOH (1 mL), H_2O (3 mL) and 2,4-dichloro-5-fluoropyrimidine (0.3 g, 1.79 mmol). The reaction mixture was stirred at 80°C for 30 min., cool to room temperature, diluted with H_2O (30 mL). Upon saturation with sodium chloride it was extracted with ethyl acetate (3 x 20 mL), dried over anhydrous sodium sulfate and the solvent was removed. The resulting residue was filtered through a pad of silica gel (200-400 mesh) using 1 to 3% MeOH in CH_2Cl_2 to obtain N4-[3-(4-(2-chloro-5-fluoropyrimidine)-N-methylaminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine **R940298.** ^{1}H NMR (DMSO-d6): δ 10.09 (1H, s), 8 88 (1H, t, *J*= 5 85 Hz), 8.40 (1H, d, *J*= 3.6 Hz), 8 23 (1H, d, *J*= 3 3 Hz), 7.74 (1H, s), 7.70 (1H, d, *J*= 8.1 Hz), 7.44 (1H, t, *J*= 7.8 Hz), 7.19 (1H, d, *J*= 8.1 Hz), 4.69 (2H, d, *J*= 5.7 Hz ; purity 92 %.
7.1.104	2-Chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine (R940302)	The reaction flask equipped with a magnetic stirring bar and a rubber septum (to prevent loss of 2,4-dichloro-5-fluoropyrimidine and N_2 inlet was charged with 3-methyloxycarbonyl-4-methoxyaniline (0.88 g, 4.86 mmol), MeOH (3 mL), H_2O (7 mL) and 2,4-dichloro-5-fluoropyrimidine (0.81 g, 4.86 mmol). The reaction mixture was stirred at 60°C for 30 min., diluted with H_2O (50 mL), acidified with 2N HCl (6 mL) and sonicated. The solid obtained was filtered, washed with H_2O and dried to produce 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine **R940302.** ^{1}H NMR (DMSO-d6): δ 10.10 (1H, s), 8.39 (1H, d, *J*= 3.6 Hz), 8.04 (1H, d, *J*= 2.7 Hz), 7.98-7.93 (1H, m), 7.30 (1H, d, *J*= 9 Hz), 3.92 (3H, s), 3.89 (3H, m) ; purity 96% ; MS (m/e): 312 (MH+).
7.1.105	2-Chloro-5-fluoro-N4-(4-phahthlimide)-4-pyrimidineamine (R940303)	In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-aminophthalimide were reacted to produce 2-chloro-5-fluoro-N4-(4-phahthlimide)-4-pyrimidineamine **R940303.** ^{1}H NMR (DMSO-d6): δ 11.38 (1H, s), 10.60 (1H, s), 8.57 (1H, d, *J*= 3.3 Hz), 8.39 (1H, d, *J*= 1.8 Hz), 8.18 (1H, dd, *J*= 8.4 Hz, *J*= 2.1 Hz), 7.93 (1H, d, *J*= 8.1 Hz) ; purity 90% ; MS (m/e): 293 (MH+).
7.1.106	2-Chloro-5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-4-pyrimidineamine (R940305)	In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-methylaminocarbonyl-4-methoxyaniline were reacted to produce 2-chloro-5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-4-pyrimidineamine **R940305.** ^{1}H NMR (DMSO-d6): δ 9.91 (1H, s), 8.31 (1H, d, *J*= 3.6 Hz), 8.11 (1H, d, *J*= 2.7 Hz), 7.78 (1H, dd, *J*= 9 Hz, *J*= 2.7 Hz), 7.59 (1H, m), 6.87 (1H, d, *J*= 9 Hz), 3.90 (3H, s), 2.96 (3H, d, *J*= 4.5 Hz) ; purity 93%.

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7.1107.	N2-Chloro-5-fluoro-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-4-pyrimidineamine (R940313)	In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-(N-morpholinomethylene)-4-methoxyaniline were reacted to produce 2-chloro-5-fluoro-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-4-pyrimidineamine **R940313.** ^{1}H NMR (DMSO-d6): δ 10.00 (1H, s), 8.35 (1H, d, *J*= 3.3 Hz), 7.72 (1H, d, *J*= 3 Hz), 7.58 (1H, d, *J*= 9.3 Hz), 7.12 (1H, d, *J*= 8.4 Hz), 3.89 (3H, s), 3.8-3.5 (6H, m), 2.58 (4H, m) ; purity 96% ; MS (m/e): 352 (M).
7.1.108	N4-[3-(N-*tert*-Butoxycarbonyl-N-methylaminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (R940315)	In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-(N-*tert*-butoxycarbonyl-N-methylaminomethylene)-aniline were reacted to produce N4-[3-(N-*tert*-butoxycarbonyl-N-methylaminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine **R940315.** ^{1}H NMR (DMSO-d6): δ 10.13 (1H, s), 8.42 (1H, d, *J*= 3.6 Hz), 7.69 (1H, m), 7.64 (1H, s), 7.45 (1H, t, *J*= 7.6 Hz), 7.09 (1H, d, *J*= 7.8 Hz), 4.48 (2H, s), 2.90 (3H, s), 1.49 (9H, m) ; purity 92% ; MS (m/e): 367 (MH+).
7.1.109	N4-(3-(N-*tert*-Butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxyphenyl)- 2-chloro-5-fluoro-4-pyrimidineamine (R940320)	In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-(N-*tert*-butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxy-aniline were reacted to produce N4-(3-(N-*tert*-butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine **R940320.** ^{1}H NMR (DMSO-d6): δ 10.01 (1H, s), 8.34 (1H, d, *J*= 3.6 Hz), 7.52 (2H, m), 7.08 (1H, d, *J*= 8.7 Hz), 4.33 (3H, m), 3.90 (3H, s), 1.50-1.30 (9H, m), 1.18 (6H, d, *J*= 6.9 Hz) ; purity 95%.
7.1.110	2-Chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine (R940322)	In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one were reacted to produce 2-chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine **R940322.** ^{1}H NMR (DMSO-d6): δ 10.89 (1H, s), 10.04 (1H, s), 8.38 (1H, d, *J*= 3.6 Hz), 7.35 (2H, m), 7.04 (1H, d, *J*= 8.4 Hz), 1.50 (6H, s) ; purity 91.4% ; MS (m/e): 322 (M).

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7.1.111	2-Chloro-N4-[3-dihydro-2,2-dimethyl-4-(2-(pyridyl-1-oxide)-benzo[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine (R940328)	In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 2-(6-amino-3-dihydro-2,2-dimethyl-benzo[1,4]oxazin-4-yl)pyridine 1-Oxide were reacted to produce 2-chloro-N4-[3-dihydro-2,2-dimethyl-4-(2-(pyridyl-1-oxide)-benzo[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine **R940328.** ^{1}H NMR (DMSO-d6): δ 9.82 (1H, s), 8.39 (1H, dd, *J*= 6.3 Hz, *J*= 1.2 Hz), 8.30 (1H, d, *J*= 3.6 Hz), 7.63 (1H, dd, *J*= 8.4 Hz, *J*= 2.4 Hz), 7.47 (1H, td, *J*= 7.5 Hz, *J*= 1.8 Hz), 7.34 (1H, m), 7.21 (1H, dd, *J*= 8.7 Hz, *J*= 2.4 Hz), 7.07 (1H, d, *J*= 2.7 Hz), 6.91 (1H, d, *J*= 8.7 Hz), 3.64 (2H, s), 1.41 (6H, s) ; purity 95.8% ; MS (m/e): 402 (MH+).
7.1.112	2-Chloro-N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine (R940336)	In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazine were reacted to produce 2-chloro-N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine **R940336.** ^{1}H NMR (DMSO-d6): δ 9.95 (1H, s), 8.38 (1H, dd, *J*= 4.8 Hz, *J*= 1.8 Hz), 8.33 (1H, d, *J*= 3.6 Hz), 7.84 (1H, d, *J*= 2.1 Hz), 7.79 (1H, ddd, *J*= 15.6 Hz, *J*= 7.2 Hz, *J*= 2.1 Hz), 7.57 (1H, d, *J*= 8.4 Hz), 7.19 (1H, dd, *J*= 8.4 Hz, *J*= 2.4 Hz), 7.01-6.95 (2H, m), 3.96 (2H, s), 1.32 (6H, s) ; purity 99.3% ; MS (m/e): 386 (MH+).
7.1.113	2-Chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine (R940342)	In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-2,2-difluoro-4H-benzo[1,4]oxazin-3-one were reacted to produce 2-chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine **R940342.** ^{1}H NMR (DMSO-d6): δ 12.24 (1H, s), 10.23 (1H, s), 8.45 (1H, dd, *J*= 3.3 Hz, *J*= 0.9 Hz), 7.66 (1H, dd, *J*= 4.2 Hz, *J*= 2.4 Hz), 7.55 (1H, dt, *J*= 9 Hz, *J*= 2.5 Hz), 7.43 (1H, d, *J*= 9 Hz+); ^{19}F NMR (DMSO-d6): δ -21582, -43415 ; purity 96.2%; MS (m/e) : 331 (MH+).
7.1.114	2-Chloro-N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-7-yl]-5-fluoro-4-pyrimidineamine (R940344)	In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one were reacted to produce 2-chloro-N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-7-yl]-5-fluoro-4-pyrimidineamine **R940344.** ^{1}H NMR (DMSO-d6): δ 11.32 (1H, s), 10.20 (1H, s), 8.45 (1H, d, *J*= 3.6 Hz), 8.33 (1H, d, *J*= 2.1 Hz), 7.84 (1H, d, *J*= 2.1 Hz), 1.54 (6H, s) ; purity 90.8% ; MS (m/e): 324 (MH+).

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Section Number	Name of compound and reference number	Experimental
7.1.115	N4-(4-Aminocarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (R945028)	In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine (250 mg, 1.50 mmol) and 4-aminocarbonylmethyleneoxyaniline (540 mg, 3.25 mmol) were reacted to yield N4-(4-aminocarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 18.34 min.; purity: 100%; MS (m/e): 298.47 (MH^+).
7.1.116	2-Chloro-5-fluoro-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-6-yl]-4-pyrimidineamine (R945298)	In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one were reacted to yield 2-chloro-5-fluoro-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-6-yl]-4-pyrimidineamine. ^1H NMR (DMSO-d_6): δ 4.63 (s, 2H), 7.34 (d, J= 8.7 Hz, 1H), 7.44 (d, J= 8.4 Hz, 1H), 8.33 (d, J= 3.3 Hz, 1H), 10 14 (s, 1H, NH), 11.19 (s, 1H, NH); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 152.35; LCMS: ret. time: 26.74 min.; purity: 85.90%; MS (m/e): 296.13 (MH^+).
7.1.117	N4-(1,4-Benzoxazin-6-yl)-N2-chloro-5-fluoropyrimidineamine	In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-1,4-benzoxazine were reacted to yield N4-(1,4-Benzoxazin-6-yl)-N2-chloro-5-fluoropyrimidineamine 1H DMSO 8.2 (d, 1H),6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.05 (m, 2H), 3.2 (m, 2H) purity 95 % MS (m/e): 281(MH^+).
7.1.118	N4-(1,4-Benzoxazin-7-yl)]-N2-chloro-5-fluoropyrimidineamine	In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-1,4-benzoxazine were reacted to yield N4-(1,4-Benzoxazin-7-yl)]-N2-chloro-5-fluoropyrimidineamine 1H DMSO 8.2 (d, 1H),6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.05 (m, 2H), 3.2 (m, 2H) purity 94 % MS (m/e):281(MH^+).
7.1.119	N4-(1,4-Benzoxazin-3-on-6-yl)-N2-chloro-5-fluoropyrimidineamine	In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-1,4-benzoxazine-3-one were reacted to yield N4-(1,4-Benzoxazin-3-on-6-yl)-N2-chloro-5-fluoropyrimidineamine 1H DMSO 8.2 (d, 1H), 6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.73 (s, 2H) purity 96 % MS (m/e): 295 (MH^+).
7.1.120	N4-(1,4-Benzoxazin-3-on-7-yl)-N2-chloro-5-fluoropyrimidineamine	In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-1,4-benzoxazine-3-one were reacted to yield N4-(1,4-Benzoxazin-3-on-7-yl)-N2-chloro-5-fluoropyrimidineamine 1H DMSO 8.2 (d, 1H),6.8 (m, 1H), 6.79 (m, 1H), 6.6 (m,1H), 4.68 (s, 2H) purity 93 % MS (m/e): 295 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.121	N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-6-yl)-pyrimidineamine	In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-4-N-methyl-1,4-benzoxazine were reacted to yield N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-6-yl)-pyrimidineamine 1H DMSO 8 2 (d, 1H),6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.05 (m, 2H), 3.2 (m, 2H) 2.8 (s, 3H) purity 95 % MS (m/e): 295 (MH^+).
7.1.122	N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-7-yl)-pyrimidineamine	In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-4-N-methyl -1,4-benzoxazine were reacted to yield N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-7-yl)-pyrimidineamine 1H DMSO 8.2 (d, 1H),6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.05 (m, 2H), 3.2 (m, 2H) 2.8 (s, 3H) purity 94 % MS (m/e): 295 (MH^+).
7.1.123	N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)-pyrimidineamine	In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-4-N-methyl -1,4-benzoxazine-3-one were reacted to yield N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)-pyrimidineamine 1H DMSO 8.2 (d, 1H),6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.73 (s, 2H) 2.8 (s, 3H) purity 96 % MS (m/e): 309 (MH^+).
7.1.124	N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)-pyrimidineamine	In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-4-N-methyl-1,4-benzoxazine-3-one were reacted to N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)-pyrimidineamine 1H DMSO 8.2 (d, 1H),6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.68 (s, 2H) 2 8 (s, 3H) purity 93 % MS (m/e): 309 (MH^+).
7.1.125	N2-chloro-N4-(3-ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoropyrimidinediamine (R909258) :	In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and ethyl 6-amino-3-carboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazine were reacted to yield N2-chloro-N4-(3-ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoropyrimidinediamine 1H (DMSO-d6) 8.42 (s, 1H), 8.30 (m, 1H), , 8.05 (m, 1H), 7.43 (m, 1H), 5.53 (s, 2H), 4.25 (q, 2H J=6.5 Hz), 1.28 (t, 2H, J=6.5 Hz), purity 90 % MS (m/e): 390 (MH^+).
7.1.126	N2-Chloro-N4-(3,3-dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-pyrimidineamine	In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-Amino-3,3-dimethyl-1,4-benzoxazine were reacted to yield N2-Chloro-N4-(3,3-dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-pyrimidineamine 1H DMSO 8.18 (d, 1H), 6.8 (d, 1H), 6.67 (m, 2H), 3.76 (s, 2H), 1.05 (s, 6H) purity 99 % MS (m/e): 309 (MH^+)

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7.1.127	2-Chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-4-pyrimidineamine (R935241)	In like manner to the preparation of 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with 5-amino-1-(methoxycarbonyl)methyl-indazoline to produce 2-chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d_6): δ 10.04 (s, 1H), 8.28 (d, 1H, J = 3.5 Hz), 8.12 (s, 1H), 8.00 (dd, 1H, J = 1.2 and 4.1 Hz), 7.64 (d, 1H, J = 8.8 Hz), 7.58-7.54 (m, 1H), 5.39 (s, 2H), 3.66 (s, 3H).
7.1.128	2-Chloro-5-fluoro-N-[4*H*-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-4-pyrimidineamine (R935257)	In like manner to the preparation of 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with 8-amino-4*H*-imidazo[2,1-*c*][1,4]-benzoxazine to produce 2-chloro-5-fluoro-N-[4*H*-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d_6): ^{1}H NMR (DMSO-d_6): δ 10.08 (s, 1H), 8.31 (s, 1H), 7.91 (d, 1H, J = 2.3 Hz), 7.74 (d, 1H, J = 1.2 Hz), 7.37 (dd, 1H, J = 2.3 and 8.8 Hz), 7.16 (d, 1H, J = 8.8 Hz), 7.14 (d, 1H, J = 1.2 Hz), 5.29 (s, 2H). LCMS: ret. time: 18.74 min.; purity: 99%; MS (*m/e*): 318 (MH^+).
7.1.129	2-Chloro-5-fluoro-N-(indazoline-6-yl)-4-pyrimidineamine (R935260)	In like manner to the preparation of 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with 6-aminoindazole to produce 2-chloro-5-fluoro-N-(indazoline-6-yl)-4-pyrimidineamine . ^{1}H NMR ($CDCl_3$): δ 13.03 (s, 1H), 10.07 (s, 1H), 8.32 (d, 1H, J = 3.5 Hz), 8.07 (s, 1H), 7.99 (s, 1H), 7.71 (d, 1H, J = 8.8 Hz), 7.34 (dd, 1H, J = 1.7 and 8.8 Hz). LCMS: ret. time: 18.52 min.; purity: 99%; MS (*m/e*): 263 (MH^+).
7.1.130	2-Chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine (R935265)	In like manner to the preparation of 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with 5-aminoindazoline. ^{1}H NMR ($CDCl_3$): δ 9.99 (s, 1H), 8.26 (d, 1H, J = 3 5 Hz), 8.07 (s, 1H), 7.99 (d, 1H, J = 1.1 Hz), 7.53 (dd, 2H, J = 1.7 and 8.8 Hz). LCMS: ret. time: 18.03 min.; purity: 97%; MS (*m/e*): 264 (MH^+).
7.1.131	2-Chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine (R935275)	In like manner to the preparation of 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with 1-aminopyrrole to produce 2-chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 11.39 (s, 1H), 8.35 (d, 1H, J = 3.5 Hz), 6.83 (t, 2H, J = 2.3 Hz), 6.07 (t, 2H, J = 2.3 Hz). LCMS: ret. time: 18.95 min.; purity: 97%; MS (*m/e*): 213 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.132	2-Chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine (R926853)	A reaction mixture containing 2,4-dichloro-5-fluoro-pyrimindine (1.2 equivalents) and 3-(tetrazol-5-yl)aniline (1 equivalents) in methanol:water (1:1; v/v) was heated at 60 °C for 24 h. Upon dilution with water and acidification, the solid formed was fitered, washed with water, dried and analyzed to give 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine (R926853). Alternatively this reaction can be achieved by treating 2,4-dichloro-5-fluoropyrimidine (1 equivalent) with 3-(tetrazol-5-yl)aniline (3 equivalents) in methanol:water (1:1; v/v) at 60 oC for 2-3 hours or at room temperature for 24 h to give 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.25 (s, 1H), 8.43 (s, 1H), 8.37 (d, 1H, J= 3.6 Hz), 7.90 (dd, 1H, J= 0.9 and 9 Hz), 7.75 (d, 1H, J= 7.5 Hz), 7.61 (t, 1H, J= 7.8 Hz); LCMS: purity: 90%; MS (m/e): 292 (MH^+).
7.1.133	2-Chloro-N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-2,4-pyrimidineamine (R950297)	A solution of 3,4-dihydro-4-hydroxy-6-amino-2H-1-benzopyran and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-2,4-pyrimidineamine as a pale brown solid. LCMS: purity: 99.3%; MS (m/e): 296.1 (MH^+).
7.1.134	2-Chloro-N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-2,4-pyrimidineamine (R950375)	A solution of 3-(p-aminophenyl)-propionic acid and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-2,4-pyrimidineamine as a pale brown solid. LCMS: purity: 93.3%; MS (m/e): 311.98 (M^-).
7.1.135	2-Chloro-N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidineamine (R950298)	A solution of 3-carboxy-4-hydroxyaniline and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidineamine as a pale brown solid. LCMS: purity: 87.4%; MS (m/e): 284.1 (MH^+).
7.1.136	2-Chloro-N4-(4-trifluoromethyl-3-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidineamine (R950390)	A solution of 4-trifluoromethyl-3-methoxycarbonylaniline and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(4-trifluoromethyl-3-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidineamine as a pale brown solid. LCMS: purity: 96.4%; MS (m/e): 366.34 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.1.137	2-Chloro-N4-(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidineamine (R950369)	A solution of 3-methylcarbonylaniline and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidineamine as a pale brown solid LCMS: purity: 99.1%; MS (m/e): 266.12 (MH^+).
7.1.138	2-Chloro-N4-(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidineamine (R950370)	A solution of 3-phenylcarbonylaniline and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidineamine as a pale brown solid. LCMS: purity: 78.5%; MS (m/e): 328.16 (MH^+).
7.1.139	2-Chloro-N4-(3-nitrophenyl)-5-fluoro-2,4-pyrimidineamine	A solution of 3-nitroaniline and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(3-nitrophenyl)-5-fluoro-2,4-pyrimidineamine as a pale brown solid. ^{1}H NMR (DMSO): δ 10.34 (s, 1H), 8.73 (d, 1H, J = 2.4 Hz), 7.66-8.29 (m, 4H).
7.1.140	2-Chloro-N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-4-aminopyridine (R950384)	A solution of 3-hydroxymethylen-4-methoxyaniline and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-4-aminopyridine as a pale brown solid. LCMS: purity: 91.8%; MS (m/e): 266.03 (MH^+).
7.1.141	2-Chloro-N4-(3-amino-4-ethoxyphenyl)-5-fluoro-4-aminopyridine (R950387)	A solution of 3-amino-4-ethoxyaniline and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(3-amino-4-ethoxyphenyl)-5-fluoro-4-aminopyridine as a pale brown solid. LCMS: purity: 93.2%; MS (m/e): 252.06 (MH^+).
7.2	Synthesis of Amines and Amine Precursors	
7.2.1	5-Amino-2-(2-hydroxyethyleneoxy)pyridine	A methanolic solution (50 mL) of 2-(2-hydroxyethyleneoxy)-5-nitropyridine (0.5 g) was hydrogenated in the presence of Pd/C (10%; 0.05 g) using a balloon filled with hydrogen for 2h. After the filtration through a pad of celite and washing with methanol the solution was concentrated to give the 5-amino-2-(2-hydroxyethyloxy)pyridine. ^{1}H NMR ($CDCl_3$): δ 7.58 (d, 1H, J= 3 Hz), 7.05 (dd, 1H, J= 2.7 and 8.1 Hz), 6 64 (d, 1H, J= 8.7 Hz), 4.36 (m, 2H), 3.89 (m, 2H)
7.2.2	4-Chloro-3-methoxyaniline	In like manner to the preparation of 5-amino-2-(2-hydroxyethyleneoxy)pyridine, the hydrogenation of 4-chloro-3-methoxynitrobenzene gave 4-chloro-3-methoxyaniline. LCMS: purity: 98%; MS: 199 (M+ acetonitrile).

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Section Number	Name of compound and reference number	Experimental
7.2.3	2-[5-Amino-2-oxo-1,3-benzoxazol-3(2H)-yl]acetamide	In like manner to the preparation of 5-amino-2-(2-hydroxyethyleneoxy)pyridine, the hydrogenation of 2-[1,3-benzoxazol-2-oxo-5-nitro-3(2H)-yl)acetamide gave 2-[5-amino-2-oxo-1,3-benzoxazol-3(2H)-yl]acetamide. LCMS: purity: 96%; MS: 208 (MH^+).
7.2.4	7-nitro-1,2,3,4-tetrahydroisoquinoline	7-nitro-1,2,3,4-tetrahydroisoquinoline was prepared by nitration of 1,2,3,4-tetrahydroisoquinoline according to the following reference: Grunewald, Gary L.; Dahanukar, Vilas H.; Caldwell, Timothy M.; Criscione, Kevin R.; Journal of Medicinal Chemistry (1997), 40(25), 3997-4005.
7.2.5	2-(t-Butoxycarbonyl)-7-nitro-1,2,3,4-tetrahydroisoquinoline	A mixture of 7-nitro-1,2,3,4-tetrahydroisoquinoline (0.55g, 3.1 mmole), di-t-butyldicarbonate (0.70g, 3.2 mmole), triethylamine (1.0 mL, 7.7 mmole) in dichloromethane (8 mL) was stirred at rt for 8h. The reaction mixture was diluted with water (50 mL) and stirred for 1h. The organic phase was separated and washed with brine. Concentration of the organic phase gave 2-(t-butoxycarbonyl)-7-nitro-1,2,3,4-tetrahydroisoquinoline. ^1H NMR ($CDCl_3$): δ 8.03-7.95 (m, 2H), 7.28 (d, 1H, J= 8.4 Hz), 4.66 (s, 2H), 3.68 (t, 2H, J= 6.0 Hz), 2.92 (t, 2H, J= 6.0 Hz),1.49 (s, 9H).
7.2.6	2,3-Dihydro-6-nitro-4-benzypyranon	3-(p-Nitrophenyl)-propionic acid is dissolved in concentrated sulfuric acid and treated with P_2O_5. The mixture is stirred for 1 hr at room temperature and poured onto ice. Filtration gave 2,3-dihydro-6-nitro-4-benzypyranon as a white solid. ^1H NMR (DMSO): δ 8.47 (d, J = 3.0 Hz, 1H), 8.35 (dd, J = 3.0, 9.0 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H), 4.70 (t, J = 7.2 Hz, 1H), 2.90 (t, J = 7.2 Hz, 1H).
7.2.7	3,4-Dihydro-4-hydroxy-6-amino-2H-1-benzopyran	A mixture 2,3-dihydro-6-nitro-4-benzypyranon and Pd/C (10%) in MeOH was hydrogenated at 22°C for 3 hours (40psi). The mixture was filtered and concentrated to dryness to give 3,4-dihydro-4-hydroxy-6-amino-2H-1-benzopyran as a brown oil. ^1H NMR (DMSO): δ 6.40-6.56 (m, 3H), 5.05 (bs, 1H), 4.45 (bs, 1H), 3.94-4.09 (m, 2H), 1.76-1.98 (m, 2H).
7.2.8	N4-(3,4-Ethylenedioxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R950287)	A solution of 2-Chloro-5-ethoxycarbonyl-N4-(3,4-ethylenedioxyphenyl)-2,4-pyrimidineamine in EtOH was treated with a 25% aqueous solution of NH_3. The mixture was stirred for 30 min at 100°C and purified by flash chromatography on silica gel to give N4-(3,4-ethylenedioxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.3%; MS (m/e): 317.28 (MH^+, 100).

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Section Number	Name of compound and reference number	Experimental
7.2.9	3-(N-morpholinocarbonyl)aniline	To a 0°C solution of 3-nitrobenzoylchloride (0.50g, 2.7 mmole) and pyridine (0.27 mL, 3.2 mmole) in anhydrous dichloromethane (15 mL) was added morpholine (0.28 mL, 3.2 mmole). The reaction mixture was allowed to warm to rt and was stirred for 20h. The solvents were removed under vacuum and the residue suspended in ethyl acetate and washed with 1N HCl The organic layer was washed with a saturated solution of $NaHCO_3$ and brine. Removal of the solvents under vacuum provided 1-(N-morpholinocarbonyl)-3-nitrobenzene which was used without further purification. A mixture of 1-(N-morpholinocarbonyl)-3-nitrobenzene (0.64 g) and 10% Pd on activated carbon (60 mg) in degassed methanol (65 mL) was stirred under a balloon of H_2 for 2h. The reaction mixture was filtered through Celite® filter aid and then concentrated under reduced pressure to provide 3-(N-morpholinocarbonyl)aniline in quantitative yield. ^1H NMR ($CDCl_3$): δ 7.19-7.14 (m, 1H), 6.75-6.69 (m, 3H), 3.58-3.71 (m, 10H).
7.2.10	3-(N-propylcarbonyl)aniline	In like manner to the preparation of 3-(N-morpholinocarbonyl)aniline, 3-nitrobenzoylchloride and n-propylamine were reacted to prepare 1-[(N-propylamino)carbonyl]-3-nitrobenzene which underwent hydrogenation to provide 3-(N-propylcarbonyl)aniline. ^1H NMR ($CDCl_3$): δ 7.18 (t, 1H, J= 7.5 Hz), 7.13 (t, 1H, J= 1.8 Hz), 7.05-7.01 (m, 1H), 6.78 (ddd, 1H, J= 1.2, 2.4, and 7.5 Hz), 6.10 (bs, 1H), 3.58-3.53 (bs, 2H), 3.43-3.34 (m, 2H), 1.68-1.57 (m, 2H), 0.97 (t, 3H, J= 7.2 Hz).
7.2.11	3-[4-(Ethoxycarbonyl)piperidinocarbonyl]aniline	In like manner to the preparation of 3-(N-morpholinocarbonyl)aniline, 3-nitrobenzoylchloride and ethyl isonipecotate were reacted to prepare 1-[4-(ethoxycarbonyl)piperidinocarbonyl]-3-nitrobenzene which underwent hydrogenation to provide 3-[4-(ethoxycarbonyl)piperidinocarbonyl]aniline.
7.2.12	3-(N-methylcarbonyl)aniline	In like manner to the preparation of 3-(N-morpholinocarbonyl)aniline, 3-nitrobenzoylchloride and methylamine hydrochloride were reacted to prepare 1-[(N-methylamino)carbonyl]-3-nitrobenzene which underwent hydrogenation to provide 3-(N-methylcarbonyl)aniline. ^1H NMR ($CDCl_3$): δ 7.18 (t, 1H, J= 7.5 Hz), 7.13 (t, 1H, J= 1.8 Hz), 7.04-6.99 (m, 1H), 6.81-6.75 (m, 1H), 6.05 (bs, 1H), 3.84 (bs, 2H), 2.99 (d, 3H, J= 4.8 Hz).

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Section Number	Name of compound and reference number	Experimental
7.2.13	7-Amino-1-tetralone	In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of 7-nitro-1-tetralone was carried out to prepare 7-amino-1-tetralone. ^{1}H NMR ($CDCl_3$): δ 7.32 (d, 1H, J= 2.4 Hz), 7.05 (d, 1H, J= 8.1 Hz), 6.82 (dd, 1H, J= 2.4 and 8.1 Hz), 2.85 (t, 2H, J= 6.6 Hz), 2.61 (t, 2H, J= 6.6 Hz), 2.14-2.04 (m, 2H).
7.2.14	7-Amino-2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline	In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of 2-(t-butoxycarbonyl)-7-nitro-1,2,3,4-tetrahydroisoquinoline was carried out to prepare 7-amino-2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline. ^{1}H NMR ($CDCl_3$): δ 6.92 (d, 1H, J= 8.4 Hz), 6.52 (dd, 1H, J= 2.4 and 8.4 Hz), 6.44 (bs, 1H), 4.47 (s, 2H), 3.63-3 48 (m, 2H), 2.71 (t, 2H, J= 5.1 Hz), 1 45 (s, 9H).
7.2.15	7-Amino-1,2,3,4-tetrahydroisoquinoline	In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of 7-nitro-1,2,3,4-tetrahydroisoquinoline was carried out to prepare 7-amino-1,2,3,4-tetrahydroisoquinoline. ^{1}H NMR (DMSO-d_6): δ 9.35 (bs, 1H), 6.82 (d, 1H, J= 8.1 Hz), 6.45 (dd, 1H, J= 2 4 and 8.4 Hz), 6.30 (d, 1H, J= 2.4 Hz), 5.05 (s, 2H), 4.05 (s, 2H), 3.24 (t, 2H, J= 6.6 Hz), 2.78 (t, 2H, J= 6.6 Hz).
7.2.16	2-(3-aminophenoxy)-N,2-dimethylpropanamide	In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of N,2-dimethyl-2-(3-nitrophenoxy)propanamide was carried out to prepare 2-(3-aminophenoxy)-N,2-dimethylpropanamide. ^{1}H NMR ($CDCl_3$): δ 7.03 (t, 1H, J= 7.8 Hz), 6.71 (bs, 1H), 6.39 (dd, 1H, J= 1.2 and 6.9 Hz), 6.29 (dd, 1H, J= 2.4 and 9.6 Hz), 6.25-6.22 (m, 1H), 2.86 (d, 3H, J= 4.2 Hz), 2.86 (d, 3H, J= 4.2 Hz), 1.50 (s, 6H).
7.2.17	Ethyl 2-(3-aminophenoxy)-2-methylpropanate	In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of ethyl 2-methyl-2-(3-nitrophenoxy)propanate was carried out to prepare ethyl 2-(3-aminophenoxy)-2-methylpropanate. ^{1}H NMR ($CDCl_3$): δ 6.99 (t, 2H, J= 8.7 Hz), 6.32 (dt, 1H, J= 1.2 and 7.2 Hz), 6.24-6.18 (m, 2H), 4.23 (q, 2H, J= 7.2 Hz), 1.58 (s, 6H), 1.24 (t, 3H, J= 6.9 Hz).
7.2.18	N-methyl-2-(5-amino-2-methylphenoxy)acetamide	In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of N-methyl-2-(2-methyl-5-nitrophenoxy)acetamide was carried out to prepare N-methyl-2-(5-amino-2-methylphenoxy)acetamide. ^{1}H NMR (CD_3OD): δ 6.86 (d, 1H, J= 7.5 Hz), 6.32-6.25 (m, 2H), 4.43 (s, 2H), 2.82 (s, 3H), 2.14 (s, 3H).

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Section Number	Name of compound and reference number	Experimental
7.2.19	6-Amino-2-(methoxycarbonyl)-(1H)-indole	6-Amino-2-(methoxycarbonyl)-(1H)-indole was prepared according to the following references: 1. Adams, Richard E.; Press, Jeffery B.; Deegan, Edward G.; Synthetic Communications (1991), 12 (5), 675-681. 2. Boger, Dale L.; Yun, Weiya; Han, Nianhe; Johnson, Douglas S.; Biiorganic & Medicinal Chemistry (1995), 3(6), 611-621

Section Number	Name of compound and reference number	Experimental
7.2.20	Preparation of 3-hydroxy-5-(methoxycarbonylmethyleneoxy)aniline and 3,5-bis(methoxycarbonylmethyleneoxy)aniline	Benzyl N-(3,5-dihydroxyphenyl)carbamate To a mixture of 5-aminobenzene-1,3-diol (0.60 g, 3.7 mmole) and sodium hydrogencarbonate (1.4 g, 16 mmole) in THF/water (15 mL, 1:1 v/v) was added dropwise benzyl chloroformate 1.6 mL, 11 mmole). After 3h at rt, THF was removed under vacuum and the remaining aqueous layer was extracted with ethyl acetate Purification by column chromatograpy over silica gel provided benzyl N-(3,5-dihydroxyphenyl)carbamate. ^{1}H NMR (CD_3OD): δ 7.42-7.25 (m, 5H), 6.46 (d, 2H, J= 2.4 Hz), 5.97-5.94 (m, 1H), 5.14 (s, 2H). Benzyl N-[3-hydroxy-5-(methoxycarbonylmethyleneoxy) phenyl]carbamate and Benzyl N-[3,5-bis(methoxycarbonyl methyleneoxy)phenyl]carbamate In like manner to the preparation of ethyl 4-nitrophenoxyacetate, benzyl N-(3,5-dihydroxyphenyl)carbamate and methyl bromoacetate were reacted to give a mixture of benzyl N-[3-hydroxy-5-(methoxycarbonylmethyleneoxy)phenyl]carbamate ^{1}H NMR (DMSO-d_6): δ 9.62 (s, 1H), 9.44 (s, 1H), 7.42-7.31 (m, 5H), 6.63 (s, 1H), 6.50 (t, 1H, J= 2.4 Hz), 5.93 (t, 1H, J= 2.4 Hz), 5.10 (s, 2H), 4.63 (s, 2H), 3.67 (s, 3H), and benzyl N-[3,5-bis(methoxycarbonylmethyleneoxy)phenyl]carbamate ^{1}H NMR ($CDCl_3$): δ 7.38-7.32 (m, 5H), 6.86 (s, 1H), 6.67 (d, 2H, J= 1.8 Hz), 6.19 (t, 1H, J= 2.4 Hz), 5.16 (s, 2H), 4.57 (s, 4H), 3.78 (s, 6H)which were separated by column chromatograpy over silica gel. 3-Hydroxy-5-(methoxycarbonylmethyleneoxy)aniline In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of benzyl N-[3-hydroxy-5-(methoxycarbonylmethyleneoxy)phenyl]carbamate was carried out to prepare 3-hydroxy-5-(methoxycarbonylmethyleneoxy)aniline. ^{1}H NMR (CD_3OD): δ 5.87-5.80 (m, 2H), 5.78-5.72 (m, 1H), 4.56 (s, 2H), 3.76 (s, 3H). 3,5-Bis(methoxycarbonylmethyleneoxy)aniline In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of benzyl N-[3,5-bis(methoxycarbonylmethyleneoxy)phenyl]carbamate was carried out to prepare 3,5-bis(methoxycarbonylmethyleneoxy)aniline. ^{1}H NMR (CD_3OD): δ 5.92 (d, 2H, J= 2.4 Hz), 5.83 (t, 1H, J= 2.4 Hz), 4.58 (s, 4H), 3.78 (s, 6H).

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Section Number	Name of compound and reference number	Experimental
7.2.21	N4-(3,4-Ethylenedioxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R950287)	A solution of 2-Chloro-5-ethoxycarbonyl-N4-(3,4-ethylenedioxyphenyl)-2,4-pyrimidineamine in EtOH was treated with a 25% aqueous solution of NH_3. The mixture was stirred for 30 min at 100°C and purified by flash chromatography on silica gel to give N4-(3,4-ethylenedioxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.3%; MS (m/e): 317.28 (MH^+, 100).
7.2.22	Ethyl 6-Nitro-3-carboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazine	Was prepared according to J. of Heterocyclic Chemistry, **26**, 205, *(1989)*
7.2.23	Ethyl 6-Amino-3-carboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazine	Ethyl 6-Nitro-3-carboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazine was reduced shaken in MeOH under 40 p.s.i. H_2 with 20 weight percent of 10% Pd/C (Degussa) for 1 h then filtered and the solvent evaporated. The compound was purified directly by column chromatograph (EtOAc/hexane) to yield Ethyl 6-Amino-3-carboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazine 1H (DMSO-d6) 8.41 (s, 1H), 6.98 (m, 1H), 6.82 (m, 1H), 6.43 (m, 1H), 5.28 ((s. 2H), 4.23 (q, 2H, J=6 2 Hz), 1 27 (t, 2H, J=6.2 Hz) purity 92 % MS (m/e): 232 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.2.24	6-Amino-3,3-dimethyl-1,4-benzoxazine	A mixture of 15 g 2-Amino-4-nitrophenol and 40 g Boc_2O in 300 mL $CHCl_3$ was refluxed overnight filtered and the filtrate was evaporated to near dryness. The residue was triturated with hexanes, collected by suction filtration, and dried to yield 2-N-Boc-amino-4-nitrophenol. The 2-N-Boc-amino-4-nitrophenol was refluxed in acetone with 15.6 mL of 1-Chloro-2-methylpropene and 25 g potassium carbonate overnight. The reaction mixture was poured into ice-slush, the solid was collected by suction filtration and washed with water. The solid was dissolved in EtOAc and the organic was washed with 10% NaOH solution, water, then brine and dried over $MgSO_4$. The organic was filtered to remove the drying agent and evaporated to yield 18 g 1-(2-N-Boc-amino-4-nitrophenoxy)-2-methyl-2-propene. 7.8 g of 1-(2-N-Boc-amino-4-nitrophenoxy)-2-methyl-2-propene was stirred overnight in methanolic HCl in a round-bottom flask with a septum wired on, and then heated with a reflux condenser attached at 80° C for 10 minutes. The reaction was cooled and the methanol was removed by rotary-evaporation. The residue was dissolved in 30 mL of 4N HCl, transferred to a new vessel to leave behind any undisolved solids and cooled to 0° C. 1.83 g of $NaNO_2$ in 5 mL water was added drop wise and the solution was neutralized with solid sodium bicarbonate. A solution of 1.64 g NaN_3 in 17 mL water was added slowly drop wise and the reaction was stirred 30 minutes. The precipitate was collected by suction filtration, washed well with water and dried on the funnel to yield 5.7 g 1-(2-Azido-4-nitrophenoxy)-2-methyl-2-propene. 7 g of 1-(2-Azido-4-nitrophenoxy)-2-methyl-2-propene was refluxed in 300 mL benzene overnight, cooled then evaporated. The crude product was recrystalized from EtOAc/Hexanes to yield 3-Methyl-6-nitro-azirino[2,1-*c*]-1,4-benzoxazine in two crops with a combined mass of 5.1 1 g of 3-Methyl-6-nitro-azirino[2,1-*c*]-1,4-benzoxazine was dissolved in 500 mL of MeOH/5% THF, 200 mg of 10% Pd/C (Degussa) was added and the resulting mixture was shaken under 30 p.s.i. H_2 atmosphere for 8 hours. The reaction mixture was filtered through a pad of celite and the solvent evaporated. The residue was dissolved in a minimum amount of DCM/THF/MeOH and loaded onto a 5 cm by 20 cm 3% MeOH/DCM SiO_2 column and the compound was eluted isocratically with a small amount of positive pressure. The appropriate fractions were combined and evaporated to yield 590 mg of 6-Amino-3,3-dimethyl-1,4-benzoxazine. 1H (DMSO-d6) 6.30 (d, 1H), 5.75 (d, 1H), 5.65 (dd, 1H), 3.58 (s, 2H), 1.08 (s, 6H) purity 99 % MS (m/e): 179 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.2.25	Ethyl 4-Aminophenoxyacetate	Ethyl 4-Nitrophenoxyacetate A dry reaction flask equipped with a reflux condenser, N_2 inlet and a magnetic stirring bar was charged with 3-nitrophenol (76.45 g, 550 mmol), K_2CO_3 (76.45 g, 550 mmol) and dry acetone (500 mL) under N_2 atmosphere. To this at room temperature was added ethyl bromoacetate (55.44 mL, 500 mmol) over a period of 15 min. The reaction mixture was refluxed for 16h, cooled and poured over ice-water (4 Kg). The resulting aqueous solution was extracted with CH_2Cl_2 (3 x 500 mL), dried over anhydrous Na_2SO_4 and solvent was removed to obtain 103g (92%) of the desired ethyl 4-nitrophenoxyacetate. ^{1}H NMR ($CDCl_3$): δ 8.20 (d, 2H, J= 8.2 Hz), 6.95 (d, 2H, J= 8.1 Hz), 4.72 (s, 2H), 4.25 (q, 2H), 1.23 (t, 3H); LCMS: ret. time: 27.07 min.; purity: 100%; MS: 267 (M+ acetonitrile). Ethyl 4-Aminophenoxyacetate A solution of ethyl 4-nitrophenoxyacetate (15 g) in EtOH (400 mL) was hydrogenated at 40 PSI for 40 minutes in the presence of 10% Pd/C (1.5 g, 10% by weight). After the filtration through a celite the solvent was removed under a reduced pressure to obtain ethyl 4-aminophenoxyacetate. ^{1}H NMR ($CDCl_3$): δ 6.77 (d, 2H, 8.1 Hz), 6.60 (d, 2H, J= 8.0 Hz), 4.50 (s, 2H), 4.24 (q, 2H), 1.24 (t, 3H), LCMS: ret. time: 12.00 min.; purity: 100%; MS (m/e): 196 (MH^+).
7.2.26	tert-Butyl 4-Aminophenoxyacetate	tert-Butyl 4-Nitrophenoxyacetate In like manner to the preparation of ethyl 4-nitrophenoxyacetate, 4-nitrophenol and tert-butyl bromoacetate were reacted to prepare tert-butyl 4-nitrophenoxyacetate. ^{1}H NMR ($CDCl_3$): δ 8.2 (d, 2H, J= 8.1 Hz), 6.95 (d, 2H, J= 8.2 Hz), 4.60 (s, 2H), 1.42 (s, 9H). tert-Butyl 4-Aminophenoxyacetate In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of tert-butyl 4-nitrophenoxyacetate was carried out to prepare tert-butyl 4-aminophenoxyacetate. ^{1}H NMR ($CDCl_3$): δ 6.74 (d, 2H, J= 9 Hz), 6.62 (d, 2H, J= 9 Hz), 4.42 (s, 2H), 1.42 (s, 9H); LCMS: ret. time: 16.35 min.; purity: 94%; MS (m/e): 224 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.2.27	Ethyl 3-Aminophenoxyacetate	Ethyl 3-Nitrophenoxyacetate In like manner to the preparation of ethyl 4-nitrophenoxyacetate, 3-nitrophenol and ethyl bromoacetate were reacted to prepare ethyl 3-nitrophenoxyacetate. ^{1}H NMR ($CDCl_3$): δ 7.88 (dt, 1H, J= 1.2 and 8.7 Hz), 7.71 (t, 1H, J= 2.4 Hz), 7.45 (t, 1H, J= 8.4 Hz), 7.27 (dt, 1H, J= 2.4 and 8.4 Hz), 4.70 (s, 2H), 4.29 (q, 2H, J= 6.9 Hz), 1.30 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 27.28 min.; purity: 96%. Ethyl 3-Aminophenoxyacetate In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of ethyl 3-nitrophenoxyacetate was carried out to prepare ethyl 3-aminophenoxyacetate. ^{1}H NMR ($CDCl_3$): δ 7.05 (t, 1H, J= 7.2 Hz), 6.30 (m, 3H), 4.56 (s, 2H), 4.25 (q, 2H, J= 7.2 Hz), 1.29 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 10.69 min.; purity: 96%; MS (m/e). 196 (MH^+).
7.2.28	(±)-Ethyl 2-(4-Aminophenoxy)propionate	In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of ethyl (±)-2-(4-nitrophenoxy)propionate was carried out to prepare (±) ethyl 2-(4-aminophenoxy)propionate. ^{1}H NMR ($CDCl_3$): δ 6.70 (d, 2H), 6.58 (d, 2H), 4.60 (m, 1H), 4.20 (q, 2H), 3.2 (bs, 2H), 1.45 (d, 3H), 1.22 (t, 3H).
7.2.29	N-Methyl 3-Aminophenoxyacetamide	N-Methyl 3-Nitrophenoxyacetamide A mixture of ethyl 3-nitrophenoxyacetate (9.12g, 40 mmol), methylamine hydrochloride (26.8g, 400 mmol) and diisopropylethylamine (35.5 mL, 200 mL) in MeOH (100 mL) was stirred in a pressure vial at 90 °C for 6h. The reaction was cooled to room temperature, diluted with water (1 liter), the solid formed was filtered, washed with water and dried to get the desired N-methyl 3-nitrophenoxyacetamide (8g, 95%) ^{1}H NMR $CDCl_3$): δ 7.91 (dd, 1H, J= 1.8 and 8.1 Hz), 7.78 (t, 1H, J= 2.4 Hz), 7.50 (t, 1H, J= 8.7 Hz), 7.29 (dd, 1H, J= 1.8 and 8.4 Hz), 6 50 (bs, 2H), 4.57 (s, 2H), 2.95 and 2.93 (2s, 3H); LCMS: ret. time: 17.54 min.; purity: 100%; MS (m/e): 211 (MH^+). N-Methyl 3-Aminophenoxyacetamide In like manner to the preparation of ethyl 4-aminophenoxyacetate, the hydrogenation of N-methyl 3-nitrophenoxyacetamide (8 g, 39 mmol) was conducted to give the desired N-methyl 3-aminophenoxyacetamide (6g, 86%). ^{1}H NMR (CD_3OD): δ 6.99 (t, 1H, J= 8.1 Hz), 6.37-6.25 (m, 3H), 4.41 (s, 2H), 2.80 (s, 3H); LCMS: ret. time: 19.80 min.; purity: 100%.

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Section Number	Name of compound and reference number	Experimental
7.2.30.	2-Methoxycarbonyl-5-aminobenzofuran (R926610)	2-Methoxycarbonyl-5-nitrobenzofuran (R926609) To a suspension of 5-nitro-2-benzofurancarboxylic acid (5 g, 24.15 mmol) in CH_2Cl_2 (250 mL) at 0 °C was added DMF (0.100 mL) followed by $(COCl)_2$ (2M in CH_2Cl_2, 36.23 mL, 72.46 mL) over a period of 10 min. The reaction was stirred at 0 °C for 1h and then at room temperature for 30 min. The reaction solvent was removed under a reduced pressure, dried under high vacuum and again suspended in CH_2Cl_2 (250 mL). The solution was cooled to 0 °C, were added pyridine (4 8 mL, 48.03 mmol) followed by MeOH (10 mL, excess) and stirred overnight. The extractive work-up with CH_2Cl_2 gave the expected 2-methoxycarbonyl-5-nitrobenzofuran (R926609). ^{1}H NMR ($CDCl_3$): δ 8.66 (d, 1H, J= 2.4 Hz), 8.36 (dd, 1H, J= 2.4 and 9.6 Hz), 7.71 (d, 1H, J= 9.3 Hz), 7.65 (s, 1H), 4.01 (s, 3H); LCMS: ret. time: 26.94 min. 2-Methoxycarbonyl-5-aminobenzofuran (R926610) In like manner to the preparation of ethyl 4-aminophenoxyacetate, the hydrogenation of 2-methoxycarbonyl-5-nitrobenzofuran (2 g) in MeOH gave 2-methoxycarbonyl-5-aminobenzofuran. ^{1}H NMR ($CDCl_3$): δ 7.38 (bt, 2H), 6.90 (bd, 1H), 6.85 (bdd, 1H), 3.98 (s, 3H).
7.2.31	Methyl 2-(2-methyl-5-nitrophenoxy)acetate	In like manner to the preparation of ethyl 4-nitrophenoxyacetate, 2-methyl-5-nitrophenol and methyl bromoacetate were reacted to prepare methyl 2-(2-methyl-5-nitrophenoxy)acetate. ^{1}H NMR (CD_3OD): δ 7.80 (dd, 1H, J= 2.4 and 8.1 Hz), 7.65 (d, 1H, J= 2.4 Hz), 7.38 (d, 1H, J= 8.1 Hz), 4.90 (s, 2H), 3 80 (s, 3H), 2.36 (s, 3H).
7.2.32	Ethyl 2-methyl-2-(3-nitrophenoxy)propanate	A mixture of 3-nitrophenol (0.50g, 3.6 mmole), ethyl bromodimethylacetate (0.64g, 3.3 mmole), K_2CO_3 (1.3 g, 9.4 mmole), potassium iodide (catalytic) in absolute ethanol (8 mL) was heated at 70°C for 18h. The reaction mixture was cooled, poured into a saturated solution of NaHCO3, and extracted with dichloromethane. The product, ethyl 2-methyl-2-(3-nitrophenoxy)propanate, was obtained after purification by column chromatography over silica gel. ^{1}H NMR ($CDCl_3$): δ 7.85 (dt, 1H, J= 1.2 and 8.1 Hz), 7.68 (t, 1H, J= 2.4 Hz), 7.40 (t, 1H, J= 8.4 Hz), 7.19-7.13 (m, 1H), 4.26 (q, 2H, J= 7.2 Hz), 1.64 (s, 6H), 1.26 (t, 3H, J= 7.21),
7.2.33	N-Methyl-2-(2-methyl-5-nitrophenoxy)acetamide	In like manner to the preparation of N-methyl 3-nitrophenoxyacetamide, methyl 2-methyl-5-nitrophenoxyacetate and methylamine hydrochloride were reacted to prepare N-methyl-2-(2-methyl-5-nitrophenoxy)acetamide. ^{1}H NMR (CD_3OD): δ 7.82 (dd, 1H, J= 2.4 and 8.1 Hz), 7.69 (d, 1H, J= 2.4 Hz), 7.40 (d, 1H, J= 8.1 Hz), 4.66 (s, 2H), 2.83 (s, 3H), 2.40 (s, 3H).

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Section Number	Name of compound and reference number	Experimental
7.2.34	N,2-Dimethyl-2-(3-nitrophenoxy)propanamide	In like manner to the preparation of ethyl 2-methyl-2-(3-nitrophenoxy)propanate, 3-nitrophenol and N,2-dimethyl-2-bromopropanamide (prepared according to the following reference: Guziec, Frank S., Jr.; Torres, Felix F. Journal of Organic Chemistry (1993), 58(6), 1604-6) were reacted to prepare N,2-dimethyl-2-(3-nitrophenoxy)propanamide. ^{1}H NMR ($CDCl_3$): δ 7.94 (dt, 1H, J= 1.2 and 8.1 Hz), 7.78 (t, 1H, J= 2.4 Hz), 7.45 (t, 1H, J= 8.4 Hz), 7.22 (ddd, 1H, J= 1.2, 2.4, and 8.1 Hz), 6.61 (bs, 1H), 2 89 (d, 3H, J= 5.1 Hz), 1.55 (s, 6H).
7.2.35	4-Amino-[(1H,1,2,3,4-tetrazolyl)methyleneoxy]benzene	4-Nitro-[(1H,1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene A mixture of 2-cyanomethoxy-4-nitrophenyl (5.8 g, 32.6 mmol), sodium azide (6.3 g, 98.0 mmol) and ammonium chloride (8.5 g, 163.3 mmol) was suspended in DMF (100 mL) containing acetic acid (1 mL) and the mixture heated at 70 °C. After 17 h, the reaction was cooled to room temperature and 2 N aqueous hydrochloric acid (100 mL) was added. The solid which precipitated out of the reaction mixture was collected by filtration, washed with water (2 x 20 mL) then hexane (30 mL), affording compound 4-nitro-[(1H,1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene (6.7 g, 99%) as an orange solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.25 (d, J = 9.2 Hz, 2H), 7.29 (d, J = 9.1 Hz, 2H), 5.68 (s, 2H); ESI MS *m/z* 220 [$C_8H_7N_5O_3$ - H]$^-$. 4-Amino-[(1H,1,2,3,4-tetrazolyl)methyleneoxy]benzene A mixture of 4-nitro-[(1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene (6.7 g, 30.4 mmol) and 5 wt % palladium on carbon (700 mg) suspended in ethanol/concentrated hydrochloric acid (14:1, 150 mL) was hydrogenated in a sealed vessel at 50 psi The mixture was shaken until no further hydrogen uptake was observed, after which the reaction was filtered through diatomaccous earth with chloroform and the filtrate concentrated to afford crude product. Purification by flash chromatography (7:2.5:0.5 $CHCl_3$/CH_3OH/NH_4OH) afforded 4-amino-[(1H,1,2,3,4-tetrazolyl)methyleneoxy)]benzene as a brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.76 (d, J = 8.7 Hz, 2H), 6 52 (d, J = 8.7 Hz, 2H), 5.07 (s, 2H); ESI MS *m/z* 190 [$C_8H_9N_5O$ - H]$^-$

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Section Number	Name of compound and reference number	Experimental
7.2.36	4-Amino-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene	4-Nitro-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene and 4-Nitro-[(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene A mixture of 4-nitro-[(1H,1,2,3,4-tetrazolyl)methyleneoxy]benzene (10.00 g, 45.2 mmol), cesium carbonate (22.09 g, 67.8 mmol) and methyl iodide (7.70 g, 54.3 mmol) in DMF (200 mL) was stirred at room temperature for 24 h. The reaction mixture was concentrated to remove most of the DMF and the crude residue was partitioned between chloroform (100 mL) and water (50 mL). The organic phase was separated, washed with brine, dried (Na_2SO_4) and concentrated to afford crude product as a orange solid. Purification by flash chromatography (chloroform) afforded 4-nitro-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (d, J = 9.2 Hz, 2H), 7.31 (d, J = 9.2 Hz, 2H), 5.72 (s, 2H), 4.15 (s, 3H); and 4-nitro-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8 24 (d, J = 9.3 Hz, 2H), 7.29 (d, J = 9.3 Hz, 2H), 5.58 (s, 2H), 4.41 (s, 3H). 4-Amino-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene A mixture of 4-nitro-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (3.60 g, 15.3 mmol) and 5% Pd/C (0.40 g) in 14:1 ethanol/concentrated hydrochloric acid (75 mL) was shaken at room temperature in a atmosphere of hydrogen at 50 psi. After 4 h no further hydrogen uptake was observed. The reaction mixture was filtered through diatomaceous earth, the solids washed with a 6:3:1 chloroform/methanol/concentrated ammonium hydroxide solution and the filtrate concentrated to afford crude 4-amino-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene, which was purified by flash chromatography (95·5 chloroform/ methanol): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.48 (br s, 2H), 6.79 (d, J = 6.9 Hz, 2H), 6.55 (d, J = 6.9 Hz, 2H), 5.36 (s, 2H), 4.10 (s, 3H).
7.2.37	4-Amino-[(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene	A mixture of 4-nitro-[(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene (3.60 g, 15.3 mmol) and 5% Pd/C (0.40 g) in 14:1 ethanol/concentrated hydrochloric acid (75 mL) was shaken at room temperature in a hydrogen atmosphere at 50 psi. After 3 h no further hydrogen uptake was observed. The reaction mixture was filtered through diatomaceous earth, the solids washed with a 6:3:1 chloroform/methanol/concentrated ammonium hydroxide solution and the filtrate concentrated to afford crude 4-amino-[(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene, which was purified by flash chromatography (95:5 chloroform/ methanol): ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.80 (br s, 2H), 6.75 (d, J = 9.0 Hz, 2H), 6.50 (d, J = 9.0 Hz, 2H), 5.17 (s, 2H), 4.37 (s, 3H).

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Section Number	Name of compound and reference number	Experimental
7.2.38	2-Ethoxycarbonyl-5-aminoindole (R926611)	In like manner to the preparation of ethyl 4-aminophenoxyacetate, the hydrogenation of 2-ethoxycarbonyl-5-nitroindole gave the 2-ethoxycarbonyl-5-aminoindol. LCMS: ret. time: 13.44 min.; purity: 93%; MS (m/e): 205 (MH^+).
7.2.39	5-[(4-Aminophenoxy)methyl]-3-phenyl-1,2,4-oaxadiazole	Preparation of 5-[4-(Nitrophenoxy)methyl]-3-phenyl-1,2,4-oxadiazole 4-Nitrophenol (0.36 g, 2.56 mmole), 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (0.5 g, 2.56 mmole) and anhydrous K_2CO_3 (0.39 g, 2.82 mmole) were dissolved in anhydrous acetone (20 mL) and heated to reflux for 12 h. Reaction mixture was cooled and the solvent removed under vacuum. The crude solid formed was collected by filtration, washed with water and dried under vacuum to provide 5-[(4-nitrophenoxy)methyl]-3-phenyl-1,2,4-oxadiazole (0.70 g, 92%). ^1H NMR ($CDCl_3$): δ 8.25 (d, 2H, J= 8.8 Hz), 8.08 (dd, 2H, J= 8.2 Hz), 7.52-7.49 (m, 3H), 7.13 (d, 2H, J= 8.8 Hz), 5.45 (s, 2H). Preparation of 5-[(4-Aminophenoxy)methyl]-3-phenyl-1,2,4-oxadiazole The 5-[(4-nitrophenoxy)methyl]-3-phenyl-1,2,4-oxadiazole (0.5 g, 1.68 mmole) was dissolved in methanol:methylenechloride (1:1) (120 mL). Aqueous solution of (15 mL) sodium hydrosulfite (0.88g, 5.05 mmole) and K_2CO_3 (0.70g, 5.06 mmole) was added dropwise under nitrogen for 10 min. The contents were allowed to stir at room temperature. After consumption of starting material, reaction mixture was concentrated, diluted with water till the homogeneous layer formed. The aqueous layer was extracted with several times with ethylacetate and methylene chloride. The turbid organic layers were combined, dried with anhydrous Na_2SO_4 and concentrated. Purification of the solid concentrate by silica gel chromatography provided 5-[(4-aminophenoxy)methyl]-3-phenyl-1,2,4-oxadiazole (0.23g, 51%). ^1H NMR ($CDCl_3$): δ 8.11 (m, 2H), 7.52-7.46 (m, 3H), 6.87 (d, 2H, J= 8.8 Hz), 6.64 (d, 2H, J= 8.8 Hz), 5.26 (s, 2H), 3.49 (br s, 2H). Preparation of 5-[(4-Nitrophenoxy)methyl]-3-methyl-1,2,4-oxadiazole A mixture of 4-nitrophenoxy acetic acid (2.25 g, 11.4 mmole), acetamideoxime, triethylamine hydrochloride (3.85g, 27.62 mmole), EDCI.HCl (4.37g, 22.79 mmole) and diisopropylethylamine (7.42g, 57.40 mmole) in anhydrous THF (250 ml) was refluxed for 18h. The unhomogenous brown colored reaction mixture was quenched with water and extracted with EtOAc (3 x 300 mL). The combined organic layers washed successively with aqueous $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. Removal of solvent and purified by chromatographic purification provided 5-[(4-nitrophenoxy)methyl]-3-methyl-1,2,4-oxadiazole (1.62 g, 60 %). ^1H NMR ($CDCl_3$): δ 8.24 (d, 2H, J= 8.8 Hz), 7.08 (d, 2H, J= 8.8 Hz), 5.36 (s, 2H), 2.44 (s, 3H).

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Section Number	Name of compound and reference number	Experimental
		Preparation of 5-[(4-Aminophenoxy)methyl]-3-methyl-1,2,4-oxadiazole In like manner to the preparation of 5-[(4-aminophenoxy)methyl]-3-phenyl-1,2,4-oxadiazole, 5-(4-nitrophenoxymethyl)-3-methyl-1,2,4-oxadiazole was reacted with aqueous solution of sodium hydrosulfite and K_2CO_3 to prepare 5-[(4-aminophenox)ymethyl]-3-methyl-1,2,4-oxadiazole. ^{1}H NMR ($CDCl_3$): δ 6.82 (d, 2H, J= 8.8 Hz), 6.63 (d, 2H, J= 8.8 Hz), 5.15 (s, 2H), 3.38 (br s, 2H), 2.41 (s, 3H).
7.2.40	Ethyl 2-(4-aminophenyl)-2-methylpropionate	Ethyl 2-methyl-2-(4-nitrophenyl)propionate A dry reaction flask charged with ethyl 4-nitrophenylacetate (5.0 g, 23.89 mmole), iodomethane (8.48 g, 3.72 mL, 59.74 mmole), 18-crown-6 (1.57 g, 5.93 mmole) in dry THF (200 mL) was cooled to –78 °C under nitrogen atmosphere. While stirring the contents, *t*-BuOK (5.90 g, 52.57 mmole) was added portionwise. The resulting violet precipitate was stirred at –78 °C for 2h and allowed the contents to warm to room temperature. The reaction was stirred at room temperature for 6h. At this time, once again the contents were cooled to –78 °C another portion of iodomethane, *t*-BuOK, and 18-crown-6 were added successively and stirred at the same temperature for 2h. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated aq. NH_4Cl (75 mL), the resulting homogenous mixture extracted with ether (4 x 200 mL), dried over anhydrous Na_2SO_4, and concentrated. The concentrate was purified by silica gel column chromatography with 1%EtOAc/hexanes to provide ethyl 2-methyl-2-(4-nitrophenyl)propionate as a pale yellow oil (2.38, 42%). ^{1}H NMR ($CDCl_3$): δ 8.17 (d, 2H, J= 8.8 Hz), 7.49 (d, 2H, J= 8.8 Hz), 4.12 (qt, 2H, J= 7.0 Hz), 1.60 (s, 6H), 1.17 (t, 3H, J= 7.0 Hz). Ethyl-2-(4-aminophenyl)-2-methylpropionate In like manner to the preparation of ethyl 4-aminophenoxyacetate, the hydrogenation of ethyl 2-methyl-2-(4-nitrophenyl)propionate provided ethyl-2-(4-aminophenyl)-2-methylpropionate. ^{1}H NMR ($CDCl_3$): δ 7.16 (d, 2H, J= 8.8 Hz), 6.63 (d, 2H, J= 8.8 Hz), 4.09 (qt, 2H, J= 7.0 Hz), 3.62 (br s, 2H), 1.52 (s, 6H), 1.17 (t, 3H, J= 7.0 Hz).
7.2.41	Anilines substituted with 1,3,4-oxadiazole moieties	N'1-(3-Chlorobenzoyl)-3-nitrobenzene-1-carbohydrazide To a solution of 3-chlorobenzohydrazide (1 equivalent) and pyridine (2 equivalents) in CH_2Cl_2 at 0 °C was added a CH_2Cl_2 solution of 3-nitrobenzoyl chloride (1 equivalents) and stirred at 0 °C for 1 h and then at room temperature for overnight. The resulting solution was concentrated and diluted with water, basified with $NaHCO_3$, the solid was filtered, washed with water, dried and analyzed to obtain N'1-(3-chlorobenzoyl)-3-nitrobenzene-1-carbohydrazide. ^{1}H NMR (DMSO-d6): δ 10.99 (s, 1H), 10.79 (s, 1H), 8.73 (bs, 1H), 8.43 (bdd, 1H, J= 1.2 and 8.1 Hz),

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Section Number	Name of compound and reference number	Experimental
		8.33 (bdd, 1J, J= 8.4 Hz), 7.95 (s, 1H), 7.87 (m, 2H), 7.67 (bdd, 1H, J= 1.2 and 8.1 Hz), 7.57 (t, 1H, J= 7.8 Hz); LCMS: purity: 85%; MS (m/e): 320 (MH^+). [2-(3-Chlorophenyl)-1,3,4-oxadiazol-5-yl]-3-nitrobenzene A suspension of N'1-(3-chlorobenzoyl)-3-nitrobenzene-1-carbohydrazide (0.321 g) in $POCl_3$ (3 mL) was stirred at 90 °C for 24 h. The resulting clear solution was quenched with ice-water, solid obtained was filtered washed with water, dried and analyzed to give [2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl]-3-nitrobenzene. ^1H NMR (DMSO-d6): δ 8.86 (t, 1H, J= 1.8 Hz), 8.59 (dt, 1H, J= 1.8 and 8.4 Hz), 8.48 (m, 1H), 8.25 (t, 1H, J= 1.8 Hz), 8.16 (dt, 1H, J= 1.2 and 7.5 Hz), 7.93 (t, 1H, J= 8.1 Hz), 7.75 (m, 1H), 7.66 (t, 1H, J= 7.5 Hz), LCMS: purity: 86%; MS (m/e): 302 (MH^+). Reduction of [2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl]-3-nitrobenzene The hydrogenation of [2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl]-3-nitrobenzene (0.2 g) using 10% Pd/C (0.04 g) in MeOH (200 mL) at 15 PSI for 1 h gave a mixture of two products viz. 3-amino-[2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl]benzene and 3-amino-(2-phenyl-1,3,4-oxadiazol-5-yl)benzene which were separated by silica gel column chromatography using n-hexanes then n-hexanes: 5-10% EtOAc as a solvent system. **3-Amino-[2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl]benzene:** ^1H NMR (DMSO-d6): δ 8.08 (m, 2H), 7.64 (m, 4H), 7.42 (m, 1H), 7.10 (m, 1H); LCMS: purity: 82%; MS (m/e): 272 (MH^+). **3-Amino-(2-phenyl-1,3,4-oxadiazol-5-yl)benzene:** ^1H NMR (DMSO-d6): δ 8.13 (m, 1H), 7.54 (m, 5H), 7.30 (m, 1H), 6.86 (dd, 1H, J= 1.5 and 8.1 Hz); LCMS: purity: 93%; MS (m/e): 238 (MH^+). N'1-(Ethoxycarbonylmethylenecabonyl)-3-nitrobenzene-1-carbohydrazide In like manner to the preparation of N'1-(3-chlorobenzoyl)-3-nitrobenzene-1-carbohydrazide, the reaction of 3-nitrobenzoyl chloride with ethoxycarbonylmethlenecarbohydrazide gave N'1-(ethoxycarbonylmethylenecabonyl)-3-nitrobenzene-1-carbohydrazide. ^1H NMR (CD_3OD): δ 8.74 (m, 1H), 8.44 (dd, 1H, 1.8 and 8 1 Hz), 8.25 (bd, 1H, J= 8.4 Hz), 7.76 (t, 1H, J= 8.4 Hz), 4.22 (q, 2H, J= 6.9 Hz), 3.44 (bs, 2H), 1.29 (t, 3H, J= 6.8 Hz); LCMS: purity: 93%; MS (m/e): 296 (MH^+). [2-(Ethoxycarbonylmethylene)-1,3,4-oxadiazol-5-yl]-3-nitrobenzene In like manner to the preparation of [2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl]-3-nitrobenzene the reaction of POCl3 with N'1-(ethoxycarbonylmethylenecabonyl)-3-nitrobenzene-1-carbohydrazide gave [2-(ethoxycarbonylmethylene)-1,3,4-oxadiazol-5-yl]-3-nitrobenzene. ^1H NMR ($CDCl_3$): δ 8.88 (t, 1H, J= 1.8 Hz), 8.42 (m, 2H), 7.74 (t, 1H, J= 7.5 Hz), 4.27 (q, 2H, J= 7.2 Hz), 4.08 (s, 2H), 1.31 (t, 3H, J= 7.2 Hz); LCMS: purity: 95%; MS (m/e): 278 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.2.42	Synthesis of (±)-5-Amino-(2,3-dihydro-2-methoxycarbonyl)benzofuran	2-Methoxycarbonyl-5-nitrobenzofuran A mixture of 2-carboxy-5-nitrobenzofuran (2.0 g), MeOH (10 mL) and Concentrated H_2SO_4 (2.1 mL) was heated in a sealed tube at 60 °C for 3 h. Upon cooling to the room temperature it was quenched with ice-water and carefully basified with addition of $NaHCO_3$. The solid obtained was filtered, washed with water, dried and analyzed to give 2-methoxycarbonyl-5-nitrobenzofuran. ^{1}H NMR ($CDCl_3$): δ 8.66 (d, 1H, J= 2.4 Hz), 8.36 (dd, 1H, J= 2.4 and 9.6 Hz), 7.71 (d, 1H, J= 9.3 Hz), 7.65 (s, 1H), 4.01 (s, 3H); LCMS: purity: 97%; MS (m/e): 222 (MH^+). (±)-5-Amino-(2,3-dihydro-2-methoxycarbonyl)benzofuran A suspension of 2-methoxycarbonyl-5-nitrobenzofuran (2.0 g), 10% Pd/C (2.0 g), Na_2SO_4 (2.0 g) in MeOH (500 mL) was hydrogenated at 55 PSI for 3 days. The resulting solution was filtered through a pad of celite, concentrated and chromatographed using n-hexanes then 10%, 20% EtOAc/n-hexanes to give (±)-5-amino-(2,3-dihydro-2-methoxycarbonyl)benzofuran. ^{1}H NMR ($CDCl_3$): δ 6.69 (d, 1H, J= 8.1 Hz), 6.56 (d, 1H, J= 1.2 Hz), 6.48 (dd, 1H, J= 1.8 and 7.5 Hz), 5.14 (dd, 1H, J= 6.6 and 7.2 Hz), 3.79 (s, 3H), 3.47 (dd, 1H, J= 10.5 and 10.8 Hz), 3.26 (dd, 1H, J= 7.2 and 6.6 Hz); LCMS: purity: 100%; MS (m/e): 194 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.2.43	3-[1-Bis(ethoxycarbonyl)ethoxy]aniline	Preparation of Diethyl 2-methyl-2-(3-nitrophenoxy)malonate Diethyl 2-bromo-2-methylmalonate (1.0 g, 3.95 mmole) was added to a stirred suspension of potassium fluoride (0.57 g, 9.8 mmole) in dry DMF (5 mL). After stirring for 20 min at room temperature, 3-nitrophenol (0.55 g, 3.95 mmole) was added. The resulting mixture was stirred at 60 ^{o}C for 6 h, cooled to room temperature, diluted with water (30 mL) and extracted with ethyl acetate (3 X 200 mL). The organic layer was washed with aq.1N NaOH (2 X 75 mL), dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo to provide diethyl 2-methyl-2-(3-nitrophenoxy)malonate (0.89 g, 80%). ^{1}H NMR ($CDCl_3$): δ 7.92 (dd, 1H, J = 2.3 and 8.2 Hz), 7 82 (t, 1H, J = 2.3 Hz), 7.41 (t, 1H, J = 8.2 Hz), 7.30 (dd, 1H, J = 2.3 and 8.2 Hz), 4.28 (qt, 4H, J = 7.0 Hz), 1 81 (s, 3H), 1.26 (t, 6H, J = 7.0 Hz). Preparation of 3-[1-Bis(ethoxycarbonyl)ethoxy]aniline Diethyl 2-methyl-2-(3-nitrophenoxy)malonate (0.75 g, 2.40 mmole) was dissolved in toluene: ethanol (1:1, 100 mL), transferred to par shaker bottle containing Pd/C (0.15 g) and anhydrous Na_2SO_4 (5.0 g) in the presence of nitrogen atmosphere. The resulting mixture was treated with hydrogen (30 PSI) till the disappearance of diethyl 2-methyl-2-(3-nitrophenoxy)malonate (2 h). The mixture was filtered through celite covered with anhydrous Na_2SO_4 followed by washing the celite pad with EtOAc. The filtrated was concentrated and dried under vacuo to furnish 3-[1-bis(ethoxycarbonyl)ethoxy]aniline in quantitative yield . ^{1}H NMR ($CDCl_3$): δ 6.98 (t, 1H, J = 8.2 Hz), 6.37-6.28 (m, 3H), 4.26 (qt, 4H, J = 7.0 Hz), 3.65 (br s, 2H), 1.72 (s, 3H), 1.24 (t, 6H, J = 7.0 Hz).
7.2.44	Preparation of 4-(4-aminophenoxymethyl)-2-methoxycarbonyl-furan	Preparation of 4-(4-nitrophenoxymethyl)-2-methoxycarbonyl-furan 3-Nitrophenol (1.0 g, 7.19 mmole), methyl 5-(chloromethyl)-2-furoate (1.38 g, 7.90 mmole) and anhydrous K_2CO_3 (1.19 g, 8.60 mmole) in acetone (30 mL) were refluxed for 8 h.. The reaction mixture was cooled and diluted with water. The resultant white solid was filtered, washed with water and air dried overnight to give 1.81 g (90%) of the desired product. ^{1}H NMR ($CDCl_3$): δ 7.86 (dd, 1H, J = 2.3 and 8.2 Hz), 7.80 (t, 1H, J = 2.3 Hz), 7.45 (t, 1H, J = 8.2 Hz), 7.27 (dd, 1H, J = 2.3 and 8.2 Hz), 7.17 (d, 1H, J = 3.5 Hz), 6.58 (d, 1H, J = 3.5 Hz), 5.13 (s, 2H), 3.90 (s, 3H). Preparation of 4-(4-aminophenoxymethyl)-2-methoxycarbonyl-furan In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 4-(4-nitrophenoxymethyl)-2-methoxycarbonyl-furan was reduced to provide 4-(4-aminophenoxymethyl)-2-methoxycarbonyl-furan. ^{1}H NMR ($CDCl_3$): δ 7.15 (d, 1H, J = 3.5 Hz), 7.05 (t, 1H, J = 8.2 Hz), 6.50 (d, 1H, J = 3.5 Hz), 6.37-6.27 (m, 3H), 5.01 (s, 2H), 3.89 (s, 3H).

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Section Number	Name of compound and reference number	Experimental
7.2.45	Preparation of 6-amino-1-(methoxycarbonyl)methylindazoline	Preparation of 1-(methoxycarbonyl)methyl-6-nitroindazoline To a solution of 6-nitroindazoline (2.0 g, 12.25 mmole) in dry DMF was added anhydrous K_2CO_3 (1.84 g, 13.31 mmole) and methyl 2-bromoacetate (2.04 g, 13.33 mmole). The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with water and the resulting solid was collected by filtration, washed with excessive water, and air dried. The yellow solid collected was purified by silica gel column chromatography using gradient solvent system to furnish two products. The desired product (1.12 g, 41%) with high R_f value on the TLC in 30% EtOAc : hexanes was collected. In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 1-(Methoxycarbonyl)methyl-6-nitro-indazoline was reduced to provide 6-amino-1-(methoxycarbonyl)methylindazoline. ^{1}H NMR ($CDCl_3$): δ 7.73 (d, 1H, J = 1.1 Hz), 7.35 (d, 1H, J = 8.2 Hz), 6.49 (dd, 1H, J= 1.8 and 8.8 Hz), 6.39 (s, 1H), 5.34 (br s, 2H), 5.10 (s, 2H), 3.64 (s, 3H). Preparation of 1-(methoxycarbonyl)methyl-5-nitroindazoline In like manner to the preparation of 1-(methoxycarbonyl)methyl-6-nitroindazoline, 1-(methoxycarbonyl)methyl-5-nitroindazoline was prepared by alkylation of 5-nitroindazoline with methyl 2-bromoacetate in presence of K_2CO_3. The desired product (1.34 g, 46%) with high R_f value on the TLC in 30% EtOAc : hexanes was collected by silica gel column chromatographic purification. ^{1}H NMR ($CDCl_3$): δ 8.75 (d, 1H, J = 1.8 Hz), 8.30 (dd, 1H, J = 2.3 and 8.2 Hz), 8.26 (s, 1H), 7.40 (d, 1H, J = 8.2 Hz), 5.22 (s, 2H), 3.78 (s, 3H). Preparation of 5-amino-1-(methoxycarbonyl)methylindazoline In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 1-(Methoxycarbonyl)methyl-5-nitro-indazoline was reduced to provide 5-amino-1-(methoxycarbonyl)methylindazoline. ^{1}H NMR ($CDCl_3$): δ 7.84 (d, 1H, J = 2.3 Hz), 7.15 (d, 1H, J = 8.8 Hz), 6.95 (d, 1H, J= 2.3 Hz), 6.88 (dd, 1H, J = 2.3 and 8.8 Hz), 5.09 (s, 2H), 3.73 (s, 3H). Preparation of 1-(2-ethoxycarbonylethyl)-6-nitroindazoline In like manner to the preparation of 1-(methoxycarbonyl)methyl-6-nitroindazoline, 1-(ethoxycarbonyl)ethyl-6-nitroindazoline was prepared by alkylation of 6-nitroindazoline with ethyl 3-bromopropionate in presence of K_2CO_3. The desired product (58%) with high R_f value on the TLC in 30% EtOAc : Hexanes was collected by silica gel column chromatographic purification. ^{1}H NMR ($CDCl_3$): δ 8.49 (s, 1H), 8.12 (s, 1H), 8.01 (dd, 1H, J = 1.7 and 8.8 Hz), 7.82 (d, 1H, J = 8.8 Hz), 4.74 (t, 2H, J = 6.4 Hz), 4.09 (qt, 2H, J = 7.0 Hz), 3.03 (t, 2H, J = 6.4 Hz), 1.18 (t, 3H, J = 7.0 Hz).

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Section Number	Name of compound and reference number	Experimental
		Preparation of 6-amino-1-(2-ethoxycarbonylethyl)indazoline In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 1-(2-ethoxycarbonylethyl)-6-nitroindazoline was reduced to provide 6-amino-1-(2-ethoxycarbonylethyl)indazoline. ^{1}H NMR ($CDCl_3$): δ 7.81 (s, 1H), 7.46 (d, 1H, J = 8.8 Hz), 6.60 (app s, 1H), 6.55 (dd, 1H, J = 2.3 and 8.8 Hz), 4.51 (t, 2H, J = 7.0 Hz), 4.11 (qt, 2H, J = 7.0 Hz), 3.52 (br s, 2H), 2.91 (t, 2H, J = 7.0 Hz), 1.18 (t, 3H, J = 7.0 Hz). Preparation of 1-(2-ethoxycarbonylethyl)-5-nitroindazoline In like manner to the preparation of 1-(methoxycarbonyl)methyl-5-nitroindazoline, 1-(ethoxycarbonyl)ethyl-5-nitroindazoline was prepared by alkylation of 5-nitroindazoline with ethyl 3-bromopropionate in presence of K_2CO_3. The desired product (43%) with high Rf value on the TLC in 30% EtOAc : Hexanes was collected by silica gel column chromatographic purification. ^{1}H NMR ($CDCl_3$): δ 8.70 (d, 1H, J = 1.7 Hz), 8.27 (dd, 1H, J = 2.3 and 8 8 Hz), 8.20 (d, 1H, J = 1.7 Hz), 7.59 (d, 1H, J = 8.8 Hz), 4.70 (t, 2H, J = 6.4 Hz), 4.07 (qt, 2H, J = 7.0 Hz), 3.01 (t, 2H, J = 6.4 Hz), 1.16 (t, 3H, J = 7.0 Hz). Preparation of 5-amino-1-(2-ethoxycarbonylethyl)indazoline In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 1-(2-ethoxycarbonylethyl)-5-nitroindazoline was reduced to provide 5-amino-1-(2-ethoxycarbonylethyl)indazoline. ^{1}H NMR ($CDCl_3$): δ 7.78 (s, 1H), 7.30 (d, 1H, J = 8.8 Hz), 6.91 (d, 1H, J = 2.3 Hz), 6.87 (dd, 1H, J = 2.3 and 8.8 Hz), 4.59 (t, 2H, J = 6.4 Hz), 4.08 (qt, 2H, J = 7.0 Hz), 3.02 (br s, 2H), 2.92 (t, 2H, J = 7.0 Hz), 1.16 (t, 3H, J = 7.0 Hz). Preparation of 5-amino-2-methylindazoline In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, commercially available 2-methyl-5-nitroindazoline was reduced to provide 5-amino-2-methylindazoline. ^{1}H NMR ($CDCl_3$): δ 7.61 (s, 1H), 7.53 (d, 1H, J = 8.8 Hz), 6.81 (dd, 1H, J = 2 3 and 8.8 Hz), 6.75 (d, 1H, J = 2.3 Hz), 4.13 (s, 3H), 3.85 (br s, 2H).

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Section Number	Name of compound and reference number	Experimental
7.2.46	Preparation of methyl 3-methoxy-4-[(6-nitroindazol-1-yl)methyl]benzoate	In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, methyl 3-methoxy-4-[(6-nitroindazol-1-yl)methyl]benzoate was reduced to provide methyl 4-[(6-aminoindazol-1-yl)methyl]benzoate. ^{1}H NMR ($CDCl_3$): δ 7.88 (s, 1H), 7.53 (d, 1H, J = 8.8 Hz), 7.51 (d, 1H, J = 8.8 Hz), 7.50 (d, 1H, J = 1.7 Hz), 6.67 (d, 1H, J = 8.8 Hz), 6.56 (dd, 1H, J = 1.7 and 8.8 Hz), 6.45 (d, 1H, J = 1.2 Hz), 5.50 (s, 2H), 3.94 (s, 3H), 3.87 (s, 3H), 3.79 (br s, 2H). Preparation of Methyl 4-[(6-aminoindazol-2-yl)methyl]benzoate In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, methyl 3-methoxy-4-[(6-nitroindazol-2-yl)methyl]benzoate was reduced to provide methyl 4-[(6-aminoindazol-2-yl)methyl]benzoate. ^{1}H NMR ($CDCl_3$): δ 7.78 (s, 1H), 7.56-7.53 (m, 2H), 7.43 (d, 1H, J = 8.8 Hz), 6.98 (d, 1H, J = 8.2 Hz), 6.81 (app s, 1H), 6.58 (dd, 1H, J = 1.8 and 8.8 Hz), 5.53 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H).
7.2.47	Preparation of 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline	Preparation of 6-nitro-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy) benzyl]indazoline Ester hydrolysis of methyl 3-methoxy-4-[(6-nitroindazol-1-yl)methyl]benzoate in presence of $LiOH:H_2O$ produced the corresponding acid. The acid (1.65 g, 5.04 mmole) thus formed was converted to the acid chloride by reacting with $SOCl_2$ (3.68 mL, 50.45 mmole) at reflux temperature for 5 h. The reaction mixture was cooled to room temperature and concentrated under vacuo. To acid chloride concentrate dissolved in dry CH_2Cl_2 (75 mL), *o*-toluylbenzenesulfonamide (0.95 g, 5.54 mmole) and 4-(dimethylamino)-pyridine (0 67 g, 5.54 mmole) were added successively at room temperature and stirred for 12 h. The reaction mixture was concentrated, dissolved in EtOAc (700 mL) and successively treated with 2 N HCl (2 X 100 mL), water (150 mL) and brine (100 mL). Usual workup and purification by silica gel column chromatography provided the product (1.57 g, 64%). ^{1}H NMR (DMSO-d_6): δ 8.75 (s, 1H), 8.31 (s, 1H), 8.00 (d, 1H, J = 8.8 Hz), 7.95-7.91 (m, 2H), 7.50 (d, 1H, J = 1.2 Hz), 7.46-7.27 (m, 4H), 6.92 (d, 1H, J = 7.6 Hz), 5.76 (s, 2H), 3.81 (s, 3H), 2.54 (s, 3H). Preparation of 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 6-nitro-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline was reduced to provide 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline. ^{1}H NMR ($CDCl_3$): δ 7.96 (dd, 1H, J = 1.2 and 8.2 Hz), 7.76 (s, 1H), 7.51 (d, 1H, J = 1.2 Hz), 7.49-7.44 (m, 1H), 7.37 (d, 2H, J = 8.8 Hz), 7.34-7.32 (m, 1H), 7.30 (d, 1H, J = 8.8 Hz), 6.51-6.47 (m, 2H), 6.35 (s, 1H), 5.35 (s, 2H), 3.89 (s, 3H), 2.54 (s, 3H). Preparation of methyl 3-methoxy-4-[(5-nitroindazol-1-yl)methyl]benzoate In like manner to the preparation of methyl 3-methoxy-4-[(6-nitroindazol-1-yl)methyl]benzoate,

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Section Number	Name of compound and reference number	Experimental
		methyl 3-methoxy-4-[(5-nitroindazol-1-yl)methyl]benzoate was prepared by alkylation of 5-nitroindazoline with methyl (4-bromomethyl)-3-methoxybenzoate in presence of K_2CO_3. The desired product (47%) with high R_f value on the TLC in 30% EtOAc : Hexanes as eluent was collected by silica gel column chromatographic purification. ^{1}H NMR ($CDCl_3$): δ 8.73 (d, 1H, J = 1.8 Hz),8.26-8.22 (m, 2H), 7.56 (s, 1H), 7.54 (dd, 1H, J = 1.8 and 8.2 Hz), 7.49 (d, 1H, J = 9.4 Hz), 6.98 (d, 1H, J = 8.2 Hz), 5.66 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H). Low R_f: Methyl 3-methoxy-4-[(5-nitroindazol-2-yl)methyl]benzoate. Preparation of 5-nitro-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline In like manner to the preparation of 6-nitro-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline, 5-nitro-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline was prepared from methyl 3-methoxy-4-[(5-nitroindazol-1-yl)methyl]benzoate. ^{1}H NMR (DMSO-d_6): δ 8.81 (d, 1H, J = 2.3 Hz), 8.39 (s, 1H), 8 21 (dd, 1H, J = 1.8 and 8.8 Hz), 7.87 (dd, 2H, J = 3.6 and 8.8 Hz), 7.48 (d, 1H, J = 1.2 Hz), 7.39 (dd, 1H, J = 1.2 and 8.2 Hz), 7.33-7.15 (m, 3H), 6.85 (d, 1H, J = 8.2 Hz), 5.65 (s, 2H), 3.76 (s, 3H), 2.49 (s, 3H). Preparation of 5-amino-1-[2-methoxy-4-(*0*-toluyl-sulfonamidocarboxy)benzyl]indazoline In like manner to the preparation of 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline, 5-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline was prepared by reduction of 5-nitro-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline . ^{1}H NMR (DMSO-d_6): δ 7.87 (dd, 1H, J = 1.2 and 7.7 Hz), 7.73 (s, 1H), 7.50 (s, 1H), 7.35-7.14 (m, 5H), 6.78 (d, 1H, J = 1.8 Hz), 6.75 (s, 1H), 6.53 (d, 1H, J = 8.2 Hz), 5.44 (s, 2H), 3.82 (s, 3H), 2.50 (s, 3H).
7.2.48	Preparation of 8-amino-4*H*-imidazo[2,1-*c*][1,4]-benzoxazine	

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Section Number	Name of compound and reference number	Experimental
7.3	Synthesis of 2,4-Pyrimidinediamines	A variety of 2,4-pyrimidinediamines of the invention were synthesized from the above starting materials and intermediates and other commercially available reagents. Conditions suitable for synthesizing N2,N4-bis-substituted-2,4-pyrimidinediamine compounds ("general SNAr" reaction conditions; Substitution Nucleophilic Aromatic Reaction) are exemplified with N2,N4-bis(4-ethoxyphenyl)-2,4-pyrimdinediamine (**R926069**) and N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (**R921218**). Conditions suitable for synthesizing asymmetric N2,N4-disubstituted-2,4-pyrimdinediamines are exemplified by N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediame (**R926210**).
7.3.1	N2,N4-Bis(4-ethoxyphenyl)-2,4-pyrimidinediamine (R926069)	To a solution of 2,4-dichloropyrimidine (0.015g, 0.1 mmol) in EtOH (1 mL) was added 4-ethoxyaniline (0.034 g, 0.025 mmol) and heated in a sealed tube at 70-80 °C for 24h. Upon cooling the reaction was diluted with H_2O (10 mL), acidified with 2N HCl, the solid obtained was filtered, washed with H_2O and dried to give N2,N4-bis(4-ethoxyphenyl)-2,4-pyrimidinediamine (**R926069**). ^{1}H NMR (CD_3OD): δ 7.63 (d, 1H), 7.45 (d, 2H), J= 9 Hz), 7.32 (d, 2H, J= 9.3 Hz), 6.95 (d, 2H, J= 6.9 Hz), 6.87 (d, 2H, J= 8.7 Hz), 6.23 (d, 1H, J= 7.2 Hz), 4.04 (m, 4H), 1.38 (m, 6H); LCMS: ret. time: 25.91 min.; purity: 99.5%; MS (m/e): 351 (MH^+).
7.3.2	N2,N4-Bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R921218)	A mixture of 2,4-dichloro-5-fluoropyrimidine (0.0167 g, 0 1 mmol) and 3-aminophenol (0.033 g, 0.3 mmol) in MeOH: H_2O (1.8:0.2 mL; v/v) was shaken in a sealed tube at 100 °C for 24h (or 80 oC for 3 days), cooled to room temperature, diluted with water (15 mL), acidified with 2N HCl (pH >2). Upon saturation with sodium chloride it was extracted with ethyl acetate (3 x 20 mL), dried over anhydrous sodium sulfate and solvent was removed. The resulting residue was filtered through a pad of silica gel (200-400 mesh) using CH_2Cl_2 - >1 >10% MeOH in CH_2Cl_2 to obtain the desired N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (**R921218**). If the reaction scale is large enough, solid of the resulting product can be isolated by filtration. ^{1}H NMR ($CDCl_3$): δ 7.73 (d, 1H, J= 5.1 Hz), 7.12-6.90 (m, 6H), 6.64 (dd, 1H, J= 1.8 and 8.1 Hz), 6.53 (dd, 1H, J=-1.2 and 5.7 Hz); LCMS: ret. time: 16.12 min.; purity: 100%; MS (m/e): 313 (MH^+).
7.3.3	N2,N4-Bis(4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926017)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-methoxyaniline were reacted to yield N2,N4-bis(4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.67 (d, 1H, J= 4.8 Hz), 7.43 (d, 2H, J= 9.3 Hz), 7.67 (d, 2H, J= 8.7 Hz), 6.87 (d, 2H, J= 9.6 Hz), 6.83 (d, 2H, J= 8.7 Hz), 3.83 (s, 3H), 3.81(s, 3H); LCMS: ret. time: 22.53 min.; purity: 100%; MS (m/e): 341 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.4	N2,N4-Bis(3-fluoro-4-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926018)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-fluoro-4-trifluoromethylaniline were reacted to yield N2,N4-bis(3-fluoro-4-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.01 (d, 1H, J= 3 Hz), 7.77 (m, 3H), 7.61 (dt, 1H, J= 4.2 and 3 Hz), 7.20 (t, 1H, 8.7 Hz), 7.12 (t, 1H, J= 9.3 Hz), 6.95 (s, 1H), 6.82 (s, 1H); ^{19}F NMR ($CDCl_3$): δ –17505 (s, 3F), -17517 (s, 3F), -17525 (s, F), -17537 (s, F), -46835 (s, 1F); LCMS: ret. time: 32.39 min ; purity: 95%, MS (m/e): 453 (MH^+).
7.3.5	N2,N4-Bis(3,4-tetrafluoroethylendioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926037)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3,4-tetrafluoroethylenedioxyaniline were reacted to yield N2,N4-bis(3,4-tetrafluoroethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.01 (d, 1H, J= 3.0 Hz), 7.71 (d, 1H, J= 2.4 Hz), 7.70 (1H, d, J= 2.4 Hz), 7.18 (dd, 2H, J= 2.4 and 6 Hz), 7.07 (d, 2H, J= 1.8 Hz), 7.00 (1H, bs), 6.81 (d, 1H, J= 2.7 Hz); ^{19}F NMR ($CDCl_3$): -26029 (sept, 8F), -46791 (s, C5-F); LCMS: ret. time: 38.20 min.; purity: 85%; MS (m/e): 541 (MH^+).
7.3.6	N2,N4-Bis(3-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926038)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-trifluoromethoxyaniline were reacted to yield N2,N4-bis(3-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.03 (bd, 1H), 7.62 (bs, 2H), 7.48 (bd, 1H), 7.39 (t, 1H, J= 8.1 Hz), 7.34 (m, 1H), 7.29 (t, 1H, J= 7.5 Hz), 7.01 (m, 2H), 6.88 (m, 2H); ^{19}F NMR ($CDCl_3$): -16447 (s, 3F), –16459 (s, 3F), -46738 (s, 1F); LCMS: ret. time: 33.77 min.; purity: 93%; MS (m/e): 449 (MH^+).
7.3.7	N2,N4-Bis(4-chloro-3-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926039)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-chloro-3-trifluoromethylaniline were reacted to yield N2,N4-bis(4-chloro-3-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.05 (bs, 1H), 7.89 (bd, 1H), 7.77 (dd, 1H, J= 2.4 and 9 Hz), 7.65 (dd, 1H, J= 2.4 and 8.7 Hz), 7.49 (d, J= 8.1 Hz), 7.40 (d, 1H, J= 6.2 Hz), 7.03 (s, 1H), 6.91 (s, 1H); ^{19}F NMR ($CDCl_3$): δ –17864 (s, 3F), -17894 (s, 3F), -46550 (s, 1F); LCMS: ret. time: 38.81 min.; purity: 75%; MS (m/e): 485 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.8	N2,N4-Bis(3-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926064)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-ethoxyaniline were reacted to yield N2,N4-bis(3-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.96 (1H, d, J= 4.8 Hz), 7.22 (m, 6H), 7.07 (t, 1H, J= 1.8 Hz), 6.95 (dt, 1H, J= 1.2 and 7.2 Hz), 6.77 (m, 2H), 3.88 (q, 4H, J= 6.3 Hz), 1.33 (two t, 6H, J= 6.3 Hz); ^{19}F NMR ($CDCl_3$): - 46175; LCMS: ret. time: 26.86 min.; purity: 97%; MS (m/e): 369 (MH^+).
7.3.9	N2,N4-Bis(3-hydroxy-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926339)	In like manner to to N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-hydroxy-4-methoxylaniline were reacted to yield N2,N4-bis(3-hydroxy-4-methoxyphenyl)-5-fluoro--2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.82 (d, 1H J= 4 Hz), 7.18 (m, 2H), 6.95 (m, 2H), 6.83 (m, 2H) 3 93 (s, 6H); LCMS· ret. time: 16.63 min.; purity: 97 %; MS (m/e): 373 (MH^+).
7.3.10	N2,N4-Bis(4-ethoxycarbonylamino-3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926340)	In like manner to to N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-ethoxycarbonylamino-3-hydroxyaniline were reacted to yield N2,N4-bis(4-ethoxycarbonylamino-3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.86 (d, 1H J= 4 Hz), 7.67 (m, 2H), 7.20 (dd, 1H, J= 8 Hz, J= 4.1 Hz), 7.13 (d, 1H), 6.90 (m, 2H), 4.2(m, 4H), 1.32 (m, 6H); LCMS: ret. time: 20.92 min.; purity: 98 %; MS (m/e): 487 (MH^+).
7.3.11	N2,N4-Bis(-3-hydroxy-4-methylphenyl)-5-fluoro-2,4-pyrimidinediaminediamine (R926341)	In like manner to N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-hydroxy-4-methylaniline were reacted to yield N2,N4-bis(-3-hydroxy-4-methylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.83 (d, 1H J= 4 Hz), 7.11 (m, 4H), 6.81 (m, 2H), 2.19 (m, 6H); LCMS: ret. time: 20.69 min.; purity: 98 %; MS (m/e): 341 (MH^+).
7.3.12	N2,N4-Bis[4-(2-methoxyethyleneoxy)phenyl]-5-fluoro--2,4-pyrimidinediamine (R926342)	In like manner to N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-(2-methoxyethyloxy)aniline were reacted to yield N2,N4-bis[4-(2-methoxyethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.89 (d, 1H J= 4 Hz), 7.54 (dd, 2H, J= 6.8 and 2.7 Hz), 7.38 (dd, 2H, J= 6.8 and 2.7 Hz), 6.87 (dd, 2H, J= 6.8 and 2.7 Hz), 6.82 (dd, 2H, J= 6.8 and 2.7 Hz) 4.6 (m, 4H), 4.11 (m, 4H), 3.35 (m, 6H); LCMS: ret. time: 21.76 min.; purity: 97 %; MS (m/e): 429 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.13	N2,N4-Bis(dihydrobenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediaminediamine (R909237)	In like manner to N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 5-amino-2,3-dihydrobenzofuran were reacted to yield N2,N4-bis(dihydrobenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediaminediamine. ^{1}H NMR (CD_3OD): δ 7.99 (d, 1H J= 4 Hz), 7.22 (m, 4H), 6.81 (m, 2H), 4.55 (m, 4H), 3.22 (m, 4H); LCMS: ret. time: 23.80 min.; purity: 98 %; MS (m/e): 438 (MH^+).
7.3.14	N2,N4-Bis(3-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926065)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-methoxyaniline were reacted to yield N2,N4-bis(3-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine ^{1}H NMR (CD_3OD): δ 7.96 (d, 1H, J= 5.4 Hz), 7.24 (m, 6H), 7.06 (t, 1H, J= 2.4 Hz), 7.00 (dt, 1H, J= 1.2 Hz), 6.79 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H); ^{19}F NMR (CD_3OD): δ - 46112; LCMS: ret. time: 23.46 min.; purity: 99%; MS (m/e): 341 (MH^+).
7.3.15	N2,N4-Bis[4-(N,N-dimethylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926086)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-N,N-dimethylaniline were reacted to yield N2,N4-bis[4-(N,N-dimethylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.84 (d, 1H, J= 3.6 Hz), 7.43 (d, 2H, J= 8.7 Hz), 7.34 (d, 2H, J= 8.7 Hz), 7.25 (s, 1H), 6.73 (m, 4H), 6.55 (s, 1H), 2.95 (s, 6H), 2.90 (s, 6H); ^{19}F NMR ($CDCl_3$): - 47770; LCMS: ret. time: 12.48 min.; purity: 99%; MS (m/e): 367 (MH^+).
7.3.16	N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926109)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3,4-ethylenedioxyaniline were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1H, J= 3.6 Hz), 7.23 (d, 1H, J= 2.3 Hz), 7.15 (d, 1H, J= 2.4 Hz), 7.00 (dd, 1H, J= 3 and 8.1 Hz), 6.98 (dd, 1H, J= 3 and 8 Hz), 6.83 (d, 1H, J=8.7 Hz), 6.81 (d, 1H, J= 8.7 17Hz), 6.7(s, 1H), 6.58 (s, 1H), 4.23 (m, 4H), 4.24(m, 4H); ^{19}F NMR ($CDCl_3$): δ - 47445; LCMS: ret. time: 21.81 min.; purity: 96%; MS (m/e): 397 (MH^+).
7.3.17	N2,N4-Bis(3,4-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926110)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3,4-dimethoxyaniline were reacted to yield N2,N4-bis(3,4-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.90 (d, 1H, J= 1.8 Hz), 7.13 (d, 2H, J= 4.8 Hz), 7.08 (d, 1H, J= 8.7 Hz), 6.94 (d, 2H, J= 10.5 Hz), 6.81 (d, 1H, J= 8.7 Hz), 6.76 (d, 1H, J= 8.7 Hz), 6.70 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.74 (s, 3H), 3..71 (s, 3H); ^{19}F NMR ($CDCl_3$): δ - 47433; LCMS: ret. time: 19.64 min.; purity: 95%; MS (m/e): 401 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.18	N2,N4-Bis[4-(N-morpholino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926114)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-N-morpholinylaniline were reacted to yield N2,N4-bis[4-N-morpholinyl)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.80 (s, 1H), 7.78 (s, 1H, partially exchanged), 7.76 (bs, 1H, partially exchanged), 7.53 (d, 2H, J= 8.1 Hz), 7.39 (d, 2H, J= 9 Hz), 6.93 (d, 2H, J= 8.7 Hz), 6.86 (bd, 2H), 3.84 (m, 8H), 3.11 (m, 8H); ^{19}F NMR (CD_3OD): δ - 47697; LCMS: ret. time: 18.15 min.; purity: 99.55%; MS (m/e): 451 (MH^+).
7.3.19	N2,N4-Bis(4-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R926206)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-chloroaniline were reacted to yield N2,N4-bis(4-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 7.80 (d, 1H, J= 4.2 Hz), 7.45 (d, 2H, J= 8.7 Hz), 7.33 (d, 2H, J= 9 Hz), 7.20 (d, 2H, J= 8.7 Hz), 7.14 (d, 2H, J= 9.6 Hz); LCMS: ret. time: 28.84 min.; purity: 87%; MS (m/e): 349 (MH^+).
7.3.20	N2,N4-Bis(3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R926209)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloroaniline were reacted to yield N2,N4-bis(3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.08 (d, 1H, J= 5.4 Hz), 7.70 (t, 1H, J= 1.8 Hz), 7.57 (t, 1H, J= 1.2 Hz), 7.54 (m, 1H), 7.35 (m, 4H), 7.28 (t, 1H, J= 1.8 Hz), 7.24 (m, 1H), 7.22 (t, 1H, J= 1.8 Hz); ^{19}F NMR (CD_3OD): - 43631; LCMS: ret. time: 28.99 min.; purity: 99%; MS (m/e): 349 (M^+).
7.3.21	N2,N4-Bis(4-tert-butylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926222)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-tert-butylaniline were reacted to yield N2,N4-bis(4-tert-butylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.77 (d, 1H, J= 3.9 Hz), 7.47 (d, 2H, J= 9Hz), 7.38 (m, 4H), 7.30 (d, 2H, J= 8.7 Hz), 1.34 (s, 9H), 1.32 (s, 9H); LCMS: ret. time: 34.09 min.; purity: 93%; MS: 393 (MH^+).
7.3.22	N2,N4-Bis(3-chloro-4-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine (R926223)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloro-4-fluoroaniline were reacted to yield N2,N4-bis(3-chloro-4-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$ + CD_3OD)): δ 7.81 (d, 1H), 7.60 (m, 1H), 7.58 (m, 1H), 7.38 (m, 1H), 7.19 (m, 1H), 7.0 (m, 2H); LCMS: ret. time: 28.98 min.; purity: 97%; MS (m/e): 385 (M^+).

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Section Number	Name of compound and reference number	Experimental
7.3.23	N2,N4-Bis(4-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine (R926224)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-fluoroaniline were reacted to yield N2,N4-bis(4-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.79 (d, 2H, J= 5.4 Hz), 7.40 (m, 2H), 7.30 (m, 2H), 6.90 (m, 4H); ^{19}NMR ($CDCl_3$): - 32425 (s, 1F), -32940 (s, 1F), -45525 (s, 1F); LCMS: ret. time: 23.53 min.; purity: 100%; MS (m/e): 317 (MH^+).
7.3.24	N2,N4-Bis(4-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926225)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-methylaniline were reacted to yield N2,N4-bis(4-methylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.73 (d, 1H, J= 4.2 Hz), 7.43 (d, 2H, J= 8.1 Hz), 7.36 (d, 2H, J= 8.4 Hz), 7.14 (d, 2H, J= 8.4 Hz), 7.10 (d, 2H, J= 8.1 Hz), 2.39 (s, 3H), 2.35 (s, 3H); LCMS: ret. time: 25.81 min.; purity: 99.65%; MS (m/e): 309 (MH^+).
7.3.25	N2,N4-Bis[(4-methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926240)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and ethyl 4-aminophenoxyacetate were reacted to yield N2,N4-bis[(4-methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.8 (bs, 1H), 7.50 (d, 2H, J= 9.3 Hz), 7.32 (d, 2H, J= 8.41 Hz), 6.88 (m, 4H), 4.72 (s, 2H), 4.70 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H); ^{19}F NMR ($CDCl_3$): -47570; LCMS: ret. time: 21.17 min.; purity: 95%; MS (m/e): 457 (MH^+).
7.3.26	(±)-N2,N4-Bis[4-methoxycarbonyl(α-methyl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R926254)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and (±)-ethyl 2-(4-aminophenoxy)propionate were reacted to yield (±)-N2,N4-bis[4-methoxycarbonyl(α-methyl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.89 (bs, 1H), 7.48 (dd, 2H, J= 2.4 and 6.9 Hz), 7.40 (dd, 2H, J= 1.8 and 6.9 Hz), 6.85 (m, 4H), 6.76 (s, 1H), 6.63 (s, 1H), 4.75 (hex, 2H, J= 6.3 Hz), 3.77 (s, 3H), 3.76 (s, 3H), 1.62 (t, 6H, J= 7.5 Hz); LCMS: ret. time: 23.76 min.; purity: 97%, MS (m/e): 485 (MH+).
7.3.27	N2,N4-Bis[(3-methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926255)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and ethyl 3-aminophenoxyacetate were reacted to yield N2,N4-bis[(3-methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.96 (d, 1H, J= 2.4 Hz), 7.71 (t, 1H, J= 2.4 Hz), 7.44 (m, 2H), 7.21 (m, 3H), 6.96 (dd, 1H, J= 1.2 and 7.8 Hz), 6.86 (d, 1H, J= 3 Hz), 6.53 (m, 1H), 4.64 (s, 2H), 4.60 (s, 2H), 3.79 (s, 6H); LCMS: ret. time: 21.72 min.; purity: 87%; MS (m/e): 457 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.28	N2,N4-Bis(3-acetyloxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926387)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-acetoxyaniline were reacted to yield N2,N4-bis[(3-acetoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. Alternatively, N2,N4-bis[(3-acetoxyphenyl]-5-fluoro-2,4-pyrimidinediamine can be prepared by acetylation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine with acetyl chloride in the presence of pyridine in CH_2Cl_2. ^1H NMR ($CDCl_3$): δ 8.00 (bs, 1H), 7.51-7.25 (m, 8H), 2.32 (s, 3H), 2.28 (s, 3H); LCMS: ret. time: 22.14 min; purity: 100%; MS (m/e): 397 (MH^+).
7.3.29	N2,N4-Bis(3-benzyloxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926394)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-benzyloxyaniline were reacted to yield N2,N4-bis(3-benzyloxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 7.98 (bs, 1H), 7.42-6.99 (m, 16H), 6.75 (d, 1H, J= 2.4 Hz), 6.71 (m, 1H), 6.60 (dd, 1H, J= 2.4 and 8.4 Hz), 6.32 (m, 1H), 4.97 (s, 2H), 4.94 (s, 2H); LCMS: ret. time: 32.56 min.; purity: 98%; MS (m/e): 493 (MH^+).
7.3.30	N2,N4-Bis(2-phenylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926398)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 2-phenylaniline were reacted to yield N2,N4-bis[(2-phenylphenyl]-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 8.35 (m, 1H), 8.0 (s, 1H), 7.85 (s, 1H), 7.45-7.00 (m, 18H); LCMS: ret. time: 30.29 min.; purity: 68%; MS (m/e): 433 (MH^+).
7.3.31	(R926404) N2, N4-Bis(2-phenylphenyl)-5-methyl-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-aminobiphenyl and 2,4-dichloro-5-methylpyrimidine were reacted to provide N2, N4-bis(2-phenylphenyl)-5-methyl-2,4-pyrimidinediamine. LCMS: ret. time: 30.47 min.; purity: 91%; MS (*m/e*): 429 (MH^+).
7.3.32	N2,N4-Bis[(4-methoxy-3-phenyl)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926399)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-methoxy-3-phenylaniline were reacted to yield N2,N4-bis[(4-methoxy-3-phenyl)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.83 (d, 1H, J= 4.2 Hz), 7.57 (bd, 1H, J= 8.7 Hz), 7.48 (d, 1H, J= 2.7 Hz), 7.47-7.22 (m, 12H), 6.85 (d, 1H, J= 8.7 Hz), 6.78 (d, 1H, 9.3 Hz), 3.72 (s, 3H), 3.69 (s, 3H); LCMS: ret. time: 29.97 min.; purity: 92%; MS (m/e): 493 (MH^+).

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7.3.33	N2,N4-Bis[(2-methoxy-5-phenyl)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926400)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 2-methoxy-5-phenylaniline were reacted to yield N2,N4-bis[(2-methoxy-5-phenyl)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.03 (d, 1H, J= 6.6 Hz), 7.76 (t, 1H, J= 2.4 Hz), 7.28-7.10 (m, 13H), 7.07 (d, 1H, J= 9 Hz), 7.01 (d, 1H, J= 8.1 Hz), 3.91 (s, 3H), 3.86 (s, 3H); LCMS: ret. time: 18.58 min.; purity: 96%; MS (m/e): MH^+).
7.3.34	N2,N4-Bis[(2-methoxy-5-methyl-4-phenyl)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926401)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 2-methoxy-5-methyl-4-phenylaniline were reacted to yield N2,N4-bis[(2-methoxy-5-methyl-4-phenyl)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.00 (d, 1H, J= 4.8 Hz), 7.73 (s, 1H), 7.66 (s, 1H), 7.43-7.24 (m, 9H), 6.91 (s, 1H), 6.82 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.14 (s, 3H), 1.99 (s, 3H); LCMS: ret. time: 19.98 min.; purity: 99%; MS (m/e): 521 (MH^+).
7.3.35	N2,N4-Bis[(2-methyl-5-phenyl)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926402)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 2-methyl-5-phenylaniline were reacted to yield N2,N4-bis[(2-methyl-5-phenyl)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.84 (bd, 1H), 7.51-7.20 (m, 16H), 2.30 (s, 3H), 2.24 (s, 3H); LCMS: ret. time: 18.57 min.; purity: 87%; MS (m/e): 461 (MH^+).
7.3.36	N2,N4-Bis[(3-phenyl)phenyl]--5-fluoro-2,4-pyrimidinediamine (R926403)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-phenylaniline were reacted to yield N2,N4-bis[(3-phenyl)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.02 (d, 1H, J= 5.1 Hz), 7.82 (t, 1H, J= 1.5 Hz), 7.67 (t, 1H, J= 1.8 Hz), 7 58 (dd, 1H, J= 1.2 and 7.2 Hz), 7.42-7.24 (m, 15H); LCMS: ret. time: 32.06 min.; purity: 94%; MS (m/e): 433 (MH^+).
7.3.37	N2,N4-Bis(4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926405)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-acetoxyaniline were reacted to yield N2,N4-bis[(4-hydroxyphenyl]-5-fluoro-2,4-pyrimidinediamine. After the work up it was observed that the acetoxy group was hydrolyzed to afford the N2,N4-bis(4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine instead of the corresponding acetate derivative. ^{1}H NMR (CD_3OD): δ 7.74 (d, 1H, J= 5.6 Hz), 7.43 (dd, 2H, J= 2.1 and 6.6 Hz), 7.28 (dd, 2H, J= 2.4 and 6.3 Hz), 6.74 (dd, 2H, J= 2.4 and 6.3 Hz), 6.66 (dd, 2H, J= 2.4 and 7.2 Hz); ^{19}F NMR (CD_3OD): - 48116 (d, 1F); LCMS: ret. time: 16.15 min; purity: 100%; MS (m/e): 313 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.38	N2,N4'-Bis(4-hydroxy-3-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926469)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-hydroxy-3-methylaniline were reacted to yield N2,N4-bis[(4-hydroxy-3-methylphenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.64 (d, 1H, J= 3.6 Hz), 7.11 (t, 2H, J= 9 Hz), 6.70-6.45 (m, 4H), 2.15 (s, 3H), 2.09 (s, 3H); ^{19}F NMR (CD_3OD): - 46278; LCMS: ret. time: 15.53; purity: 84%; MS (m/e): 341 (MH^+).
7.3.39	N2,N4-Bis[4-(tert-butoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926574)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and tert-butyl 4-aminophenoxyacetate were reacted to yield N2,N4-bis[4-(tert-butoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine ^{1}H NMR ($CDCl_3$): δ 7.88 (s, 1H), 7.48 (d, 2H, J= 8.4 Hz), 7.40 (d, 2H, J= 8.7 Hz), 6.86 (m, 4H), 4.52 (s, 2H), 4.48 (s, 2H), 1.49 (s, 9H), 1.48 (s, 9H); LCMS: ret. time: 28.48 min ; purity: 95%; MS (m/e): 541 (MH^+).
7.3.40	N2,N4-Bis(indol-5-yl)-5-fluoro-2,4-pyrimidinediamine (R926582)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 5-aminoindole were reacted to yield N2,N4-bis(indol-5-yl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 20.26 min.; purity: 99%; MS (m/e): 359 (MH^+).
7.3.41	N2,N4-Bis(4-cyanomethylphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R926319)	In like manner to N2,N4-bis(3-hydroxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine, 2,4-dichloro-5-ethoxycarbonylpyrimidine and 4-cyanomethylaniline were reacted to yield N2,N4-bis(4-cyanomethylphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.72 (s, 1H), 7.64 (m, 4H), 7.32 (d, 2H, J= 8.7 Hz), 7.21 (d, 2H, J= 8.4 Hz), 4.3 (q, 2H, J= 7.0 Hz), 3.97 (s, 2H,), 3.89 (s, 2H), 1.32 (3H, J= 7 Hz); LCMS: ret. time: 30.83 min.; purity: 90 %; MS (m/e): 413 (MH^+).
7.3.42	N2,N4-Bis(3-indazol-6-yl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R926320)	In like manner to N2,N4-bis(3-hydroxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine, 2,4-dichloro-5-ethoxycarbonylpyrimidine and 6-aminoindazole were reacted to yield N2,N4-bis(6-indazolyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.76 (s, 1H), 7.73(d, 2H J= 8.8), 7.54 (m, 4H), 7.36 (d, 2H, J= 9.5 Hz), 4.3 (q, 2H, J= 7.0 Hz), 1.34 (3H, J= 7 Hz); LCMS: ret. time 27.59 min.; purity: 95 %; MS (m/e): 415 (MH^+).

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7.3.43	N2,N4-Bis(3-indazol-7-yl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R926321)	In like manner to N2,N4-bis(3-hydroxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine, 2,4-dichloro-5-ethoxycarbonylpyrimidine and 7-aminoindazole were reacted to yield N2,N4-bis(7-indazolyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.70 (s, 1H), 7.54 (d, 2H J= 8.4 Hz), 7.37 (m, 6H), 4.3 (q, 2H, J= 7.0 Hz), 1.33 (3H, J= 7 Hz); LCMS: ret. time 23.61 min.; purity: 94 %; MS (m/e): 415 (MH^+).
7.3.44	N2,N4-Bis[6-(1,4-benzoxazine-3-onyl)]-5-ethoxycarbonyl-2,4-pyrimidinediamine (R926325)	In like manner to to N2,N4-bis(3-hydroxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine, 2,4-dichloro-5-ethoxycarbonylpyrimidine and 6-amino-1,4-benzoxazine-3-one were reacted to yield N2,N4-bis[6-(1,4-benzoxazine-3-onyl)]-5-ethoxycarbonyl-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.66 (s, 1H), 7.21 (dd, 2H J= 8.8 and J= 2.2 Hz), 6.89 (d, 2H J= 8.4 Hz), 4.54 (s, 2H) 4.49 (s, 2H) 4.3 (q, 2H, J= 7.0 Hz), 1.33 (3H, J= 7 Hz); LCMS: ret. time 23.08 min.; purity: 88 %; MS (m/e): 477 (MH^+).
7.3.45	N2,N4-Bis(4-ethoxycarbonylmethyleneaminophenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R926331)	In like manner to to N2,N4-bis(3-hydroxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine, 2,4-dichloro-5-ethoxycarbonylpyrimidine and 4-ethoxycarbonylmethyleneaminoaniline were reacted to yield N2,N4-bis(4-ethoxycarbonylaminophenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.72 (s, 1H), 7.70 (d, 2H J= 8 8 Hz), 7.28 (d, 2H J= 8.4 Hz), 7.05 (d, 2H, J= 8.4 Hz) 6.82 (d, 2H J= 8.4 Hz) 4.5 (m, 4H), 4.23 (m, 6H) 1.53 (m, 9H); LCMS: ret. time 18.08 min.; purity: 85%; MS (m/e): 537 (MH^+).
7.3.46	N2,N4-Bis(4-ethoxyphenyl)-6-methoxycarbonyl-2,4-pyrimidinediamine (R926058)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-6-methoxycarbonylpyrimidine with 4-ethoxyaniline gave N2,N4-bis(4-ethoxyphenyl)-6-methoxycarbonyl-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.42 (bs, 1H), 7.35 (bd, 4H), 6.85 (bs, 1H), 6.75 (bd, 4H), 3.97 (q, 4H, J= 4.8 Hz), 3.92 (s, 3H), 1.36 (t, 6H, J= 6.3 Hz); LCMS: ret. time: 27.47 min.; purity: 97%; MS (m/e): 409 (MH^+).
7.3.47	N2,N4-Bis(4-ethoxyphenyl)-5-methyl-2,4-pyrimidinediamine (R926068)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-methylpyrimidine with 4-ethoxyaniline gave N2,N4-bis(4-ethoxyphenyl)-5-methyl-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.55 (s, 1H), 7.40 (d, 2H), 7.21 (d, 2H, J= 8.7 Hz), 6.90 (dd, 4H, J= 8.7 Hz), 4.04 (q, 4H, J= 6.6 Hz), 2.17 (m, 6H); LCMS: ret. time: 26.51 min.; purity: 95%; MS (m/e): 365 (MH^+).

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7.3.48	N2,N4-Bis(4-ethoxyphenyl)-6-chloro-2,4-pyrimidinediamine (R926072)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4,6-trichloropyrimidine with 4-ethoxyaniline gave N2,N4-bis(4-ethoxyphenyl)-6-chloro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.42 (d, 2H, J= 9 Hz), 7.18 (d, 2H, J= 8.7 Hz), 6.89 (d, 2H, J= 6.3 Hz), 6.84 (d, 2H, J= 8.7 Hz), 6.58 (bs, 1H), 4.02 (m, 4H), 1.43 (m, 6H); LCMS: ret. time: 83.21 min.; purity: 87%; MS (m/e): 385 (MH^+).
7.3.49	N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-methyl-2,4-pyrimidinediamine (R926242)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-methylpyrimidine with 3,4-ethyleneoxyaniline gave N2,N4-bis(3,4-ethylenedioxyphenyl)-5-methyl-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.75 (bs, 1H), 7.06 (d, 1H, J= 2.4 Hz), 6.96 (d, 1H, J= 2.1 Hz), 6.94 (d, 1H, J= 2.1 Hz), 6.85-6.77 (m, 2H), 6.70 (d, 1H, J= 9 Hz), 4.23 (s, 4H), 4.19 (s, 4H), 2.09 (s, 3H); LCMS: ret. time: 22.01 min.; purity: 100%; MS (m/e): 393 (MH^+).
7.3.50	N2,N4-Bis(3,4-ethylenedioxyphenyl)-2,4-pyrimidinediamine (R926243)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloropyrimidine with 3,4-ethyleneoxyaniline gave N2,N4-bis(3,4-ethylenedioxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.95 (s, 1H), 10.50 (s, 1H), 7.84 (bd, 2H), 7.24 (bd, 2H), 6.79 (bd, 2H), 6.40 (bd, 2H), 4.24 (s, 8H); LCMS: ret. time: 21.68 min.; purity: 100%; MS (m/e): 379 (MH^+).
7.3.51	N2,N4-Bis(3-hydroxyphenyl)-5-methyl-2,4-pyrimidinediamine (R926248)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-methylpyrimidine with 3-hydroxyaniline gave N2,N4-bis(3-hydroxyphenyl)-5-methyl-2,4-pyrimidinediamine. LCMS: ret. time: 16.76 min.; purity: 100%, MS (m/e): 309 (MH^+).
7.3.52	N2, N4-Bis(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926249)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloropyrimidine with 3-hydroxyaniline gave N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 16.21 min.; purity: 100%; MS (m/e): 295 (MH^+).
7.3.53	N2,N4-Bis[(4-methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R926256)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloropyrimidine with methyl 4-aminophenoxyacetate gave N2,N4-bis[(4-methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.7 (bs, 1H), 10.28 (bs, 1H), 7.84 (d, 1H, J= 6.9 Hz), 7.48 (bd, 2H), 7.35 (d, 2H, J= 8.7 Hz), 6.95 (d, 2H, J= 9 Hz), 6.90 (d, 2H, J= 8.7 Hz), 6.35 (d, 1H, J= 6.9 Hz), 4.81 (s, 2H), 4.79 (s, 2H), 3.69 (s, 3H), 3.68 (s, 3H); LCMS: ret. time: 21.27 min.; purity: 98%; MS (m/e): 439 (MH^+).

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7.3.54	(±)-N2,N4-Bis[4-methoxycarbonyl(alpha-methyl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R926257)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloropyrimidine with (±)-methyl 2-(4-aminophenoxy)propionate gave (±)-N2,N4-bis[4-methoxycarbonyl(alpha-methyl)methyleneoxyoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 24.09 min.; purity: 90%; MS (m/e): 467 (MH^+).
7.3.55	N2,N4-Bis(4-methoxycarbonylmethyleneoxyphenyl)-5-methyl-2,4-pyrimidinediamine (R926258)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-methylpyrimidine with methyl-4-aminophenoxyacetate gave N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-5-methyl-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 10.21 (s, 1H), 9.65 (s, 1H), 7.78 (s, 1H), 7.42 (dd, 2H), J= 2.7 and 8.7 Hz), 7.28 (dd, 2H, J= 8.1 Hz), 6.94 (d, 2H, J= 8.47 Hz), 6.85 (d, 2H, J= 8.7 Hz), 4.82 (s, 2H), 4.77 (s, 2H), 3.69 (s, 3H), 3.68 (s, 3H), 2.12 (s, 3H); LCMS: ret. time: 21.76 min.; purity: 100%; MS (m/e): 453 (MH^+).
7.3.56	(±)-N2,N4-Bis[4-ethoxycarbonyl(alpha-methyl)methyleneoxyphenyl]-5-methyl-2,4-pyrimidinediamine (R926259)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-methylpyrimidine with (±)-ethyl 2-(4-aminophenoxy)propionate gave (±)-N2,N4-bis[4-ethoxycarbonyl(alpha-methyl)methyleneoxyphenyl]-5-methyl-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 9.9 (bs, 1H), 9.35 (bs, 1H), 7.79 (s, 1H), 7.43 (dd, 2H, J= 3.6 and 8.7 Hz), 7.32 (d, 2H, J= 7.5 Hz), 6.86 (d, 2H, J= 9 Hz), 6.78 (d, 2H, J= 8.7 Hz), 4.95 (q, 1H, J= 7.2 Hz), 4.90 (q, 1H, J= 7.2 Hz), 4.12 (2q, 4H, J= 5.7 Hz), 2.10 (s, 3H), 1.51 (d, 3H, J= 6.3 Hz), 1.47 (d, 3H, J= 6.3 Hz), 1.16 (2t, 6H, J= 5.7 Hz); LCMS: ret. time: 27.41 min.; purity: 96%; MS (m/e): 509 (MH^+).
7.3.57	N2,N4-Bis[2-(4-hydroxyphenyl)ethyl]-5-methyl-2,4-pyrimidinediamine (R926397)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-methylpyrimidine with 2-(4-hydroxyphenyl)ethylamine gave N2,N4-bis[2-(4-hydroxyphenyl)ethyl]-5-methyl-2,4-pyrimidinediamine. LCMS: ret. time: 19.94 min.; purity: 100%; MS (m/e): 365 (MH^+).
7.3.58	N2,N4-Bis-(3,4-dimethoxypenyl)-5-nitro-2,4-pyrimidinediamine (R940089)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-nitropyrimidine with 3,4-dimethoxyaniline gave N2,N4-bis-(3,4-dimethoxyphenyl)-5-nitro-2,4-pyrimidinediamine. LCMS: ret. time: 28.30 min.; purity: 100%; MS (m/e): 428 (MH^+); ^1H NMR ($CDCl_3$): δ 10 30 (1H, s), 9.14 (1H, s), 7.52 (1H, s), 7.08 (3H, m), 7.00 (1H, d, J= 8.4 Hz), 6.84 (1H, d, J= 8.4 Hz), 6.76 (1H, d, J= 8.4 Hz), 3.90 (3H, s), 3.87 (3H, s), 3.68 (3H, s), 3.60 (3H, s).

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Section Number	Name of compound and reference number	Experimental
7.3.59	N2,N4-Bis-(4-ethoxypenyl)-5-nitro-2,4-pyrimidinediamine (R940090)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-nitropyrimidine with 4-ethoxyaniline gave N2,N4-bis-(4-ethoxyphenyl)-5-nitro-2,4-pyrimidinediamine. LCMS: ret. time: 35.91 min.; purity: 100%; MS (m/e): 396 (MH^+); ^1H NMR ($CDCl_3$): δ 10.25 (1H, s), 9.11 (1H, s), 7.44 (2H, d, J= 8.6 Hz), 7.37 (2H, d, J= 9Hz), 6.88 (2H, d, J= 8.6 Hz), 6.80 (2H, d, J= 8 6 Hz), 4.06 (2H, q, J= 7.2 Hz), 4.02 (2H, q, J= 7.2 Hz), 1.45 (3H, t, J= 7.2 Hz), 1.42 (3H, t, J= 7.2 Hz).
7.3.60	N2,N4-Bis-(3,4-ethylenedioxyphenyl)-5-nitro-2,4-pyrimidinediamine (R940095)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-nitropyrimidine with 3,4-ethylenedioxyaniline gave N2,N4-bis-(3,4-ethylenedioxyphenyl)-5-nitro-2,4-pyrimidinediamine LCMS: ret. time: 30.78 min.; purity: 100%; MS (m/e): 424 (MH^+); ^1H NMR ($CDCl_3$): δ 10.21 (1H, s), 9.10 (1H, s), 7.40 (1H, s), 7.11-6.71 (6H, m), 4.29 (4H, s), 4.25 (4H, s).
7.3.61	N2,N4-Bis-[(4-ethoxycarbonylmethyleneoxy)phenyl]-5-nitro-2,4-pyrimidinediamine (R940096)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-nitropyrimidine with ethyl-4-aminophenoxyacetate gave N2,N4-bis-[(4-ethoxycarbonylmethyleneoxy)phenyl]-5-nitro-2,4-pyrimidinediamine. LCMS: ret. time: 32.48 min.; purity: 94%; MS (m/e): 512 (MH^+); 1H NMR ($CDCl_3$): δ 10.22 (1H, s), 9.13 (1H, s), 7.50 (1H, s), 7.45 (2H, d, J= 8.7 Hz), 7.38 (2H, d, J= 8.7 Hz), 6.93 (2H, d, J= 8.7 Hz), 6.83 (2H, d, J= 8.7 Hz), 4.67 (2H, s), 4.63 (2H, s), 4.29 (2H, q, J= 7.2 Hz, 4.28 (2H, q, J= 7.2 Hz), 1.31 (3H, t, J= 7.2 Hz), 1.30 (3H, t, J= 7.2 Hz).
7.3.62	N2,N4-Bis-(2,2-difluoro-1,3-benzodioxol-5-yl)-5-nitro-2,4-pyrimidinediamine (R940100)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-nitropyrimidine with 2,2-difluoro-5-amino-1,3-benzodioxole gave N2,N4-bis-(2,2-difluoro-1,3-benzodioxol-5-yl)-5-nitro-2,4-pyrimidinediamine. LCMS: ret. time: 38.15 min.; purity: 96%; MS (m/e): 467 (M^+); ^1H NMR ($CDCl_3$): δ 10.76 (1H, s), 10.49 (1H, s), 9.20 (1H, s), 7.74 (2H, s), 7.56 (1H, d, J= 11.4 Hz), 7.33 (2H, m), 7.20 (1H, m).
7.3.63	N2,N4-Bis-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R940215)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with 3,5-dichloro-4-hydroxyaniline gave N2,N4-bis-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 21.26 min.; purity: 88%; MS (m/e): 450 (M^+); ^1H NMR (DMSO-d6): δ 9.96 (1H, s), 9.59 (1H, s), 9.47 (1H, s), 9.37 (1H, s), 8.22 (1H, d, J= 3.6 Hz), 7.79 (2H, s), 7.74 (2H, s).

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Section Number	Name of compound and reference number	Experimental
7.3.64	N2,N4-Bis-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R940216)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-chloro-4-hydroxy-5-methylaniline gave N2,N4-bis-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 20.55 min.; purity: 99%; MS (m/e). 410 (MH^+); ^1H NMR (DMSO-d6): δ 9.23 (1H, s), 9.07 (1H, s), 8.99 (1H, s), 8.66 (1H, s), 8.13 (1H, d, J= 3.6 Hz), 7.59 (2H, t, J= 3.1 Hz), 7.50 (1H, d, J= 2.3 Hz), 7.34 (1H, d, J= 2.3 Hz), 2.27 (3H, s), 2.18 (3H, s).
7.3.65	N2,N4-Bis-(2,3-dimethyl-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R940217)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with 2,3-dimethyl-4-hydroxyaniline gave N2,N4-bis-(2,3-dimethyl-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 19.07 min.; purity: 99%; MS (m/e): 369 (MH^+); ^1H NMR (DMSO-d6): δ 9.21 (1H, s), 8.99 (1H, s), 8.63 (1H, s), 7.92 (1H, s), 7.84 (1H, d, J= 3.6 Hz), 6.94 (1H, d, J= 8.5 Hz), 6.85 (1H, d, J= 8.5 Hz), 6.70 (1H, d, J= 8.5 Hz), 6.58 (1H, d, J= 8.5 Hz), 2.12 (3H, s), 2.06 (3H, s), 2.02 (3H, s), 1.94 (3H, s).
7.3.66	N2,N4-Bis-(4-Acetamidophenyl)-5-fluoro-2,4-pyrimidinediamine (R940222)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-acetamidoaniline gave N2,N4-bis-(4-acetamidophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 14.82 min.; purity: 95%; MS (m/e): 395 (MH^+); ^1H NMR (DMSO-d6): δ 10.33 (1H, s), 10.14 (1H, s), 10.07 (2H, s), 8.39 (1H, d, J= 5.1 Hz), 7.64 (8H, m), 2.15 (3H, s), 2.13 (3H, s).
7.3.67	N2,N4-Bis(3-isopropylphenyl)-5-fluoro-2,4-pyrimidinediamine R940297	In like manner to the preparation of N2,N4-bis-(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-isopropylaniline were reacted to give N2,N4-bis-(3-isopropylphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 29.58 min.; Purity: 98 %; MS (m/e): 365 (MH^+); ^1H NMR (DMSO-d6): δ 10.5 (1H, s), 10.34 (1H, s), 8.41 (1H, d, J= 5.1 Hz), 7.62 (1H, d, J= 8.1 Hz), 7.53 (1H, s), 7.43 (1H, d, J= 8.1 Hz), 7.37 (2H, m), 7.29 (1H, t, J= 8.1 Hz), 7.19 (1H, d, J= 7.8 Hz), 7 08 (1H, d, J= 7.8 Hz), 2.88 (2H, m), 1.25 (6H, d, J= 7.2 Hz), 1.201 (6H, d, J= 7.2 Hz).
7.3.68	N2,N4-Bis(3,4,5-trimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926688)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3,4,5-trimethoxyaniline were reacted to yield N2,N4-bis(3,4,5-trimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 19.55 min.; purity: 99 %; MS (m/e): 461 (MH^+).

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7.3.69	N2,N4-Bis(2-methyl-5-phenylphenyl)-5-bromo-2,4-pyrimidinediamine R925800	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 5-bromo-2,4-dichloropyrimidine and 5-phenyl-*ortho*-toluidine were reacted to yield N2,N4-bis(2-methyl-5-phenylphenyl)-5-bromo-2,4-pyrimidinediamine. LCMS: ret. time: 19.54 min.; purity: 90 %; MS (m/e): 422 (MH^+).
7.3.70	N2,N4-Bis(2-methoxy-5-methyl-4-phenylphenyl)-5-bromo-2,4-pyrimidinediamine (R925801)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 5-bromo-2,4-dichloropyrimidine 5-methyl-4-phenyl-*ortho*-anisidine were reacted to yield N2,N4-bis(2-methoxy-5-methyl-4-phenylphenyl)-5-bromo-2,4-pyrimidinediamine. LCMS: ret. time: 20.99 min.; purity: 85 %; MS (m/e): 583 (MH^+).
7.3.71	N2,N4-Bis(indol-6-yl)-5-fluoro-2,4-pyrimidinediamine (R926594)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 6-aminoindole were reacted to yield N2,N4-bis(indol-6-yl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 22.39 min.; purity: 85%; MS (m/e): 359 (MH^+).
7.3.72	N2,N4-Bis(2-methoxycarbonyl benzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine (R926604)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 2-methoxycarbonyl-5-aminobenzofuran were reacted to yield N2,N4-bis(2-methoxycarbonyl benzofuran-5-yl))-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 10.3 (bs, 1H), 10 05 (bs, 1H), 8.25 (d, 1H, J= 5.4 Hz), 8.06 (s, 1H), 7.94 (s, 1H), 7.77-7.49 (m, 5H), 7.36 (bs, 1H), 3.89 (s, 3H), 3.87 (s, 3H).
7.3.73	N2,N4-Bis[4-(methoxycarbonylmethyl)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926605)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and ethyl 4-aminophenyl acetate were reacted to yield N2,N4-bis[4-(methoxycarbonylmethyl)phenyl]-5-fluoro-2,4-pyrimidinediamine. The cross esterification reaction of ethyl ester to obtain the corresponding methyl ester was observed. ^1H NMR ($CDCl_3$): δ 10.62 (s, 1H), 8.06 (s, 1H), 7.69 (d, 1H, J= 4.5 Hz), 7.53 (d, 2H, J= 8.1 Hz), 7.43 (d, 2H, J= 8.7 Hz), 7.30 (d, 2H, J= 8.4 Hz), 7.20 (d, 2H, J= 8.4 Hz), 3.73 (s, 3H), 3.72 (s, 3H), 3.67 (s, 2H), 3.63 (s, 2H).
7.3.74	N2,N4-Bis(2-ethoxycarbonylindol-5-yl)-5-fluoro-2,4-pyrimidinediamine (R926616)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 2-ethoxycarbonyl-5-indoleamine were reacted to yield N2,N4-bis(2-ethoxycarbonylindol-5-yl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 11.83 (s, 1H), 11.63 (s, 1H), 9.21 (s, 1H), 8.99 (s, 1H), 8.08 (s, 1H), 8.01 (m, 2H), 7.49-7.22 (m, 4H), 6.92 (s, 1H), 6.63 (s, 1H), 4.29 (q, 4H, J= 7.2 Hz), 1.32 (m, 6H); LCMS: ret. time: 24.74 min.; purity: 99%; MS (m/e): 503 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.75	N2,N4-Bis(coumarin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R926617)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 6-aminocoumarin were reacted to yield N2,N4-bis(coumarin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.17 (d, 2H, J= 3.6 Hz), 7.97-7.74 (m, 5H), 7.40 (1H, d, J= 8.7 Hz), 7.30 (d, 1H, J= 9Hz), 6.50 (d, 1H, J= 10.2 Hz), 6.40 (d, 1H, J= 9.3 Hz); LCMS: ret. time: 19.05 min.; purity: 94%; MS (m/e): 417 (MH^+).
7.3.76	N2,N4-Bis(4-methoxymethyl)coumarin-7-yl)-5-fluoro-2,4-pyrimidinediamine (R926620)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-4-methoxymethylcoumarin were reacted to yield N2,N4-bis(coumarin-7-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.38 (s, 1H), 8.42 (d, 1H, J= 3 Hz), 8.28 (m, 1H), 8.05-7.93 (m, 2H), 7.77-7.50 (m, 4H), 6.31 (s, 1H), 6.29 (s, 1H), 4.66 (s, 2H), 4.65 (s, 2H), 3.43 (s, 3H), 3,41 (s, 3H); LCMS: MS (m/e): 505 (MH^+).
7.3.77	N2,N4-Bis(3-(hydroxymethyl)phenyl)-5-fluoro-2,4-pyrimidinediamine (R925757)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-aminobenzylalcohol were reacted to yield N2,N4-bis(3-(hydroxymethyl)phenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.90 (d, 1H, J= 3.3 Hz), 7.71 (m, 1H), 7.61 (d, 1H, J= 6.9 Hz), 7.50 (d, 1H, J= 6.0), 7.47 (s, 1H), 7.31 (t, 1H, J= 8.1 Hz), 7.22 (t, 1H, J= 8.1 Hz), 7.10 (d, 1H, J= 6.9), 6.97 (d, 1H, J= 7.5 Hz), 4.63 (s, 4H); LCMS: ret. time: 15.36 min.; purity: 100%; MS (m/e): 342 (MH^+).
7.3.78	N2,N4-Bis[(2R)-hydroxy-(1S)-methyl-2-phenylethyl]-5-fluoro-2,4-pyrimidinediamine (R925767)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and (1R,2S)-(-)-norephedrine were reacted to yield N2,N4-bis[(2R)-hydroxy-(1S)-methyl-2-phenylethyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (acetone-d_6): δ 7.67 (s, 1H), 7.49-7.42 (m, 4H), 7.38-7.19 (m, 6H), 6.09 (d, 1H, J= 9.0 Hz), 5.73 (d, 1H, J= 7.5 Hz), 5.61 (d, 1H, J= 9.3 Hz), 5.04 (d, 1H, J= 3.6 Hz), 4.97 (d, 1H, J= 2.7 Hz), 4.74 (bs, 1H), 4.48 (bs, 1H), 4.30-4.25 (m, 1H), 1.09 (d, 1H, J= 6 9 Hz), 1.03 (d, 1H, J= 6.6 Hz); LCMS: ret. time: 21.56 min.; purity: 98%; MS (m/e): 397(MH^+).
7.3.79	N2,N4-Bis(2-hydroxy-2-phenylethyl)-5-fluoro-2,4-pyrimidinediamine (R925768)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 2-amino-1-phenylethanol were reacted to yield N2,N4-bis(2-hydroxy-2-phenylethyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (acetone-d_6): δ 8.15 (s, 1H), 7.46-7.22 (m, 10H), 5.01 (dd, 1H), 4.91 (dd, 1H), 4.78 (dd, 1H), 3.86-3.18 (m, 5H); LCMS: ret. time: 19.64 min.; purity: 89 %; MS (m/e): 369 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.80	N2,N4-Bis(furfuryl)-5-fluoro-2,4-pyrimidinediamine (R925769)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and furfurylamine were reacted to yield N2,N4-bis(furfuryl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.72 (bs, 1H), 7.38 (dd, 2H, J= 1.8 and 7.5 Hz), 6.34-6.30 (m, 2H), 6.22 (dd, 2H, J= 2.4 and 9.9 Hz), 5.163 (bs, 2H), 4.63 (d, 2H, J= 6.0), 4.54 (d, 2H, J= 6.0).; ^{19}F NMR ($CDCl_3$): - 48621; LCMS: ret. time: 97.27min.; purity: 97%; MS (m/e): 289 (MH^+).
7.3.81	N2,N4-Bis(piperonyl)-5-fluoro-2,4-pyrimidineamine (R925770)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and piperonylamine were reacted to yield N2,N4-bis(piperonyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.60 (bs, 1H), 6.78-6.69 (m, 6H), 5.93 (s, 2H), 5.91 (s, 2H), 4.51 (d, 2H, J= 5.7 Hz), 4.43 (d, 2H, J= 5.1 Hz), ^{19}F NMR ($CDCl_3$): - 45257; LCMS: ret. time: 22.06 min.; purity: 96%; MS (m/e): 397 (MH^+).
7.3.82	N2,N4-Dibenzyl-5-fluoro-2,4-pyrimidinediamine (R925772)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and benzylamine were reacted to yield N2,N4-bis(benzyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.69 (bs, 1H), 7.35-7.24 (m, 10H), 5.63 (bs, 1H), 5.27 (bs, 1H), 4.61 (d, 2H, J= 6.0 Hz), 4.55 (d, 2H, J= 6.0 Hz); ^{19}F NMR ($CDCl_3$): - 48580; LCMS: ret time· 23.73 min.; purity: 100%; MS (m/e): 309 (MH^+)
7.3.83	N2,N4-Bis(3,4-methylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R925776)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3,4-methylenedioxyaniline were reacted to yield N2,N4-bis(3,4-methylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.86 (bs, 1H), 7.27 (m, 1H), 7.19 (m, 1H), 6.89 (dd, 2H, J= 2.1 and 8.1 Hz), 6.80 (dd, 2H, J= 1.8 and 8.1 Hz), 6.73 (t, 2H, J= 8.1 Hz), 5.97 (s, 2H), 5.92 (s, 2H); ^{19}F NMR ($CDCl_3$): - 47591; LCMS: ret. time: 21.74 min.; purity: 97%; MS (m/e): 369 (MH^+).
7.3.84	N2,N4-Bis[2-(4-hydroxyphenyl)ethyl]-5-fluoro-2,4-pyrimidinediamine (R925791)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and tyramine were reacted to yield N2,N4-bis[2-(4-hydroxyphenyl)ethyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.17 (bs, 1H), 8.22 (bs, 1H), 6.99 (d, 4H, J= 8.1 Hz), 6 65 (d, 4H, J= 8.1 Hz), 3.48-3.43 (m, 4H), 2.72 (t, 4H, J= 7.7 Hz); LCMS: ret. time: 19.19 min.; purity: 100 %; MS (m/e): 369 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.85	N2,N4-Bis(4-cyanophenyl)-5-fluoro-2,4-pyrimidinediamine (R945057)	In like manner to the preparation of N2,N-4-bis(3-hydroxyphenyl)-5-fluoro-4-pyrimidineamine, 4-aminobenzonitrile and 2,4-dichloro-5-fluoropyrimidine gave N2,N4-bis(4-cyanophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 7.26 (d, J= 8.7 Hz, 2 H), 7.36 (d, J= 9.0 Hz, 2 H), 7.43 (d, J= 8.7 Hz, 2 H), 7.60 (d, J= 8.7 Hz, 2 H), 7.86 (d, J= 3.6 Hz, 1 H), 9.49 (br, 1 H, NH), 9.51 (br, 1 H, NH); ^{19}F NMR (282 MHz, DMSO-d6): δ - 161.48; LC: 27.15 min.; 100%; MS (m/e): 331.00 (MH^+).
7.3.86	N2,N4-Bis(4-ethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926234)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-ethylaniline were reacted to yield N2,N4-bis(4-ethylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.83 (bs, 1H), 7.77 (d, 1H. J= 3.9 Hz), 7.48 (d, 2H, J= 8.7 Hz), 7.40 (d, 2H, J= 8.7 Hz), 7.31 (bs, 1H), 7.18 (d, 2H, J= 8.7 Hz), 7.11 (d, 2H, J= 8.7 Hz), 2.68-2.61 (m, 4H), 1.28-1.21 (m, 6H); LCMS: ret. time: 29.17 min.; purity: 100 %; MS (m/e): 337(MH^+).
7.3.87	N2,N4-Bis(3-chloro-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926675)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloro-4-hydroxyaniline were reacted to yield N2,N4-bis(3-chloro-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.83 (d, 1H, J= 4.2 Hz), 7.59 (d, 1H, J= 2.4 Hz), 7.53 (d, 1H, J= 2.4 Hz), 7.40 (dd, 1H, J= 2.4 and 8.7 Hz), 7.20 (dd, 1H, J= 2.4 and 8.7 Hz), 6.89 (d, 1H, J= 8.7 Hz), 6.81 (d, 1H, J= 8.7 Hz); ^{19}F NMR (CD_3OD): - 47862; LCMS: ret. time: 17.89 min.; purity: 99 %; MS (m/e): 382 (MH^+).
7.3.88	N2,N4-Bis[3-chloro-4-(ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926676)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloro-4-(ethoxycarbonylmethyleneoxy)aniline were reacted to yield N2,N4-bis[3-chloro-4-(ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.93 (bs, 1H), 7.67-7.65 (m, 2H), 7.41 (dd, 1H, J= 3.0 and 9.3 Hz), 7.26 (dd, 1H, J= 2.7 and 9.3 Hz), 6.92-6.85 (m, 3H), 6.69 (d, 1H, J= 2.4 Hz), 4.71 (s, 2H), 4.66 (s, 2H), 4.32-4 23 (m, 4H), 1.33-1.27 (m, 6H); ^{19}F NMR ($CDCl_3$): - 47274; LCMS: ret. time: 27.51 min.; purity: 97 %; MS (m/e): 553 (M^+).

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Section Number	Name of compound and reference number	Experimental
7.3.89	N2,N4-Bis(3-fluoro-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926681)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-fluoro-4-hydroxyaniline were reacted to yield N2,N4-bis(3-fluoro-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.83 (d, 1H), 7.53 (dd, 1H), 7.42 (dd, 1H), 7.22 (dq, 1H), 7.03 (dq, 1H), 6.89 (d, 1H), 6.83 (s, 1H), 6.80 (s, 1H), 6.78 (d, 1H); ^{19}F NMR ($CDCl_3$): - 390060, - 39165, - 47835; LCMS: ret. time: 15.27 min.; purity: 95 %; MS (m/e): 349 (MH^+).
7.3.90	N2,N4-Bis(3-acetamidophenyl)-5-fluoro-2,4-pyrimidinediamine (R926682)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-aminoacetanilide were reacted to yield N2,N4-bis(3-acetamidophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR *(DMSO-d6)*: δ 10.24 (bs, 1H), 10.03 (s, 1H), 9.94 (s, 1H), 8.20 (d, 1H, J= 4.8 Hz), 7.91 (bs, 1H), 7.68 (bs, 1H), 7.43 (d, 1H, J= 8.1 Hz), 7.35-7.30 (m, 2H), 7.24-7.19 (m, 2H), 7.11 (t, 1H, J= 8.1 Hz), 2.03 (s, 3H), 2.01 (s, 3H); LCMS: ret. time: 15.10 min.; purity: 99 %; MS (m/e): 395 (MH^+).
7.3.91	N2,N4-Bis(2-fluoro-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926683)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 2-fluoro-4-hydroxyaniline were reacted to yield N2,N4-bis(2-fluoro-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.78 (s, 1H), 9.50 (s, 1H), 8.75 (s, 1H), 8.06 (s, 1H), 7.87 (d, 1H, J= 4.2 Hz), 7.25-7.18 (m, 2H), 6.61 (dd, 1H, J= 2.4 and 12.3 Hz), 6.56-6.47 (m, 2H), 6.39 (dd, 1H, J= 1.8 and 8.7 Hz); LCMS: ret. time: 15.52 min.; purity: 99 %; MS (m/e): 349 (MH^+).
7.3.92	N2,N4-Bis(4-isopropoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926701)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-isopropoxyaniline were reacted to yield N2,N4-bis(4-isopropoxy)phenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.89 (bs, 1H), 7.47 (d, 2H, J= 8.7 Hz), 7.38 (d, 2H, J= 9.0 Hz), 6.87 (d, 2H, J= 9 0 Hz), 6.83 (d, 2H, J= 8.7 Hz); LCMS: ret. time: 27.51 min.; purity: 98 %; MS (m/e): 397 (MH^+).
7.3.93	N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine (R925771)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 5-bromo-2,4-dichloropyrimidine and 3,4-ethylenedioxyaniline were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.07 (bs, 1H), 7.16 (d, 1H, J= 3.0 Hz), 7.10 (d, 1H, J= 2.7 Hz), 6.98-6.93 (m, 2H), 6.90-6.75 (m, 3H), 4.28-4.21 (m, 8H); LCMS: ret. time: 22.61 min.; purity: 100%; MS (m/e): 458 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.94	N2,N4-Bis(3-hydroxyphenyl)-5-bromo-2,4-pyrimidinediamine (R925778)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 5-bromo-2,4-dichloropyrimidine and 3-aminophenol were reacted to yield N2,N4-bis(3-hydroxyphenyl)-5-bromo-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.99 (bs, 1H), 9.34 (bs, 1H), 8.30 (s, 1H), 7.15 (t, 1H, J= 8.4 Hz), 7.06-6.97 (m, 2H), 6.94-6.92 (m, 2H), 6.80 (bs, 1H), 6.62 (s, 1H, J= 8.1 Hz), 6.43 (d, 1H, J= 7.8 Hz); LCMS: ret. time: 18.48 min.; purity: 97%; MS (m/e): 374 (MH^+).
7.3.95	N2,N4-Bis[4-(ethoxycarbonylmethyleneoxy)phenyl]-5-bromo-2,4-pyrimidinediamine (R925779)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 5-bromo-2,4-dichloropyrimidine and ethyl 4-aminophenoxyacetate were reacted to yield N2,N4-bis[4-(ethoxycarbonylmethyleneoxy)phenyl]-5-bromo-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.12 (s, 1H), 8.48 (s, 1H), 8.11 (s, 1H), 7.42 (d, 4H, J= 8.7 Hz), 6.89 (d, 2H, J= 9.0 Hz), 6.71 (d, 2H, J= 9.3 Hz), 4.78 (s, 2H), 4.66 (s. 2H), 4.20-4.10 (m, 4H), 1.23-1.16 (m, 6H); LCMS: ret. time: 25.82 min.; purity: 94%; MS (m/e): 546 (MH^+).
7.3.96	N2,N4-Bis[2-(4-hydroxyphenyl)ethyl]-5-bromo-2,4-pyrimidinediamine (R925792)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 5-bromo-2,4-dichloropyrimidine and tyramine were reacted to yield N2,N4-bis[2-(4-hydroxyphenyl)ethyl]-5-bromo-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 7.83 (s, 1H), 6.96 (d, 4H, J= 8.1 Hz), 6.63 (d, 4H, J= 8.1 Hz), 3.54-3.42 (m, 2H), 2.74-2.66 (m, 2H), 2.74-2.66 (m, 4H); ret. time: 20.10 min.; purity: 100 %; MS (m/e): 430 (MH^+).
7.3.97	N2,N4-Bis(2-phenylphenyl)-5-bromo-2,4-pyrimidinediamine (R925798)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 5-bromo-2,4-dichloropyrimidine and 2-aminobiphenyl were reacted to yield N2,N4-bis(2-phenylphenyl)-5-bromo-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.34 (d, 1H, J= 8.1 Hz), 8.27 (d, 1H, J= 8.1 Hz), 8.00 (s, 1H), 7.51-7.18 (m, 17H), 6.95 (s, 1H); LCMS: ret. time: 18.87 min.; purity: 97 %; MS (m/e): 495 (MH^+).
7.3.98	N2,N4-Bis(2-methoxy-5-phenylphenyl)-5-bromo-2,4-pyrimidinediamine (R925799)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 5-bromo-2,4-dichloropyrimidine and 5-phenyl-*ortho*-anisidine were reacted to yield N2,N4-bis(2-methoxy-5-phenylphenyl)-5-bromo-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.26 (m, 2H), 8.05 (m, 2H), 7.39-7.21 (m, 12H), 7.17 (dd, 1H, J= 2.4 and 8.1 Hz), 7.11 (d, 1H, J= 8.7 Hz), 7.05 (d, 1H, J= 9.0 Hz), 3.88 (s, 3H), 3.83 (s, 3H); LCMS: ret. time: 20.51 min.; purity: 98 %; MS (m/e): 554 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.99	N2,N4-Bis(4-methoxy-3-phenylphenyl)-5-bromo-2,4-pyrimidinediamine (R925802)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, with the addition of triethylamine, 5-bromo-2,4-dichloropyrimidine and 3-phenyl-*para*-anisidine hydrochloride were reacted to yield N2,N4-bis(4-methoxy-3-phenylphenyl)-5-bromo-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.26 (m, 2H), 8.06 (m, 2H), 7.38-7.25 (m, 12H), 7.18 (dd, 1H, J= 2.4 and 8.1 Hz), 7.12 (d, 1H, J= 8.7 Hz), 7.05 (d, 1H, 8.7 Hz), 3.89 (s, 3H), 3.83 (s, 3H); LCMS: ret. time: 36.77 min.; purity: 98 %; MS (m/e): 554 (MH^+).
7.3.100	N2,N4-Bis(3-phenylphenyl)-5-bromo-2,4-pyrimidinediamine (R925803)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 5-bromo-2,4-dichloropyrimidine and 3-aminobiphenyl were reacted to yield N2,N4-bis(3-phenylphenyl)-5-bromo-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.86 (bs, 1H), 9.20 (bs 1H), 8.33 (s, 1H), 7.79 (bs, 1H), 7.18 (bs, 1H), 7.61 (d, 1H), 7.56-7.51 (m, 2H), 7.48-7.23 (m, 11H), 7.17-7.04 (m, 2H); LCMS: ret. time: 19.52 min.; purity: 80 %; MS (m/e): 494 (MH^+).
7.3.101	N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-cyano-2,4-pyrimidinediamine (R925773)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-cyanopyrimidine and 3,4-ethylenedioxyaniline were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-cyano-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.69 (bs, 1H), 9.28 (bs, 1H), 8.40 (s, 1H), 7.16-6.89 (m, 4H), 6.79 (d, 1H, J= 9.0 Hz), 6.65 (bs, 1H), 4.22 (s, 4H), 4.16 (s, 4H); LCMS: ret. time: 24.42 min.; purity: 93 %; MS (m/e): 404 (MH^+).
7.3.102	N2,N4-Bis(3-hydroxyphenyl)-5-cyano-2,4-pyrimidinediamine (R925774)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-cyanopyrimidine and 3-hydroxyaniline were reacted to yield N2,N4-bis(3-hydroxyphenyl-5-cyano-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.73 (bs, 1H), 9.40 (s, 1H), 9.33 (bs, 1H), 9.24 (s, 1H), 8.47 (s, 1H), 7 20 (d, 1H, J= 7.5 Hz), 7.11 (t, 1H, J= 7.5 Hz), 7.09-7.02 (m, 2H), 6.99-6.89 (m, 3H), 6.54 (d, 1H, J= 7.2 Hz), 6.37 (dd, 1H, J= 1.8 and 8.4 Hz); LCMS: ret. time: 19.71 min.; purity: 97%; MS (m/e): 320 (MH^+).
7.3.103	N2,N4-Bis[4-(ethoxycarbonylmethyleneoxy)phenyl]-5-cyano-2,4-pyrimidinediamine (R925775)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-cyanopyrimidine and ethyl 4-aminophenoxyacetatewere reacted to yield N2,N4-bis[4-(ethoxycarbonylmethyleneoxy)phenyl]-5-cyano-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.80 (s, 1H), 7.40 (d, 4H, J= 8.7 Hz), 6.90 (4H, J= 9.0 Hz), 6.82-6.75 (m, 2H). 4.60 (bs, 4H), 4.29-4.25 (m, 4H), 1.32-1.26 (m, 5H), LCMS: ret. time: 28.50 min.; purity: 100 %; MS (m/e): 493 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.104	R935192: N2, N4-Bis(1-methyl-indazolin-5-yl)-5-fluoro-2,4-pyrimidinediamine:	In like manner to the preparation of N2, N4-bis (3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-5-fluoropyrimidine and 1-methyl-5-aminoindazole were reacted to produce N2, N4-bis(1-methyl-indazolin-5-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.65 (s, 1H), 10.41 (s, 1H), 8.29 (d, 1H, J= 5.3 Hz), 7.98 (s, 1H), 7.79 (d, 2H, J= 9.4 Hz), 7.69-7.54 (m, 4H), 7.35 (dd, 1H, J= 1.7 and 9.4 Hz), 4.03 (s, 3H), 4.01 (s, 3H). LCMS: ret. time: 16.86 min.; purity: 99%; MS (*m/e*): 389 (MH^+).
7.3.105	R935205: N2, N4-Bis[1-(methoxycarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N2, N4-bis (3-hydroxyphenyl)-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrmidine and 6-amino-1-(methoxycarbonyl)methyl-indazoline were reacted to produce N2, N4-bis[1-(methoxycarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.59 (s, 1H), 9.45 (s, 1H), 8.18 (d, 1H, J= 3.5 Hz), 8.11 (s, 1H), 8.04 (s, 1H), 7.95 (s, 1H), 7.93 (s, 1H), 7.69 (d, 1H, J= 8.8 Hz), 7.58 (d, 1H, J= 8.8 Hz), 7.48 (dd, 1H, J= 1.7 and 8.8 Hz), 7.32 (d, 1H, J= 8.8 Hz), 5.17 (s, 2H), 4.88 (s, 1H), 3.58 (s, 3H), 3.58 (s, 3H). LCMS: ret. time: 17.80 min.; purity: 99%; MS (*m/e*): 505 (MH^+).
7.3.106	R935211: N2, N4-Bis[1-(methoxycarbonyl)methyl-indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrmidine and 6-amino-1-(methoxycarbonyl)methyl-indazoline was reacted to produce N2, N4-bis[1-(methoxycarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.37 (s, 1H), 9.17 (s, 1H), 8.11-8.06 (m, 3H), 7.94 (s, 1H), 7.70 (s, 1H), 7.63 (s, 2H), 7.46 (s, 2H), 5.40 (s, 2H), 5.31 (s, 2H), 3.67 (s, 3H), 3.64 (s, 3H). LCMS: ret. time. 17.06 min.; purity: 96%; MS (*m/e*): 505 (MH^+).
7.3.107	R935188: N2,N4-Bis(indazolin-6-yl)-5-fluoro-2,4-pyrimidinediamine:	In like manner to the preparation of 5-fluoro-N2, N4-bis (3-hydroxyphenyl)-2,4-pyrimidinediamine, 2,4-dichlro-5-fluoropyrimidine and 6-aminoindazoline were reacted to produce N2,N4-bis(indazolin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.80 (s, 1H), 9.65 (s, 1H), 8.20 (d, 1H, J= 4.1 Hz), 8.01 (s, 1H), 7.96 (s, 1H), 7.93 (s, 1H), 7.89 (s, 1H), 7.69 (d, 1H, J= 8.8 Hz), 7.57 (d, 1H, J= 8.3 Hz), 7.54 (dd, 1H, J= 1.7 and 8.8 Hz), 7.29 (dd, 1H, J= 1.7 and 8.8 Hz); LCMS: ret. time:15.17 min.; purity: 94%; MS (*m/e*): 361 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.108	R935189: N2, N4-Bis(indazolin-5-yl)-5-fluoro-2,4-pyrimidinediamine:	In like manner to the preparation of N2, N4-bis (3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 5-aminoindazole were reacted to produce N2, N4-bis(indazolin-5-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10 05 (s, 1H), 9.76 (s, 1H), 8 16 (d, 1H, J= 4.7 Hz), 8.05 (s, 1H), 7.92 (s, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.52-7.52 (m, 2H), 7.44 (d, 1H, J= 8.8 Hz), 7.34 (dd, 1H, J= 1.7 and 8.8 Hz); LCMS: ret. time: 14.33 min.; purity: 100%; MS (*m/e*): 361 (MH^+).
7.3.109	N2,N4-Bis(1-ethoxycarbonyl-2-methylpropyl)-5-cyano-2,4-pyrimidinediamine (R925814)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-cyanopyrimidine and valine ethyl ester were reacted to yield N2,N4-bis(1-ethoxycarbonyl-2-methylpropyl)-5-cyano-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8 15 (s, 1H), 6.10 (d, 1H, J= 8.4 Hz), 5.67 (d, 1H, J= 8.1 Hz), 4.66-4.62 (m, 1H), 4.50-4.46 (m, 1H), 4.25-4.13 (m, 4H), 2.27-2.14 (m, 2H), 1.31-1.24 (m, 6H), 1.00-0.94 (m, 12H); LCMS: ret. time: 30.41 min.; purity: 98 %; MS (m/e): 392 (MH^+).
7.3.110	N2,N4-Bis(1-methoxycarbonyl-3-methylbutyl)-5-cyano-2,4-pyrimidinediamine (R925815)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-cyanopyrimidine and leucine methyl ester were reacted to yield N2,N4-bis(1-methoxycarbonyl-3-methylbutyl)-5-cyano-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): mixture of rotamers δ 8.15 (s, 1H), 6.10 and 5.49 (2d, 1H, J= 8.1 Hz), 5.53 (d, 1H, J= 8.4 Hz), 4.80-4.67 (m, 1H), 4.57-4.48 (m, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 1.78-1.60 (m, 6H), 0.97-0.89 (m, 12H); LCMS: ret. time: 30.33 min.; purity: 91 %; MS (m/e): 392 (MH^+).
7.3.111	N2,N4-Bis(methoxycarbonylbenzyl)-5-cyano-2,4-pyrimidinediamine (R925819)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-cyanopyrimidine and phenyl glycine methyl ester were reacted to yield N2,N4-bis(methoxycarbonylbenzyl)-5-cyano-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): mixture of rotamers δ 8.15 (s, 1H), 7.69-7.60 (m, 1H), 7.42-7.32 (m, 10H), 6.20 and 5.73 (2d, 1H, J= 6.6 Hz), 6.14 and 5.65 (2d, 1H, J= 6.3 Hz), 5.55 (d, 1H, J= 6.3 Hz), 5.39 (t, 1H, J= 7.2 Hz), 3.79 and 3.78 (2s, 3H), 3.67 and 3.65 (2s, 3H); LCMS: ret. time: 30.22 min.; purity: 91 %; MS (m/e): 432 (MH^+).
7.3.112	N2,N4-Bis[4-(ethoxycarbonylmethyl)phenyl]-5-cyano-2,4-pyrimidinediamine (R926662)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-cyanopyrimidine and ethyl 4-aminophenylacetate were reacted to yield N2,N4-bis[4-(ethoxycarbonylmethyl)phenyl]-5-cyano-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.29 (bs, 1H), 7.46 (2d, 4H, J= 7.8 Hz), 7.28 (d, 2h, J= 8.1 Hz), 7.19 (d, 2H, J= 8.1 Hz), 4.16 (2q, 4H, J= 6.3 Hz), 3.64 (s, 2H), 3.59 (s, 2H), 1.30-1.23 (m, 6H); LCMS: ret. time: 29.29 min.; purity: 93%; MS (m/e): 461 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.113	R935000: N2,N4-Bis(2-methoxy-5-phenylphenyl)-5-methyl-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine, 5-phenyl-2-anisidine and 2,4-dichloro-5-methylpyrimidine were reacted to provide N2,N4-bis(2-methoxy-5-phenylphenyl)-5-methyl-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 7.76 (d, 1H, J= 2.3 Hz), 7.57 (s, 1H), 7.56 (s, 1H), 7.02-6.85 (m, 8H), 6.86-6.80 (m, 4H), 6.72 (d, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 2.07 (s, 3H); LCMS: ret. time: 31.53 min.; purity: 97%; MS (*m/e*): 489 (MH^+).
7.3.114	R935001: N2,N4-Bis[(2-methyl-5-phenyl)phenyl]-5-methyl-2,4-pyrimidinediamine	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 5-phenyl-2-toluidine and 2,4-dichloro-5-methylpyrimidine were reacted to produce N2,N4-bis[(2-methyl-5-phenyl)phenyl]-5-methyl-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$). δ 7.59-7.55 (m, 1H), 7.45 (d, 2H, J= 3.6 Hz), 7.26-7.17 (m, 6H), 7.09-6.98 (m, 8H), 2.36 (s, 3H), 2.22 (s, 3H), 2.21(s, 3H); LCMS: ret. time: 32.44 min.; purity: 90%; MS (*m/e*): 457 (MH^+).
7.3.115	R935002: N2,N4-Bis[(4-methoxy-3-phenyl)phenyl]-5-methyl-2,4-pyrimidinediamine	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 3-phenyl-4-anisidine hydrochloride and 2,4-dichloro-5-methylpyrimidine with an added diisopropylethylamine were reacted to produce N2,N4-bis[(4-methoxy-3-phenyl)phenyl]-5-methyl-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H, J= 2.3 Hz), 7.76 (t, 1H, J= 2.3 Hz), 7.71 (s, 1 H), 7.59 (s, 1H), 7.16 –7.03 (m, 8H), 6.98-6.81 (5H), 3.96 (s, 3H), 3.89 (s, 3H), 2.21 (s, 3H); LCMS: ret. time: 32.01 min.; purity: 90%; MS (*m/e*): 489 (MH^+).
7.3.116	R935003: N2,N4-Bis[(4-phenyl-2-methoxy-5-methyl)phenyl]-5-methyl-2,4-pyrimidinediamine	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 5-methyl-4-phenyl-2-anisidine and 2,4-dichloro-5-methylpyrimidine were reacted to produce N2,N4-bis[(4-phenyl-2-methoxy-5-methyl)phenyl]-5-methyl-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 9.25 (br s, 1H), 8.17 (s, 1H), 7.77 (t, 1H, J= 6.4 Hz), 7.66 (s, 2H), 7.43-7.25 (m, 10H), 6.79 (s, 2H), 3.91 (s, 3H), 3.85 (s, 3H), 2.20 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H); LCMS: ret. time: 31.10 min.; purity: 100%; MS (*m/e*): 517 (MH^+).
7.3.117	R935004: N2,N4-Bis[[di-(4-methoxyphenyl)]methyl]-5-fluoro-2,4-pyrimidinediamine	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 1,1-di(4-anisyl)methylamine and 2,4-dichloro-5-fluoropyrimidine were reacted to produce N2,N4-bis[[di-(4-methoxyphenyl)]methyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 7.91 (d, 1H, J= 2.3 Hz), 7.18 (d, 8H, J= 9.0 Hz), 6.85 (d, 8H, J= 9.0 Hz), 6.40 (d, 1H, J= 8.2 Hz), 5.39 (d, 1H, J= 7.1 Hz), 3.81 (s, 6H), 3.78 (s, 6H); LCMS: ret. time: 32.76 min.; purity: 95%; MS (*m/e*): 581 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.118	R935005: N2,N4-Bis(diphenylmethyl)-5-fluoro-2,4-pyrimidinediamine	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 1,1-diphenyl methylamine and 2,4-dichloro-5-fluoropyrimidine were reacted to produce N2, N4-bis(diphenylmethyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.91 (d, 1H, J= 2.3 Hz), 7.39-7.25 (m, 20H), 6.51 (d, 1H, J= 8.2 Hz), 5.77 (d, 1H, J= 7.0 Hz); LCMS: ret. time: 33.46 min.; purity: 92%; MS (*m/e*): 461 (MH^+).
7.3.119	R935006: N2,N4-Bis[di-(4-chlorophenyl)methyl]-5-fluoro-2,4-pyrimidinediamine	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, benzhydrylamine and 2,4-dichloro-5-fluoropyrimidine were reacted to yield N2,N4-bis[di-(4-chlorophenyl)methyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 7.94 (d, 1H, J= 2.3 Hz), 7.40-7.20 (m, 16H), 6.46 (d, 1H, J= 8.2 Hz), 5.69 (d, 1H, J= 7.0 Hz); LCMS: ret. time: 32.83 min.; purity: 90%; MS (*m/e*): 599 (MH^+).
7.3.120	R935016: N2,N4-Bis[1(*R*)-4-methoxyphenylethyl]-5-bromo-2,4-pyrimidineamine	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, (R)-(+)-1-(4-methoxyphenyl)ethylamine and 5-bromo-2,4-dichloropyrimidine were reacted to produce N2,N4-bis[1(*R*)-4-methoxyphenylethyl]-5-bromo-2,4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 7.81 (s, 1H), 7.25 (d, 4H, J= 8.4 Hz), 6.86 (app t, 4H, J= 8.4 and 8.7 Hz), 5.27-5.20 m (2H), 5.09 (dq, 1H, J= 6.4 and 7.0 Hz), 4.89 (dq, 1H, J= 6.4 and 7.0 Hz), 3.80 (s, 3H), 3.79 (s, 3H), 1.40 (d, 6H, J= 7.0 Hz).
7.3.121	R935075: N2, N4-Bis[3-(2-hydroxyethoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 2-(3-aminophenoxy)ethanol were reacted to produce N2,N4-bis[3-(2-hydroxyethoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.50 (br s, 1H), 9.35 (br s, 1H), 8.13 (d, 1H, J= 4.1 Hz), 7.44 (d, 1H, J= 7.6 Hz), 7.26-7.19 (m, 4H), 7.10 (t, 1H, J= 7.6 Hz), 6.65 (dd, 1H, J= 2 3 and 8.2 Hz), 6.50 (dd, 1H, J= 2.3 and 8.2 Hz), 5.0 (br s, 2H), 3.91 (t, 2H, J= 5.2 Hz), 3.85 (t, 2H, J= 5.2 Hz), 3.68 (qt, 2H, J= 5.2 Hz), 3.66 (qt, 2H, J= 5.2 Hz); LCMS: ret. time: 15.76 min.; purity: 97%; MS (*m/e*): 401 (MH^+).
7.3.122	R935076: N2,N4-Bis[3-(2-methoxyethyl)oxyphenyl]-5-fluoro-2,4-pyrimidinediamine:	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-(2-methoxyethoxy)aniline were reacted to produce N2,N4-bis[3-(2-methoxyethyl)oxyphenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.96 (d, 1H, J= 2.9 Hz), 7.36 (t, 1H, J= 1.7 Hz), 7.28 (t, 1H J= 1.7 Hz), 7.25-7.06 (m, 4H), 6.98 (br s, 1H), 6.75 (d, 1H, J= 2.3 Hz), 6.70 (dd, 1H, J= 1.7 and 8.2 Hz), 6.58 (dd, 1H, J= 1.7 and 8.2 Hz), 4.08-4.03 (m, 4H), 3.74-3.69 (m, 4H), 3.44 (s, 3H), 3.43 (s, 3H); LCMS: ret. time: 21.01 min.; purity: 97%; MS (*m/e*): 429 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.123	R935077: N2,N4-Bis(5-hydroxy-2-isopropylphenyl)-5-fluoro-2,4-pyrimidinediamine	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 3-amino-4-isopropylphenol and 2,4-dichloro-5-fluoropyrimidine were reacted to produce N2,N4-bis(5-hydroxy-2-isopropylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.93 (d, 1H, J= 3.5 Hz), 7.79 (br s, 1H), 7.64 (br s, 1H), 7.13 (d, 1H, J= 8.7 Hz), 7.06 (d, 1H, J= 2.3 Hz), 7.05 (d, 1H, J= 8.7 Hz), 6.89 (d, 1H, J= 2.3 Hz), 6.66 (d, 1H, J= 2.3 and 8.7 Hz), 6.57 (d, 1H, J= 2.3 and 8.7 Hz), 2.96 (m, 2H), 1.25 (d, 6H, J= 7.0 Hz), 1.13 (dd, 6H, J= 7.0 Hz); LCMS: ret. time: 24.27 min.; purity: 97%; MS (*m/e*): 397 (MH^+).
7.3.124	R935114: N2,N4-Bis(3-methoxycarbonylmethylenephenyl)-5-fluoro-2,4-pyrimidinediamine	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-(methoxycarbonylmethylene)aniline were reacted to produce the desired N2,N4-bis(3-methoxycarbonylmethylenephenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.23 (br s, 1H), 10.05 (br s, 1H), 8.26 (d, 1H, J= 4.6 Hz), 7.64 (d, 1H, J= 8.2 Hz), 7.51 (br s, 1H), 7.46 (d, 1H, J= 8.2 Hz), 7.33 (br s, 1H), 7.29 (t, 1H, J= 7.6 Hz), 7.20 (t, 1H, J= 7.6 Hz), 7.06 (d, 1H, J= 7.6 Hz), 6.93 (d, 1H, J= 7.6 Hz), 3.63 (s, 2H), 3.58 (s, 3H), 3.57 (s, 3H), 3.56 (s, 2H); LCMS: ret. time: 21.74 min., purity: 92%, MS (*m/e*): 425 (MH^+).
7.3.125	R935162: N2, N4-Bis(3,4-propylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine:	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and (3,4-propylenedioxy)aniline were reacted to give N2,N4-bis(3,4-propylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.18 (s, 1H), 9.07 (s, 1H), 8.03 (d, 1H, J= 3.5 Hz), 7.38 (dd, 1H, J= 2.3 and 8.2 Hz), 7.35 (d, 1H, J= 2.3 Hz), 7.33 (d, 1H, J= 2.3 Hz), 7.18 (dd, 1H, J= 2.3 and 8.8 Hz), 6.90 (d, 1H, J= 8.8 Hz), 6.80 (d, 1H, J= 8.2 Hz), 4.11-3.98 (m, 8H), 2.09-2.01 (m, 4H); LCMS: ret. time: 21.40 min.; purity: 97%; MS (*m/e*): 425 (MH^+).
7.3.126	R935163: N2,N4-Bis(3-chloro-4-fluoropheny)-2,4-pyrimidinediamine:	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloro-4-fluoroaniline were reacted to produce N2, N4-bis(3-chloro-4-fluoropheny)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.58 (s, 1H), 9.48 (s, 1H), 8.17 (d, 1H, J= 4.1 Hz), 7.94-7.90 (m, 2H), 7.73-7.67 (m, 1H), 7.51-7.45 (m, 1H), 7.38 (t, 1H, J= 8.8 Hz), 7.26 (t, 1H, J= 8.8 Hz); LCMS: ret. time: 27.83 min.; purity: 99%; MS (*m/e*): 386 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.127	N2,N4-Bis(3-hydroxyphenyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine (R925849)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-6-ethoxycarbonyl-5-nitropyrimidine and 3-aminophenol were reacted to yield N2,N4-bis(3-hydroxyphenyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.56 (bs, 1H), 10.32 (bs, 1H), 9.54 (s, 1H), 9.32 (bs, 1H), 7.22-7.15 (m, 2H), 7.02-6.96 (m, 1H), 6.93-6.82 (m, 2H), 6.81-6.74 (m, 1H), 6.67 (d, 1H, J= 9 3 Hz), 6.43 (d, 1H, J= 8.1 Hz), 4.35 (q, 2H, J= 6.9 Hz), 1.30 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 26.01 min.; purity· 96 %; MS (m/e): 412 (MH^+).
7.3.128	N2,N4-Bis(3,4-ethylendioxyphenyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine (R925852)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-6-ethoxycarbonyl-5-nitropyrimidine and 3,4-ethylenedioxyaniline were reacted to yield N2,N4-bis(3,4-ethylendioxyphenyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.52 (s, 1H), 10.28 (s, 1H), 7.07-7.01 (m, 2H), 6.96 (dd, 1H, J= 1 8 and 8.7 Hz), 6.90-6 84 (m, 2H), 6.61 (d, 1H, J= 8.7 Hz), 4.33 (q, 2H, J= 6.9 Hz), 4.24 (s, 4H), 4.17 (s, 4H), 1.29 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 30.40 min.; purity: 100 %; MS (m/e): 496 (MH^+).
7.3.129	N2,N4-Bis(ethoxycarbonylmethyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine (R925864)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, with the addition of triethylamine, 2,4-dichloro-6-ethoxycarbonyl-5-nitropyrimidine and glycine ethyl ester hydrochloride were reacted to yield N2,N4-bis(ethoxycarbonylmethyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$)· mixture of rotamers δ 8.99 and 8.80 (2bs, 1H), 6.22 and 6.00 (2bs, 1H), 4 45 (t, 2H, J= 7.2 Hz), 4.31-4.21 (m, 6H), 4.14 (d, 2H, J= 5.1 Hz), 1.39 (t, 3H, J= 7.2 Hz), 1.34-1.28 (m, 6H); LCMS: ret. time: 26.06 min.; purity:·99 %; MS (m/e): 400 (MH^+).
7.3.130	N2,N4-Bis[2-(4-hydroxyphenyl)ethyl]-2,4-pyrimidinediamine (R925790)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and tyramine were reacted to yield N2,N4-bis[2-(4-hydroxyphenyl)ethyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.56 (bs, 1H), 9.23 (s, 1H), 8.89 (bs, 1H), 7.92 (bs, 1H), 7.60 (d, 1H, J= 6.9 Hz), 6.99 (d, 4H, J= 8.1 Hz), 6.65 (d, 4H, J= 8.1 Hz), 6.00 (d, 1H, J= 7.2 Hz), 3.59-3.42 (m, 4H), 2.76-2.67 (m, 4H); LCMS: ret. time: 17.93 min.; purity: 95 %; MS (m/e): 351 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.131	N2,N4-Bis(2-phenylphenyl)-2,4-pyrimidinediamine (R925804)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 2-aminobiphenyl were reacted to yield N2,N4-bis(2-phenylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.36 (d, 1H, J= 8.1 Hz), 7.97 (d, 1H, J= 5.7 Hz), 7.80 (d, 1H, J= 7.5 Hz), 7.50-7.21 (m, 15H), 7.12-7.05 (m, 1H), 6.91 (bs, 1H), 6.38 (bs, 1H), 6.07 (d, 1H, J= 6.0 Hz); LCMS: ret. time: 29.94 min.; purity: 100 %; MS (m/e): 415 (MH^+).
7.3.132	N2,N4-Bis(2-methoxy-5-phenylphenyl)-2,4-pyrimidinediamine (R925805)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 5-phenyl-*ortho*-anisidine were reacted to yield N2,N4-bis(2-methoxy-5-phenylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.88-7.84 (m, 2H), 7.82 (d, 1H, J= 6.9 Hz), 7.30-7.14 (m, 14H), 7.10 (dd, 2H, J= 3.0 and 8.1 Hz), 6.48 (d, 1H, J= 6.9 Hz), 3.93 (s, 3H), 3.92 (s, 3H); LCMS: ret. time: 30.09 min.; purity: 94 %; MS (m/e): 476 (MH^+).
7.3.133	N2,N4-Bis(3-carboxy-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R945041)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, from 5-amino-2-hydroxybenzoic acid (458 mg, 3 mmol) and 2,4-dichloro-5-fluoropyrimidine (100 mg, 0.6 mmol) gave N2,N4-bis(3-carboxy-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (235 mg, 98%). ^{1}H NMR (DMSO-d6): δ 6.76 (d, J= 9.0 Hz, 1 H), 6.88 (d, J= 9.6 Hz, 1 H), 7.75 (dd, J= 3.0, 9.0 Hz, 1 H), 7.90-7.94 (m, 3 H), 8.02 (d, J= 3.9 Hz, 1 H), 9.04 (s, 1 H, NH), 9.28 (s, 1 H, NH); ^{19}F NMR (282 MHz, DMSO-d6): δ -165.79; LC: 16.02 min, 86.82%; MS (m/z): 400.94 (MH^+).
7.3.134	N2,N4-Bis(4-methoxy-3-phenylphenyl)-2,4-pyrimidinediamine (R925806)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, with the addition of triethylamine, 2,4-dichloropyrimidine and 3-phenyl-*para*-anisidine hydrochloride were reacted to yield N2,N4-bis(4-methoxy-3-phenylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.93 (d, 1H, J= 2.4 Hz), 7 88 (d, 1H, J= 2.4 Hz), 7.29 (dd, 1H, J= 1.8 and 9.0 Hz), 7.26-7.18 (m, 13H), 7.10 (d, 2H, J= 8.7 Hz), 6.46 (d, 1H, J= 7.2 Hz), 3.93 (s, 3H), 3.92 (s, 3H); LCMS: ret. time: 29.99 min.; purity: 92%; MS (m/e): 476 (MH^+).
7.3.135	N2,N4-Bis(2-methyl-5-phenylphenyl)-2,4-pyrimidinediamine (R925807)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 5-phenyl-*ortho*-toluidine were reacted to yield N2,N4-bis(2-methyl-5-phenylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR *(DMSO-d6):* δ 10.45 (bs, 1H), 10.01 (bs, 1H), 7.86 (bs, 1H), 7.69-7.22 (m, 17H), 2.28 (s, 6H); LCMS: ret. time: 18.69 min.; purity: 98 %; MS (m/e): 443 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.136	N2,N4-Bis(2-methoxy-5-methyl-4-phenylphenyl)-2,4-pyrimidinediamine (R925808)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 5-methyl-4-phenyl-*ortho*-anisidine were reacted to yield N2,N4-bis(2-methoxy-5-methyl-4-phenylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.99 (bs, 1H), 9.22 (bs, 1H), 7 98 (d, 1H, J= 6.3 Hz), 7.75 (s, 1H), 7.59 (s, 1H), 7.46-7.29 (m, 10H), 6.92 (s, 1H), 6.87 (s, 1H), 6.49 (d, 1H, J= 5.4 Hz), 3.82 (s, 3H), 3.81 (s, 3H), 2.07 (s, 3H), 1.98 (s, 3H); LCMS: ret. time: 19.69 min.; purity: 93 %; MS (m/e): 503 (MH^+).
7.3.137	N2,N4-Bis[4-(ethoxycarbonylmethyleneoxy)phenyl]-5-trifluoromethyl-2,4-pyrimidinediamine (R925862)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-trifluoromethylpyrimidine and ethyl 4-aminophenoxyacetate were reacted to yield N2,N4-bis[4-(ethoxycarbonylmethyleneoxy)phenyl]-5-trifluoromethyl-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.64 (bs, 1H), 8.80 (bs, 1H), 8.29 (s, 1H), 7.36 (d, 2H, J= 8.1 Hz), 7.31 (d, 2H, J= 9.3 Hz), 6.93 (d, 2H, J= 8.7 Hz), 6.70 (d, 2H, J= 9.0 Hz), 4.80 (s, 2H), 4.67 (s, 2H), 4.18 (q, 2H, J= 6.9 Hz), 4.15 (q, 2H, J= 6.9 Hz), 1.20 (t, 3H, J= 6.9 Hz), 1.19 (t, 3H, J= 6.9 Hz); ^{19}F NMR (DMSO-d6): -16932; LCMS: ret. time· 26.33 min.; purity: 98 %; MS (m/e): 535 (MH^+).
7.3.138	N2,N4-Bis(3-hydroxyphenyl)-5-trifluoromethyl-2,4-pyrimidinediamine (R925863)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-trifluoromethylpyrimidine and 3-aminophenol were reacted to yield N2,N4-bis(3-hydroxyphenyl)-5-trifluoromethyl-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.82 (bs, 1H), 8.88 (bs, 1H), 8.36 (s, 1H), 7 18-7.11 (m, 2H), 6.96 (m, 4H), 6.63 (dd, 1H, J= 2.4 and 8.1 Hz), 6.38 (d, 1H, J= 8.1 Hz); ^{19}F NMR (DMSO-d6): -16979; LCMS: ret time: 19.04 min.; purity: 95 %; MS (m/e): 363 (MH^+).
7.3.139	N2,N4-Bis[4-(ethoxycarbonylmethyl)phenyl]-5-trifluoromethyl-2,4-pyrimidinediamine (R926663)	In a manner similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-trifluoromethylpyrimidine and ethyl 4-aminophenylacetate were reacted to yield N2,N4-bis[4-(ethoxycarbonylmethyl)phenyl]-5-trifluoromethyl-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.31 (s, 1H), 7.46 (d, 2H, J= 9.0 Hz), 7.45 (d, 2H, J= 8.7 Hz), 7.30 (d, 2H, J= 9.0 Hz), 7.18 (d, 2H, J= 8.7 Hz), 7.16 (bs, 1H), 6.82 (bs, 1H), 4.16 (2q, 4H, J= 7.8 Hz), 3.64 (s, 2H), 3.57 (s, 2H), 1.27 (t, 3H, J= 7.8 Hz), 1.26 (t, 3H, J= 7.8 Hz); ^{19}F NMR ($CDCl_3$): -17223; LCMS: ret. time: 28.07 min.; purity: 99 %; MS (m/e). 504 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.140	N2,N4-Bis(2,5-dimethyl-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926623)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 2,5-dimethyl-4-hydroxyaniline were reacted to yield N2,N4-bis(2,5-dimethyl-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.63 (d, 1H, J= 4.2 Hz), 7.05 (s, 1H), 6.97 (s, 1H), 6.64 (1H), 6.54 (s, 1H), 2.12 (s, 6H), 2.06 (s, 3H), 2.03 (s, 3H), 2.03 (s, 3H); ^{19}F NMR (CD_3OD): -48488, LCMS: ret. time: 18.28; purity; 94%; MS (m/e): 369 (MH^+).
7.3.141	N2,N4-Bis(3-sodiumphenoxy)-5-fluoro-2,4-pyrimidinediamine (R926461)	The reaction of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine with 2 equivalents of sodium methoxide in methanol followed by removal of solvent gave the requisite compound, N2,N4-bis(3-sodiumphenoxy)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (D_2O): δ 7.65 (bd, 1H), 7.00-6.90 (m, 2H), 6.71 (m, 2H), 6.55 (dd, 1H, J= 1.2 and 6.3 Hz), 6.31 (bd, 1H, J= 8.1 Hz), 6 23 (bd, 1H, J= 8.7 Hz), ^{19}F NMR (D_2O): -47016; LCMS. ret. time: 15.68 min.; purity: 99%; MS (m/e): 313 (MH^+).
7.3.142	N2,N4-Bis(3-cyanophenyl)-5-fluoro-2,4-pyrimidinediamine (R945051)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 3-aminobenzonitrile (177 mg, 1.5 mmol) and 2,4-dichloro-5-fluoropyrimidine (50 mg, 0.3 mmol) gave N2,N4-bis(3-cyanophenyl)-5-fluoro-2,4-pyrimidinediamine (75 mg, 76%). ^{1}H NMR (acetone-d_6): δ 7.33 (dt, J= 1.8, 7.8 Hz, 1 H), 7.46-7.52 (m, 2 H), 7.59 (t, J= 7.8 Hz, 1 H), 7.90 (ddd, J= 0.9, 2.1 and 8.4 Hz, 1 H), 8.09 (ddd, J= 1.2, 2.4 and 8.4 Hz, 1 H), 8.17 (d, J= 3.3 Hz, 1 H), 8.31 (m, 1 H), 8.35 (t, J= 2.1 Hz, 1 H), 8.98 (br, 1 H, NH), 9.02 (br, 1 H, NH); ^{19}F NMR (282 MHz, acetone-d_6): δ -165.80; LCMS: 24.64 min.; purity: 98.02%; MS (m/e): 331.01 (MH^+).
7.3.143	N2,N4-Bis(benzothiophen-3-ylmethyl)-5-fluoro-2,4-pyrimidinediamine (R945145)	Using procedure similar to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, benzothiophen-3-ylmethylamine and 2,4-dichloro-5-fluoropyrimidine gave N2,N4-bis(benzothiophen-3-ylmethyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 4.82 (dd, J= 0.9 and 5.7 Hz, 2 H), 4.86 (dd, J= 0.9 and 5.7 Hz, 2 H), 5.14 (br, 2 H), 7.31-7.40 (m, 6 H), 7.75-7.89 (m, 5 H); ^{19}F NMR (282 MHz, $CDCl_3$): δ -172.12; LCMS: 27.79 min.; purity: 96.47%; MS (m/e): 420.92 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.144	N2,N4-Bis[4-(N-benzylpiperazino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R945152)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 4-(N-benzylpiperazino)aniline (400 mg, 1.5 mmol) and 2,4-dichloro-5-fluoropyrimidine (50 mg, 0.3 mmol) resulted N2,N4-bis[4-(N-benzylpiperazino)phenyl]-5-fluoro-2,4-pyrimidinediamine (120 mg, 64%). ^{1}H NMR ($CDCl_3$): δ 2.63 (p, J= 2.4 Hz, 8 H), 3.14 (t, J= 4.8 Hz, 4 H), 3.19 (t, J= 4.8 Hz, 4 H), 3.58 (s, 4 H), 6.58 (d, 1 H, NH), 6.67 (br, 1 H, NH), 6.87 (d, J= 9.3 Hz, 2 H), 6.90 (d, J= 9.0 Hz, 2 H), 7.33-7.39 (m, 12 H), 7.46 (d, J= 9.0 Hz, 2 H), 7.87 (d, J= 3.3 Hz, 1 H); ^{19}F NMR (282 MHz, $CDCl_3$): δ -169.06; LCMS: 16.82 min ; purity: 96.88%; MS (m/e): 629.12 (MH^+).
7.3.145	N2,N4-Bis(3-hydroxy-2-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R945038)	In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 3-hydroxy-2-methylaniline (369 mg, 3 mmol) and 2,4-dichloro-5-fluoropyrimidine (100 mg, 0.6 mmol) gave N2,N4-bis(3-hydroxy-2-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (180 mg, 88%). ^{1}H NMR (acetone-d_6): δ 2.14 (s, 3 H), 2.22 (s, 3 H), 6.61 (d, J= 8.1 Hz, 1 H), 6.78 (t, J= 8.7 Hz, 1 H), 6.87 (d, J= 7.8 Hz, 1 H), 6.99 (d, J= 9.0 Hz, 1 H), 7.08 (t, J= 7.8 Hz, 1 H), 7.13 (dd, J= 3.9, 8.4 Hz, 1 H), 8.24 (d, J= 5 1 Hz, 1 H), 8.32 (br, 1 H, NH), 8.57 (br, 1 H, NH); LCMS: ret. time: 16.51 min.; purity· 90.47%; MS (m/e): 341.07 (MH^+).
7.3.146	N2,N4-Bis(3-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine (R950160)	2,4-Dichloro-5-fluoropyrimidine (4.7 g, 28.1 mmol) was dissolved in a mixture of MeOH (150 ml) and H_2O (15 ml). 3-nitroaniline (15.5 g, 112 mmol) was added and the mixture was refluxed for 20 hours (100 °C oil-bath temperature). The mixture was cooled to 22 °C and filtered. The residue was washed carefully with 200 ml MeOH–H_2O (1:1; v/v) and dried under vacuum to give 7.89 g (76%) of N2,N4-bis(3-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine as yellow crystals. ^{1}H NMR (DMSO-d6 + D_2O): δ 8.63 (m, 2H), 8.21 (m, 1H), 8.08 (d, 1H, J= 8.41 Hz), 7.88 (d, 1H, J= 8.4 Hz), 7.79 (d, 1H, J= 8 4 Hz), 7.70 (d, 1H, J= 8.4 Hz), 7.57 (d, 1H, J= 8.4 Hz), 7.45 (t, 1H, J= 8.4 Hz); LCMS: purity: 100%; MS (m/e): 371.30 (M^+, 100).

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Section Number	Name of compound and reference number	Experimental
7.3.147	N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine (R921302)	N2,N4-Bis(3-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine (4.0 g, 10.8 mmol) and Pd/C 10% (1.2 g, 50% water content) were suspended in 300 ml EtOH–10% aqueous HCl (1 : 1) and hydrogenated in a Parr apparatus for 6 hours (22 °C, 50 psi). The suspension was filtered over celite and carefully washed with 20 ml DMF–H_2O (1:1; v/v) followed by 50 ml H_2O. The combined filtrates were concentrated under reduced pressure to give pale yellow oil, which was triturated with MeOH to give the product as fine white needles. The precipitate was filtered off and washed with MeOH followed by Et_2O. The remaining crystals were dried under vacuum to give 4.00 g of pure material (100%) as determined by LCMS. The free amine was obtained by adding 10 ml 1 N NaOH to a solution of 1g HCl-salt in 5 ml H_2O. The resulting precipitate was filtered, washed with H_2O and dried under vacuum for 24 hours to give N2,N4-bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine (770 mg) as a white solid. ^1H NMR (CD_3OD): δ 7.92 (d, 1H, J= 3.6 Hz), 7.31 (t, 1H, J= 2.1 Hz), 7.21 (t, 1H, J= 2.4 Hz), 7.08, (t, 1H, J= 8.1 Hz), 6.99 (t, 1H, J= 8.1 Hz), 6.88 (m, 1H), 6.77 (m, 1H), 6.47 (m, 1H), 6.34 (m, 1H); LCMS: purity: 100%; MS (m/e): 311.07 (M^+, 100).
7.3.148	N2,N4-Bis(4-aminophenyl)-5-fluoro-2,4-pyrimidinediamine (R950122)	In like manner to the preparation of N2,N4-bis(3-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 1,4-diaminobenzene were reacted to prepare N2,N4-bis(4-aminophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 11.15 min.; purity: 100%; MS (m/e): 311.09 (MH^+).
7.3.149	N2,N4-Bis[3-(dimethylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R950182)	2,4-Dichloro-5-fluoropyrimidine (50 mg, 0.30 mmol) was dissolved in a mixture of MeOH (0.3 ml) and H_2O (0.03 ml). N,N-3-dimethyldiaminoaniline (163 mg, 1.2 mmol) was added and the mixture was refluxed for 24 hours (70 °C oil-bath temperature). The mixture was cooled to 22 °C, concentrated to dryness under reduced pressure and subjected to column chromatography on silica gel ($CHCl_3$–Acetone, 2 : 1) to give N2,N4-bis[3-(dimethylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS purity: 99.0%; MS (m/e): 367.13 (M^+, 100).
7.3.150	N2,N4-Bis(3-amino-4-methylphenyl)-2,4-pyrimidinediamine (R950130)	2,4-Dichloropyrimidine (45 mg, 0.30 mmol) was dissolved in a mixture of MeOH (1 ml) and H_2O (0.1 ml). 3-amino-4-methylaniline (146 mg, 1.2 mmol) was added and the mixture was refluxed for 20 hours (70 °C oil-bath temperature). The mixture was cooled to 22 °C, concentrated to dryness under reduced pressure and subjected to column chromatography on silica gel ($CHCl_3$–Acetone, 2:1) to give N2,N4-bis(3-amino-4-methylphenyl)-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 8.13 (s, 1H), 6.95 (d, 2H, J= 7.5 Hz), 6.82 (d, 2H, J= 1.8 Hz), 6.60 (dd, 2H, J= 1.8, 7.5 Hz), 6.17 (s, 1H), 2.12 (s, 6H); LCMS purity: 97.3%; MS (m/e): 321.09 (M^+, 100).

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Section Number	Name of compound and reference number	Experimental
7.3.151	N2,N4-Bis(3-amino-4-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950129)	2,4-Dichloro-5-fluoropyrimidine (50 mg, 0.30 mmol) was dissolved in a mixture of MeOH (1 ml) and H_2O (0.1 ml). 3-amino-4-methylaniline (146 mg, 1.2 mmol) was added and the mixture was refluxed for 20 hours (70 °C oil-bath temperature). The mixture was cooled to 22 °C, concentrated to dryness under reduced pressure and subjected to column chromatography on silica gel ($CHCl_3$–Acetone, 2:1) to give N2,N4-bis(3-amino-4-methylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 8.11 (d, 1H, J= 5.1 Hz), 7.98 (bs, 1H) (7.68 (dd, 1H, J= 2.4, 8.1 Hz), 7.40-7.55 (m, 4H), 2.43 (s, 3H), 2.42 (s, 3H); LCMS: purity: 95.0%; MS (m/e): 338.66 (M^+, 70).
7.3.152	N2,N4-Bis[(4-methylsulfonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R950083)	2,4-Dichloro-5-fluoropyrimidine (50 mg, 0.30 mmol) was dissolved in a mixture of MeOH (1 ml) and H_2O (0.1 ml). 4-methylsulfonylaminoaniline (335 mg, 1.8 mmol) was added and the mixture was refluxed for 24 hours (100 °C oil-bath temperature). The mixture was cooled to 22 °C and filtered. The residue was washed carefully with MeOH–H_2O (1:1) and dried under vacuum to give N2,N4-bis[(4-methylsulfonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 8.86 (s, 1H), 8.65 (s, 1H), 8.53 (bs, 1H), 8.39 (bs, 1H), 7.32 (d, 1H, J= 3.3 Hz), 7.12 (d, 1H, J= 8.7 Hz), 6.98 (d, 1H, J= 8.7 Hz), 6.62 (d, 1H, J= 8.7 Hz), 6.52 (d, 1H, J= 8.7 Hz), 2.32 (s, 3H), 2.27 (s, 3H); LCMS: purity: 96.8%; MS (m/e): 466.94 (M^+, 100).
7.3.153	N2,N4-Bis(4-benzyloxy-3-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950090)	2,4-Dichloro-5-fluoropyrimidine (50 mg, 0.30 mmol) was dissolved in a mixture of MeOH (1 ml) and H_2O (0.1 ml). 4-benzyloxy-3-trifluoromethylaniline (481 mg, 1.8 mmol) was added and the mixture was refluxed for 2 days (70 °C oil-bath temperature). The mixture was cooled to 22 °C, concentrated to dryness under reduced pressure and subjected to column chromatography on silica gel ($CHCl_3$–Acetone, 9:1) to give N2,N4-bis(4-benzyloxy-3-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 8.51 (s, 1H), 8.05 (s, 1H), 7.38-7.64 (m, 5H), 6.94-7.14 (m, 11H), 6.44-6.73 (m, 4H), 4 84 (s, 2H), 4.79 (s, 2H); LCMS purity: 94.7%; MS (m/e): 628.93 (M^+, 100).
7.3.154	N2,N4-Bis(3-cyano-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950092)	2,4-Dichloro-5-fluoropyrimidine (50 mg, 0.30 mmol) was dissolved in a mixture of MeOH (1 ml) and H_2O (0.1 ml). 3-cyano-4-hydroxyaniline (241 mg, 1.8 mmol) was added and the mixture was refluxed for 2 days (70 °C oil-bath temperature). The mixture was cooled to 22 °C, concentrated to dryness under reduced pressure and subjected to column chromatography on silica gel ($CHCl_3$–Acetone, 9:1) to give N2,N4-bis(4-hydroxy-3-cyanophenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 7.96 (d, 1H, J= 3.5 Hz), 7.82 (d, 1H, J= 3.0 Hz), 7.79 (d, 1H, J= 3.0 Hz), 7.71 (dd, 1H, J= 3.0, 8.8 Hz), 7.54 (dd, J= 3.0, 8.8 Hz), 6.94 (d, 1H, J= 8.8 Hz), 6.84 (d, 1H, J= 8.8 Hz); LCMS: purity: 97.2%; MS (m/e): 362.98 (M^+, 100).

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Section Number	Name of compound and reference number	Experimental
7.3.155	N2,N4-Bis[3-methylsulfonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R950100)	2,4-Dichloro-5-fluoropyrimidine (50 mg, 0.3 mmol) was dissolved in a mixture of MeOH (1 ml) and H_2O (0.1 ml). 3-methylsulfonylaminoaniline (300 mg, 1.5 mmol) was added and the mixture was refluxed for 24 hours (70 °C oil-bath temperature). The mixture was cooled to 22 °C, concentrated to dryness under reduced pressure and subjected to column chromatography on silica gel ($CHCl_3$–Acetone, 9:1) to give N2,N4-bis[3-methylsulfonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6 + CD_3OD): δ 8.01 (d, 1H, J= 3.5 Hz), 7.46-7.68 (m, 4H), 7.49 (t, 1H, J= 8.2 Hz), 7.13 (t, 1H, J= 8.2 Hz), 6.89 (dd, 1H, J= 2.4, 8.2 Hz), 6.72 (m, 1H), 2.95 (s, 3H), 2.91 (s, 3H); LCMS: purity: 97.2%; MS (m/e): 466.89 (M^+, 100).
7.3.156	N2,N4-Bis[3-(tert-butoxycarbonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R950108)	2,4-Dichloro-5-fluoropyrimidine (75 mg, 0.45 mmol) was dissolved in a mixture of MeOH (2 ml) and H_2O (0.2 ml). 3-tert-butoxycarbonylaminoaniline (374 mg, 1.8 mmol) was added and the mixture was refluxed for 40 hours (70 °C oil-bath temperature). The mixture was cooled to 22 °C, concentrated to dryness under reduced pressure and subjected to column chromatography on silica gel ($CHCl_3$–Acetone, 9.1) to give N2,N4-bis[3-(tert-butoxycarbonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6 + CD_3OD): δ 7.96 (d, 1H, J= 4.1 Hz), 7.83 (m, 1H), 7.60 (m, 1H), 7.34-7.42 (m, 2H), 7.15-7.19 (m, 2H), 7.06 (t, 1H, J= 8.2 Hz), 6.93 (d, 1H, J= 8.2 Hz), 1.43 (s, 9H), 1.40 (s, 9H); LCMS: purity: 93.2%; MS (m/e): 511.06 (M^+, 100).
7.3.157	N2,N4-Bis[4-(tert-butoxycarbonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R950120)	2,4-Dichloro-5-fluoropyrimidine (75 mg, 0.45 mmol) was dissolved in a mixture of MeOH (2 ml) and H_2O (0.2 ml). 4-tert-butoxycarbonylaminoaniline (374 mg, 1.8 mmol) was added and the mixture was refluxed for 24 hours (70 °C oil-bath temperature). The mixture was cooled to 22 °C, concentrated to dryness under reduced pressure and subjected to column chromatography on silica gel ($CHCl_3$–Acetone, 9:1) to give N2,N4-bis[4-(tert-butoxycarbonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6 + CD_3OD): δ 7.96 (d, 1H, J= 3.5 Hz), 7.63 (d, 2H, J= 8.8 Hz), 7.49 (d, 2H, J= 8.8 Hz), 7.37 (d, 2H, J= 8.8 Hz), 7.24 (d, 2H, J= 8.8 Hz), 1.45 (s, 9H), 1.43 (s, 9H); LCMS: purity: 97.9%; MS (m/e): 511.04 (M^+, 100).
7.3.158	N2,N4-Bis[2-[2-(methylamino)ethyleneaminocarbonyl]-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine (R950170)	N2,N4-Bis[2-(ethoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine (10 mg, 0.02 mmol) was dissolved in EtOH. To this was added N-methyl-1,2-aminoethane (0.1 ml : 0.1 ml) and the mixture was refluxed for 3 days (70 °C oil-bath temperature). The mixture was cooled to 22 °C, diluted with water and filtered. The residue was subjected to column chromatography on silica gel ($CHCl_3$–Acetone, 2:1) to give N2,N4-bis[2-[2-(methylamino)ethyleneaminocarbonyl]-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6 + CD_3OD): δ 8.14 (s, 1H), 8.02 (s, 1H), 7.99 (d, 1H, J= 2.4 Hz), 7.35-7.68 (m, 5H), 7.17 (s, 1H), 3.41 (m, 2H), 2.75 (m, 2H), 2.35 (s, 3H); LCMS: purity: 84.2%; MS (m/e): 561.08 (M^+, 100).

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Section Number	Name of compound and reference number	Experimental
7.3.159	N2,N4-Bis[2-(2-hydroxyethyleneamoinocarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine (R950167)	In like manner to the preparation of N2,N4-bis[2-[2-(methylamino)ethyleneamino carbonyl]-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis[2-(ethoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine and 2-aminoethanol were reacted to prepare N2,N4-bis[2-(2-hydroxyethyleneamoinocarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 14.22 min.; purity: 95.7%; MS (m/e): 535.01 (MH^+).
7.3.160	N2,N4-Bis[2-(2-aminoethyleneamoinocarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine (R950168)	In like manner to the preparation of N2,N4-bis[2-[2-(methylamino)ethyleneamino carbonyl]-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis[2-(ethoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine and 1,2-diaminoethane were reacted to prepare N2,N4-bis[2-(2-aminoethyleneamoinocarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 13.15 min.; purity: 95.8%; MS (m/e): 532.99 (MH^+).
7.3.161	N2,N4-Bis[2-(2-(N-benzylamino)ethyleneamoinocarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine (R950169)	In like manner to the preparation of N2,N4-bis[2-[2-(methylamino)ethyleneamino carbonyl]-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis[2-(ethoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine and N-benzyl-1,2-diaminoethane were reacted to prepare N2,N4-bis[2-(2-(N-benzylamino)ethyleneamoino carbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 13.15 min.; purity: 95.8%; MS (m/e): 713.10 (MH^+).
7.3.162	N2,N4-Bis[2-(N-morpholinocarbonyl)benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine (R950172)	In like manner to the preparation of N2,N4-bis[2-[2-(methylamino)ethyleneamino carbonyl]-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis[2-(ethoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine and morpholine were reacted to N2,N4-bis[2-(N-morpholinocarbonyl)benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6 + CD_3OD): δ 8.13 (d, 1H, J= 2.7 Hz), 8.06 (d, 1H, J= 2.4 Hz), 8.03 (d, 1H, J= 3.6 Hz), 7.63 (dd, 1H, J= 2.4, 8.8 Hz), 7.57 (d, 1H, J= 9.3 Hz), 7.49 (dd, 1H, J= 2.4, 8.4 Hz), 7.42 (d, 1H, J= 8.8 Hz), 7.25 (s, 1H), 7.05 (s, 1H), 4.09 (m, 4H), 3.65 (m, 4H); LCMS: ret. time: 18.04 min.; purity: 83.2%; MS (m/e): 587.04 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.163	N2,N4-Bis[2-(2-N-morpholinoethyleneamoinocarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine (R950173)	In like manner to the preparation of N2,N4-bis[2-[2-(methylamino)ethyleneamino carbonyl]-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis[2-(ethoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine and N-(2-aminoethyleneamino)morpholine were reacted to prepare N2,N4-bis[2-(2-N-morpholinoethyleneamoinocarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6 + CD_3OD): δ 8.16 (d, 1H, J= 2.4 Hz), 8.03-8.05 (m, 2H), 7.71 (dd, 1H, J= 1.8, 8.8 Hz), 7.56 (d, 1H, J= 8.8Hz), 7.42 (d, 1H, J= 8.8 Hz), 7.36 (s, 1H), 7.19 (s, 1H), 4.19 (m, 4H), 3.38 (m, 4H), 3.16 (t, 2H, J= 6.3 Hz), 2.28 (t, 2H, J= 6.3 Hz); LCMS: ret. time: 12.85 min.; purity: 93.8%; MS (m/e): 673.35 (MH^+).
7.3.164	N2,N4-Bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine (R950135)	2,4-Dichloro-5-fluoropyrimidine (50 mg, 0.3 mmol) was dissolved in a mixture of MeOH (1 ml) and H_2O (0.1 ml). 3-amino-4-nitroaniline (184 mg, 1.2 mmol) was added and the mixture was refluxed for 3 days (70 °C oil-bath temperature). The mixture was cooled to 22 °C, concentrated to dryness under reduced pressure and subjected to column chromatography on silica gel ($CHCl_3$–Acetone, 2:1) to give N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6 + CD_3OD): δ 8.21 (d, 1H, J= 2.9 Hz), 7.89 (m, 3H), 7.56 (d, 1H, J= 2.3 Hz), 7.01 (m, 1H), 6.81 (dd, 1H, J= 2.3, 9.4 Hz); LCMS: purity: 91.1%; MS (m/e): 401.00 (M^+, 100).
7.3.165	N2,N4-Bis(3-amino-2,4-difluorophenyl)-5-fluoro-2,4-pyrimidinediamine (R950138)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-amino-2,4-difluoroaniline were reacted to prepare N2,N4-bis(3-amino-2,4-difluorophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 16.98 min.; purity: 91.7%; MS (m/e): 382.97 (MH^+).
7.3.166	N2,N4-Bis(3-amino-4-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950139)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-amino-4-ethoxyaniline were reacted to prepare N2,N4-bis(3-amino-4-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 14.29 min.; purity: 93.4%; MS (m/e): 399.09 (MH^+).
7.3.167	N2,N4-Bis(3-amino-5-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950134)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-amino-5-methoxycarbonylaniline were reacted to prepare N2,N4-bis(3-amino-5-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 14.72 min.; purity: 93.8%; MS (m/e): 427.02 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.168	N2,N4-Bis(3-amino-5-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950140)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-amino-5-trifluoromethylaniline were reacted to prepare N2,N4-bis(3-amino-5-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 23.35 min.; purity: 100%; MS (m/e): 446.92 (MH^+).
7.3.169	N2,N4-Bis(3-amino-5-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R950141)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-amino-5-chloroaniline were reacted to prepare N2,N4-bis(3-amino-5-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 19.25 min.; purity: 99.3%; MS (m/e): 378.91 (MH^+).
7.3.170	N2,N4-Bis(4-hydroxy-3-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950093)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-hydroxy-3-trifluoromethylaniline were reacted to prepare N2,N4-bis(4-hydroxy-3-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 22.06 min.; purity: 99.1%; MS (m/e): 448.88 (MH^+).
7.3.171	N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine Hydrogen Chloride salt (R950107)	N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine was treated with 2 equivalents of HCl in dioxane. The volatiles were removed under reduced pressure to give N2,N4-bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine hydrogen chloride salt. LCMS: ret. time: 9.74 min.; purity: 91.3%; MS (m/e): 311.06 (MH^+).
7.3.172	N2,N4-Bis(4-aminophenyl)-5-fluoro-2,4-pyrimidinediamine Hydrogen Chloride Salt (R950121)	N2,N4-Bis(4-aminophenyl)-5-fluoro-2,4-pyrimidinediamine was treated with 2 equivalents of HCl in dioxane. The volatiles were removed under reduced pressure to give N2,N4-bis(4-aminophenyl)-5-fluoro-2,4-pyrimidinediamine Hydrogen Chloride Salt. LCMS: ret. time: 11.15 min.; purity: 100%; MS (m/e): 311.09 (MH^+).
7.3.173	N2,N4-Bis(3-aminophenyl)-2,4-pyrimidinediamine (R950109)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 3-aminoaniline were reacted to prepare N2,N4-bis(3-aminophenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 8.90 min.; purity: 91%; MS (m/e): 293.06 (MH^+).
7.3.174	N2,N4-Bis(3-amino-2,4-difluorophenyl)-2,4-pyrimidinediamine (R950131)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 3-amino-2,4-difluoroaniline were reacted to prepare N2,N4-bis(3-amino-2,4-difluorophenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 16.62 min.; purity: 96.7%; MS (m/e): 364.99 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.175	N2,N4-Bis(3-amino-4-ethoxyphenyl)-2,4-pyrimidinediamine (R950142)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 3-amino-4-ethoxyaniline were reacted to prepare N2,N4-bis(3-amino-4-ethoxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 14.38 min.; purity: 99.7%; MS (m/e): 381.07 (MH^+).
7.3.176	N2,N4-Bis(3-amino-5-methoxycarbonylphenyl)-2,4-pyrimidinediamine (R950132)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 3-amino-5-methoxycarbonylaniline were reacted to prepare N2,N4-bis(3-amino-5-methoxycarbonylphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 15.25 min.; purity: 93.6%; MS (m/e): 409.02 (MH^+).
7.3.177	N2,N4-Bis(3-amino-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R950143)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 3-amino-5-trifluoromethylaniline were reacted to prepare N2,N4-bis(3-amino-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 23.23 min.; purity: 99.1%; MS (m/e): 428.95 (MH^+).
7.3.178	N2,N4-Bis(3-amino-5-chlorophenyl)-2,4-pyrimidinediamine (R950133)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 3-amino-5-chloroaniline were reacted to prepare N2,N4-bis(3-amino-5-chlorophenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 19.45 min.; purity: 100%; MS (m/e): 360.93 (MH^+).
7.3.179	N2,N4-Bis[3-amino-4-(N-phenylamino)-phenyl]-5-fluoro-2,4-pyrimidinediamine (R950125)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-amino-4-(N-phenylamino)-aniline were reacted to prepare N2,N4-bis[3-amino-4-(N-phenylamino)-phenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 23.67 min.; purity: 100%; MS (m/e): 476.36 (MH^+).
7.3.180	N2,N4-Bis[3-amino-4-(N-phenylamino)-phenyl]-2,4-pyrimidinediamine (R950123)	In like manner the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 3-amino-4-(N-phenylamino)-aniline were reacted to prepare N2,N4-bis[3-amino-4-(N-phenylamino)-phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 23.77 min.; purity: 77.8%; MS (m/e): 475.04 (MH^+).
7.3.181	N2,N4-Bis(5-amino-2-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950157)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 5-amino-2-methylaniline were reacted to prepare N2,N4-bis(5-amino-2-methylphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 10.61 min.; purity: 83.4%; MS (m/e): 339.13 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.182	N2,N4-Bis(5-amino-2-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine (R950158)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 5-amino-2-fluoroaniline were reacted to prepare N2,N4-bis(5-amino-2-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 11.48 min.; purity: 95.6%; MS (m/e): 347.04 (MH^+).
7.3.183	N2,N4-Bis(3-amino-4-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine (R950159)	In like manner to the preparation of N2,N4-bis(3-amino-4-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-amino-4-fluoroaniline were reacted to prepare N2,N4-bis(3-amino-4-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 18.74 min.; purity: 95.6%; MS (m/e): 347.29 (MH^+).
7.3.184	N2,N4-Bis(2-methyl-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine (R950146)	2,4-Dichloro-5-fluoropyrimidine (33 mg, 0.2 mmol) was dissolved in a mixture of MeOH (1 ml) and H_2O (0.1 ml). 2-Methyl-5-nitroaniline (122 mg, 0.8 mmol) was added and the mixture was refluxed for 2 days (70 °C oil-bath temperature). The mixture was cooled to 22 °C, concentrated to dryness under reduced pressure and subjected to column chromatography on silica gel ($CHCl_3$–Acetone, 9:1) to give N2,N4-bis(2-methyl-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6 + CD_3OD): δ 8.31 (d, 1H, J= 2.3 Hz), 8.20 (d, 1H, J= 2.3 Hz), 8.06 (d, 1H, J= 3.5 Hz), 7.91 (dd, 1H, J= 2.3, 8.2 Hz), 7.65 (dd, 1H, J= 2 9, 8.8 Hz), 7.41 (m, 1H), 7.28 (d, 1H, J= 8.2 Hz), 2.28 (s, 3H), 2.24 (s, 3H); LCMS purity: 87.4%; MS (m/e): 399.20 (M^+, 100).
7.3.185	N2,N4-Bis(2-fluoro-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine (R950147)	In like manner to the preparation of N2,N4-bis(2-methyl-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 2-fluoro-5-nitroaniline were reacted to prepare N2,N4-bis(2-fluoro-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 31.07 min.; purity: 93.6%; MS (m/e): 407.14 (MH^+).
7.3.186	N2,N4-Bis(4-fluoro-3-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine (R950148)	In like manner to the preparation of N2,N4-bis(2-methyl-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-fluoro-3-nitroaniline were reacted to prepare N2,N4-bis(4-fluoro-3-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 27.17 min.; purity: 94.3%; MS (m/e): 406.96 (MH^+).
7.3.187	N2,N4-Bis(4-methyl-3-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine (R950144)	In like manner to the preparation of N2,N4-bis(2-methyl-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-methyl-3-nitroaniline were reacted to prepare N2,N4-bis(4-methyl-3-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 27.40 min.; purity: 96.6%; MS (m/e): 399.00 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.188	N2,N4-Bis(4-chloro-3-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine (R950149)	In like manner to the preparation of N2,N4-bis(2-methyl-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-chloro-3-nitroaniline were reacted to prepare N2,N4-bis(4-chloro-3-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 35.63 min.; purity: 98.9%; MS (m/e): 439.09 (MH^+).
7.3.189	N2,N4-Bis(2-hydroxyethyleneamino-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine (R950150)	In like manner to the preparation of N2,N4-bis(2-methyl-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 2-hydroxyethyleneamino-5-nitroaniline were reacted to prepare N2,N4-bis(2-hydroxyethyleneamino-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 17.90 min.; purity: 97.8%; MS (m/e): 489.19 (MH^+)
7.3.190	N2,N4-Bis(2-methoxy-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine (R950151)	In like manner to the preparation of N2,N4-bis(2-methyl-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 2-methoxy-5-nitroaniline were reacted to prepare N2,N4-bis(2-methoxy-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 31.46 min.; purity: 95.9%; MS (m/e): 431.22 (MH^+).
7.3.191	N2,N4-Bis(4-fluoro-3-nitrophenyl)-2,4-pyrimidinediamine (R950152)	In like manner to the preparation of N2,N4-bis(2-methyl-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 4-fluoro-3-nitroaniline were reacted to prepare N2,N4-bis(4-fluoro-3-nitrophenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 30.92 min.; purity: 94.4%; MS (m/e): 389.31 (MH^+).
7.3.192	N2,N4-Bis(4-methyl-3-nitrophenyl)-2,4-pyrimidinediamine (R950153)	In like manner to the preparation of N2,N4-bis(2-methyl-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 4-methyl-3-nitroaniline were reacted to prepare N2,N4-bis(4-methyl-3-nitrophenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 31.22 min.; purity: 99.6%; MS (m/e): 381.35 (MH^+).
7.3.193	N2,N4-Bis(4-chloro-3-nitrophenyl)-2,4-pyrimidinediamine (R950154)	In like manner to the preparation of N2,N4-bis(2-methyl-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 4-chloro-3-nitroaniline were reacted to prepare N2,N4-bis(4-chloro-3-nitrophenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 37.24 min.; purity: 99.1%; MS (m/e): 421.30 (MH^+).
7.3.194	N2,N4-Bis(2-hydroxy-5-nitrophenyl)-2,4-pyrimidinediamine (R950155)	In like manner to the preparation of N2,N4-bis(2-methyl-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 2-hydroxy-5-nitroaniline were reacted to prepare N2,N4-bis(2-hydroxy-5-nitrophenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 23.26 min.; purity: 100%; MS (m/e): 385.33 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.195	N2,N4-Bis(2-hydroxyethyleneamino-5-nitrophenyl)-2,4-pyrimidinediamine (R950156)	In like manner to the preparation of N2,N4-bis(2-methyl-5-nitrophenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloropyrimidine and 2-hydroxyethyleneamino-5-nitroaniline were reacted to prepare N2,N4-bis(2-hydroxyethyleneamino-5-nitrophenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 17.87 min.; purity: 97.2%; MS (m/e): 470.99 (MH^+).
7.3.196	N2,N4-Bis[3-(N-isopropyl)aminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950166)	N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, acetone and sodiumcyanoborohydride were reacted together to give N2,N4-bis[3-(N-isopropyl)aminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 14.07 min.; purity: 90.3%; MS (m/e): 395.14 (MH^+).
7.3.197	N2,N4-Bis[3-N-(2-hydroxy-1-methylethyl)aminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950171)	N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, 1-hydroxyacetone and sodiumcyanoborohydride were reacted to give N2,N4-bis[3-N-(2-hydroxy-1-methylethyl)aminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 11.97 min.; purity: 79.01%; MS (m/e): 427.12 (MH^+).
7.3.198	N2,N4-Bis(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine (R950177)	N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine and tert-butyl bromoacetate were reacted together to give N2,N4-bis(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 29.34 min.; purity: 97.2%; MS (m/e): 427.07 (MH^+).
7.3.199	N4-(3-Aminophenyl)-N2-(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine (R950178)	In like manner to the preparation of N2,N4-bis(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine and tert-butyl bromoacetate were reacted together to give N4-(3-aminophenyl)-N2-(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 18 33 min.; purity: 94.5%; MS (m/e): 369.09 (MH^+).
7.3.200	N2-(3-Aminophenyl)-N4-(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine (R950179)	In like manner to the preparation of N2,N4-bis(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine and tert-butyl bromoacetate were reacted together to give N2-(3-aminophenyl)-N4-(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 18.82 min.; purity: 85.8%; MS (m/e): 369.11 (MH^+).
7.3.201	N2,N4-Bis(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine (R950184)	In like manner to the preparation of N2,N4-bis(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine and ethyl bromoacetate were reacted together to give N2,N4-bis(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 23.41 min.; purity: 96.3%; MS (m/e): 483.08 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.202	N2,N4-Bis(3-ethoxycarbonylmethyleneaminophenyl)-N2-(ethoxycarbonylmethyl)-5-fluoro-2,4-pyrimidinediamine (R950183)	In like manner to the preparation of N2,N4-bis(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine and ethyl bromoacetate were reacted together to give N2,N4-bis(3-ethoxycarbonylmethyleneaminophenyl)-N2-(ethoxycarbonylmethyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 25.65 min.; purity: 92.5%; MS (m/e): 569.08 (MH^+).
7.3.203	N2-(3-Aminophenyl)-N4-(3-hydroxyethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine and N4-(3-Aminophenyl)-N2-(3-hydroxyethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine (R950180)	In like manner to the preparation of N2,N4-bis(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine and 1-bromo-2-hydroxyethane were reacted together to give a unseparable mixture of N2-(3-aminophenyl)-N4-(3-hydroxyethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine and N4-(3-aminophenyl)-N2-(3-hydroxyethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 9.84 min.; purity: 89.5%; MS (m/e): 355.10 (MH^+).
7.3.204	N2,N4-Bis(3-hydroxyethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine (R950181)	In like manner to the preparation of N2,N4-bis(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine and 1-bromo-2-hydroxyethane were reacted together to give N2,N4-bis(3-hydroxyethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 11.46 min.; purity: 83.3%; MS (m/e): 399.12 (MH^+).
7.3.205	N2,N4-Bis[3-(N-benzyloxyethyleneamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R950174)	In like manner to the preparation of N2,N4-bis(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine and 1-benzyloxy-2-bromoethane were reacted together to give N2,N4-bis[3-(N-benzyloxyethyleneamino)phenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 32.92 min.; MS (m/e): 579.17 (MH^+).
7.3.206	N2-(3-Aminophenyl)-N4-[3-(N-benzyloxyethyleneamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R950175)	In like manner to the preparation of N2,N4-bis(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine and 1-benzyloxy-2-bromoethane were reacted together to give N2-(3-aminophenyl)-N4-[3-(N-benzyloxyethyleneamino)phenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 23.79 min.; MS (m/e): 445.11 (MH^+).
7.3.207	N4-(3-Aminophenyl)-N2-[3-(N-benzyloxyethyleneamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R950176)	In like manner to the preparation of N2,N4-bis(3-tert-butoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine and 1-benzyloxy-2-bromoethane were reacted together to give N4-(3-aminophenyl)-N2-[3-(N-benzyloxyethyleneamino)phenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 23.64 min.; MS (m/e): 445.13 (MH^+).

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7.3.208	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926210)	To a solution of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (0.028g, 0.1 mmol) in MeOH: H_2O (1.8: 0.2 mL) was added 3-hydroxyaniline (0.033g, 0.3 mmol) and heated in a sealed tube at 100 °C for 24h. The resulting reaction was diluted with H_2O (10 mL), acidified with 2N HCl (pH >2), saturated and the resulting solid was filtered to give the desired product, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl))-2,4-pyrimidinediamine (**R926210**). Purification can be done by filtration through a pad of silica gel using 1-5% MeOH in CH_2Cl_2 or by crystallization using an appropriate solvent system. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 7.76 (bs, 1H), 7.30 (d, 1H, J= 2.4 Hz), 7.10 (m, 1H), 7.03 (t, 1H, J= 8.1 Hz), 6.89 (dd, 2H, J= 2.4 and 9 Hz), 6.78 (d, 1H, J= 8.7 Hz), 6.42 (dd, 1H, J= 2.4 and 9 Hz), 4.22 (m, 4H); ^{19}F NMR ($CDCl_3$ + CD_3OD): - 47196; LCMS: ret. time: 19.55 min.; purity: 95%; MS (m/e): 355 (MH^+). Note: When the substrate has ethyl, butyl, benzyl etc. ester functions and the reaction is carried out in methanol as a solvent, the cross esterification to produce methyl ester was observed.
7.3.209	N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[3-(hydroxymethyl)phenyl]-2,4-pyrimidinediamine (R925758)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[3-(hydroxymethyl)phenyl]-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to yield N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[3-(hydroxymethyl)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.92 (d, 1H, J= 3.0 Hz), 7.78 (bs, 1H), 7.41-7.31 (m, 3H), 7.12 (d, 1H, J= 7.2 Hz), 6.94 (bs, 1H), 6.81-6.75 (m, 3H), 4.68 (s, 2H), 4.25 (s, 4H); ^{19}F NMR ($CDCl_3$): - 47438; LCMS: ret. time: 17.73 min.; purity: 100 %; MS (m/e): 369 (MH^+).
7.3.210	N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[4-(hydroxymethyl)phenyl]-2,4-pyrimidinediamine (R925760)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[4-(hydroxymethyl)phenyl]-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to yield N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[4-(hydroxymethyl)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.92 (bs, 1H), 7.62 (d, 2H, J= 8.7 Hz), 7.36 (d, 2H, J= 8.7 Hz), 7.19 (d, 1H, J= 2.1), 6.87 (dd, 1H, J= 2.7 and 8.7 Hz), 6.79 (d, 1H, J= 8.7 Hz), 4.68 (s, 2H), 4.28-4.23 (m, 4H); ^{19}F NMR ($CDCl_3$): - 4.7466; LCMS: ret. time: 17.86 min.; purity: 93 %; MS (m/e): 369 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.211	N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-hydroxy-2-phenylethyl)-2,4-pyrimidinediamine (R925765)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(2-hydroxy-2-phenylethyl)-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to yield N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-hydroxy-2-phenylethyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.79 (s, 1H), 7.48 (m, 5H), 6.89-6.71 (m, 3H), 5.41-5.38, 4.97 (dd, 1H, J= 3.6 and 7.5 Hz), 4.28-4.22 (m, 4H), 3.88 (ddd, 1H, J= 4.2, 7.2, and 14.1), 3.64-3.55 (m, 1H); ^{19}F NMR ($CDCl_3$): - 47910, LCMS: ret. time: 20.47 min.; purity: 88 %; MS (m/e): 383 (MH^+).
7.3.212	N2-(3,4-Ethylendioxyphenyl)-5-fluoro-N4-[(2R)-hydroxy-(1S)-methyl-2-phenylethyl)-2,4-pyrimidinediamine (R925766)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(2R)-hydroxy-(1S)-methyl-2-phenylethyl)-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to yield N2-(3,4-ethylendioxyphenyl)-5-fluoro-N4-[(2R)-hydroxy-(1S)-methyl-2-phenylethyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.80 (bs, 1H), 7.71 (bs, 1H), 7.36-7.23 (m, 6H), 6.91 (dd, 1H, J= 3.0 and 9.0 Hz), 6.80 (d, 1H, J= 9.0 Hz), 5.17 (d, 1H, J= 8.1 Hz), 5.01 (d, 1H, J= 3.0 Hz), 4.56-4.50 (m, 1H), 4.24 (s, 4H), 1.10 (d, 3H, J= 6.3 Hz); ^{19}F NMR ($CDCl_3$): - 47840; LCMS: ret. time: 21.43 min.; purity: 99 %; MS (m/e): 397 (MH^+).
7.3.213	N4-Cyclohexyl-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R925794)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-cyclohexyl-5-fluoro-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to yield N4-cyclohexyl-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.62 (d, 1H, J= 4.2 Hz), 7.31 (d, 1H, J= 2.1 Hz), 6.86 (dd, 1H, J= 2.4 and 8.7 Hz), 6.68 (d, 1H, J= 8.7 Hz), 4.23-4.16 (m, 4H), 3.99-3.89 (m, 1H), 2.03 (dd, 2H, J= 2.1 and 12.3 Hz), 1.80 (dt, 2H, J= 3.0 and 13.5 Hz), 1.72-1.65 (m, 1H), 1.49-1.20 (m, 5H); ^{19}F NMR (CD_3OD): - 48332; LCMS: ret. time: 24.54 min.; purity: 95 %; MS (m/e): 345 (MH^+).
7.3.214	N4-(4-Carboxycyclohexyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R925795)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-(4-carboxycyclohexyl)-2-chloro-5-fluoro-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to yield N4-(4-carboxycyclohexyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.62 (d, 1H, J= 4.2 Hz), 7.31 (d, 1H, J= 2.4 Hz), 6.84 (dd, 1H, J= 2.4 and 8.7 Hz), 6.70 (d, 1H, J= 8.7 Hz), 4.23-4.18 (m, 4H), 3.99-4.08 (m, 1H), 2.59 (t, 1H, J= 3.9 Hz), 2.16-2.09 (m, 2H), 1.91-1.84 (m, 2H), 1.78-1.57 (m, 4H); ^{19}F NMR (CD_3OD): - 48152; LCMS: ret. time: 19.31 min.; purity: 96 %; MS (m/e): 389 (MH^+).

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7.3.215	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925796)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.30 (s, 1H), 9.12 (bs, 1H), 8.91 (bs, 1H), 8.02 (d, 1H, J= 3.3 Hz), 7.35-7.30 (m, 1H), 7.24-7.21 (m, 1H), 7.12 (t, 1H, J= 1.8 Hz), 7.09-7.04 (m, 2H), 6.67 (d, 1H, J= 9.0), 6.46 (dd, 1H, J= 1.8 and 8.4 Hz), 4.18-4.12 (m, 4H); ^{19}F NMR (DMSO-d6): - 46594; LCMS: ret. time: 18.43 min.; purity: 97 %; MS (m/e): 355 (MH^+).
7.3.216	N2-Allyl-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R925823)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and allylamine were reacted to yield N2-allyl-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.71 (bs, 1H), 7.37 (d, 1H, J= 2.4 Hz), 7.07 (dd, 1H, J= 2.4 and 8.7 Hz), 6.75 (d, 1H, J= 8.7 Hz), 5.98-5.85 (m, 1H), 5.19 (dq, 1H, J= 1.8 and 16.8 Hz), 5.06 (dq, 1H, J= 1.8 and 10.5 Hz), 4.24-4.18 (m, 4H), 3.92-3.68 (m, 2H); ^{19}F NMR (CD_3OD): - 48552; LCMS: ret. time: 19.36 min.; purity: 95 %; MS (m/e): 303 (MH^+).
7.3.217	N4-(3,4-Ethylenedioxyphenyl)-N2-(4-ethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926237)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-ethylaniline were reacted to yield N4-(3,4-ethylenedioxyphenyl)-N2-(4-ethylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.87 (bs, 1H), 7.42 (d, 2H, J= 8.7 Hz), 7.26 (d, 1H, J= 3.0 Hz), 7.13-7.08 (m, 3H), 6.95 (dd, 1H, J= 2.4 and 8.7 Hz), 6.82 (d, 1H, J= 9.0 Hz), 6.60 (bs, 1H), 4.23 (s, 4H), 2.59 (q, 2H, J= 7.5 Hz), 1.20 (t, 3H, J= 7.5 Hz); ^{19}F NMR ($CDCl_3$): - 47549; LCMS: ret. time: 25.31min.; purity: 99 %; MS (m/e): 367 (MH^+).
7.3.218	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine (R926690)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 2-methoxycarbonyl-5-aminobenzofuran were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.68 (bs, 1H), 8.13-8.10 (m, 2H), 7.63-7.54 (m, 3H), 7.27 (bs, 1H), 7.10 (d, 1H, J= 8.7 Hz), 6.80 (d, 1H, J= 8.1 Hz), 4.21 (s, 4H), 3.88 (s, 3H); LCMS: ret. time: 23.22 min.; purity: 95 %; MS (m/e): 437 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.219	5-Fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-N4-(4-isopropoxyphenyl)- 2,4-pyrimidinediamine (R926704)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[4-(isopropoxy)phenyl]-4-pyrimidineamine and 2-methoxycarbonyl-5-aminobenzofuran were reacted to yield 5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-N4-(4-isopropoxyphenyl)- 2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.04 (d, 1H, J= 1.8 Hz), 7.49-7.41 (m, 4H), 7.35 (dd, 1H, J= 2.4 and 8.7 Hz), 7.14 (bs, 1H), 6.90 (d, 2H, J= 9.3 Hz), 6.70 (bs, 1H), 4.56 (2q, 1H, J= 5.7 Hz), 3.98 (s, 3H), 1.37 (d, 6H, J= 5.7 Hz); LCMS: ret. time: 25.52 min.; purity: 98 %; MS (m/e). 437 (MH^+).
7.3.220	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(2-hydroxyethyl)oxyphenyl]-2,4-pyrimidinediamine (R926376)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)]-4-pyrimidineamine and 4-(2-hydroxyethyloxy)aniline were reacted to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(2-hydroxyethyl)oxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (D_2O): δ 8.40 (d, 1H J= 4 Hz), 7.57 (m, 6H), 7.12 (m, 2H), 6.90 (m, 2H), 4.40 (m, 4H) 2,2 (s, 3H); LCMS: ret. time: 13.61 min.; purity: 97 %; MS (m/e): 357 (MH^+).
7.3.221	N2-[4-(2-N,N-Dimethylamino)ethoxyphenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R909236)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)]-4-pyrimidineamine and 4-(2-N,N-dimethylamino)ethoxyaniline were reacted to yield N2-[4-(2-N,N-dimethylamino)ethoxyphenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.80 (d, 1H J= 4 Hz), 7.47 (dd, 1H, J= 6.8 Hz, 2.7 Hz), 7.44 (m, 1H), 7.05 (m, 1H), 6.85 (m, 1H), 6.78 (m, 2H), 4.16 (m, 2H), 3.03 (m, 2H), 2.55 (s, 6H); LCMS: ret. time: 12.74 min.; purity: 98 %; MS (m/e): 384 (MH^+).
7.3.222	N2-(1,4-Benzoxazin-3-on-6-yl)- 5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R909238)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)]-4-pyrimidineamine and 6-amino-1,4-benzoxazin-3-one were reacted to yield N2-(1,4-benzoxazin-3-on-6-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.18 (d, 1H J= 4 Hz), 7.17 (m, 3H), 7.09 (m, 1H), 7.06 (m, 1H), 6.58 (m, 1H) 4.52 (s, 3H); LCMS: ret. time: 17.18 min.; purity: 99 %; MS (m/e): 368 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.223	N2-(1,4-Benzoxazin-6-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R909241)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)] pyrimidineamine and 6-amino-1,4-benzoxazine were reacted to yield N2-(1,4-benzoxazin-6-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ □□□(d, 1H, J= 4 Hz), 7.15 (m, 3H), 6.68 (m, 2H), 6.52 (m, 2H), 6.52 (m, 1H), 4.18 (m, 2H), 3.37 (m, 2H); LCMS: ret. time 17.42 min.; purity: 95%; MS (m/e): 354 (MH^+).
7.3.224	N4-(1,4-Benzoxazin-6-yl)-N2-[3-ethoxyocarbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R909242)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-(1,4-benzoxazin-6-yl)-N2-chloro-5-fluoro-4-pyrimidineamine and 3-ethoxyocarbonylmethyleneoxyaniline were reacted to yield N4-(1,4-benzoxazin-6-yl)-N2-(3-ethoxyocarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ □□(d, 1H, J= 4 Hz), 7.15 (m, 4H), 6.84 (m, 2H), 6.62 (m, 1H), 4.65 (s, 2H), 4.15 (m, 4H), 3.28 (m, 2H), 1.19 (t, 3H. J= 7 Hz); LCMS: ret. time 22.6 min ; purity: 94%; MS (m/e): 439 (MH^+).
7.3.225	N2-(1,4-Benzoxazin-6-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4- pyrimidinediamine (R909243)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-(1,4-benzoxazin-6-yl)-N2-chloro-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to yield N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ □□□(d, 1H, J= 4 Hz), 7.18 (m, 3H), 6.68 (m, 2H), 6.45 (m, 2H), 6.52 (m, 1H), 4.22 (m, 2H), 3.31 (m, 2H); LCMS: ret. time: 17.24; purity: 96%; MS (m/e): 354 (MH^+).
7.3.226	N4-(1,4-Benzoxazin-6-yl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R909245)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-(1,4-benzoxazin-6-yl)-N2-chloro-5-fluoro-4-pyrimidineamine and 3,5-dimethoxyaniline were reacted to yield N4-(1,4-benzoxazin-6-yl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ □1□ (d, 1H, J= 4 Hz), 6.80 (m, 4H), 6.60 (m, 1H), 6.05 (m, 1H), 4.02 (m, 2H), 3.65 (s, 6H), 3.31 (m, 2H); LCMS: ret. time: 22.38 min.; purity: 99 %; MS (m/e): 398 (MH^+).
7.3.227	N4-(1,4-Benzoxazin-6-yl)-N2-(3-*tert*-butylphenyl)-5-fluoro-2,4-pyrimidinediamine (R909246)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-(1,4-benzoxazin-6-yl)-N2-chloro-5-fluoro-4-pyrimidineamine and 3-*tert*-butylaniline were reacted to yield N4-(1,4-benzoxazin-6-yl)-N2-(3-*tert*-butylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ □□ (d, 1H, J= 4 Hz), 7.5 (m, 1H), 7.4 (m, 1H), 7.18 (m, 1H), 7.02 (m, 1H), 6.80 (m, 2H), 6.60 (m, 1H), 4.02 (m, 2H), 3.31 (m, 2H), 1.2 (s, 9H); LCMS: ret. time: 26.64 min.; purity: 99 %; MS (m/e): 508 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.228	N4-(1,4-Benzoxazin-6-yl)-5-fluoro-N2-[4-(2-hydroxyethyl)oxyphenyl]-2,4-pyrimidinediamine (R909248)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-(1,4-benzoxazin-6-yl)-N2-chloro-5-fluoro-4-pyrimidineamine and 4-(2-hydroxyethyl)oxyaniline were reacted to yield N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[4-(2-hydroxyethyl)oxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ □□□(d, 1H, J= 4 Hz), 7.52 (m, 1H), 7.4 (m, 3H), 6.90 (m, 2H), 6.68 (m, 1H), 4.56 (s, 2H), 4.02 (m, 2H), 3.75 (m, 2H), 3.31 (m, 4H); LCMS: ret. time: 26 67 min.; purity: 93 %; MS(m/e): 399 (MH^+).
7.3.229	N2-(2,3-Dihydrobenzofuran-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R909250)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)]-4-pyrimidineamine and 5-amino-2,3-dihydrobenzofuran were reacted to yield N2-(2,3-dihydrobenzofuran-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}HNMR (DMSO-d6): δ 8.09 (d, 1H), 8.00 (m, 1H), 7.82 (m, 1H), 7.57 (m, 1H), 7.22 (m, 1H), 7.08 (m, 1H), 6.99 (m, 1H), 6.82 (m, 1H), 6.70 (m, 1H), 6.42 (m, 1H), 4.49 (m, 2H), 3.15 (m, 2H); LCMS: ret time: 19.39 min.; MS (m/e): 338 (MH^+).
7.3.230	N4-(1,4-Benzoxazin-6-yl)-N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R909255)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-(1,4-benzoxazin-6-yl)-N2-chloro-5-fluoro-4-pyrimidineamine and 3-chloro-4-hydroxy-5-methylaniline were reacted to yield N4-(1,4-benzoxazin-6-yl)-N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ □□□(d, 1H, J= 4 Hz), 7.25 (m, 1H), 7.14 (m, 1H), 6.80 (m, 2H), 6.82 (m, 1H), 4.29 (s, 2H), 3.35 (m, 2H), 2.20 (s, 3H); LCMS: ret. time: 17.05 min., purity: 99 %; MS(m/e): 402 (MH^+).
7.3.231	5-Fluoro-N2-(2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R926706)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(4-isopropoxyphenyl)-4-pyrimidineamine and 5-amino-2,3-dihydro-2-(methoxycarbonyl)benzofuran were reacted to yield 5-fluoro-N2-(2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 1H, J= 3.0 Hz), 7.47-7.42 (m, 3H), 7.12 (dd, 1H, J= 2.4 and 8.4 Hz), 6.87 (d, 2H, J= 9.6 Hz), 6.80 (d, 1H, J= 8.7 Hz), 6.63 (d, 1H, J= 2.4 Hz), 5.21 (dd, 1H, J= 6.3 and 10.5 Hz), 4.53 (2q, 1H, J= 5.7 Hz), 3.80 (s, 3H), 3.52 (dd, 1H, J= 10.5 and 15.9 Hz), 3.35 (dd, 1H, J= 6.3 and 15.9 Hz), 1.34 (d, 6H, J= 5.7 Hz); ^{19}F NMR ($CDCl_3$): - 47664; LCMS: ret. time: 23.78 min.; purity: 95 %; MS (m/e): 439 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.232	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926699)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-hydroxyphenyl)-5-fluoro-4-pyrimidineamine and 4-[2-(N-morpholino)ethyleneoxy]aniline were reacted to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.34 (s, 1H), 9.17 (bs, 1H), 8.95 (bs, 1H), 8.02 (d, 1H, J= 3.3 Hz), 7.53 (d, 2H, J= 9.0 Hz), 7.28-7.23 (m, 1H), 7.12-7.04 (m, 2H, 6.79 (d, 2H, J= 9.0 Hz), 6.47 (dd, 1H, J= 1.2 and 5.7 Hz), 4.00 (t, 2H, J= 6.0 Hz), 3.56 (t, 4H, J= 4.5 Hz), 2.64 (t, 2H, J= 6.0 Hz), 2 44 (t, 4H, J= 4.5 Hz); ^{19}F NMR (DMSO-d6): - 46715; LCMS: ret. time: 12.66 min.; purity: 95 %; MS (m/e): 426 (MH^+).
7.3.233	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[4-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926709)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-[2-(N-morpholino)ethyleneoxy]aniline were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[4-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.80 (d, 1H, J= 3.6 Hz), 7.72 (bs, 1H), 7.62 (bs, 1H), 7.41 (d, 1H, J= 9.3 Hz), 7.24 (d, 1H, J= 5.4 Hz), 7.05 (dd, 1H, J= 2.4 and 8.7 Hz), 6.84 (d, 2H, J= 8.7 Hz), 6.75 (d, 1H, J= 9.0 Hz), 4.24 (bs, 4H), 4.11 (t, 2H, J= 5.4 Hz), 3.74-3.69 (m, 4H), 2.80 (t, 2H, J= 5.4 Hz), 2.62-2.58 (m, 4H); ^{19}F NMR (CD_3OD): - 47912; LCMS: ret. time: 15.16 min.; purity: 91 %; MS (m/e): 468 (MH^+).
7.3.234	5-Fluoro-N2-(3-hydroxyphenyl)-N4-[4-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926710)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[4-[2-(N-morpholino)ethyleneoxy]phenyl]-4-pyrimidineamine and 3-aminophenol were reacted to yield 5-fluoro-N2-(3-hydroxyphenyl)-N4-[4-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.84 (d, 1H, J= 4.2 Hz), 7 60 (d, 1H. J= 9.3 Hz), 7.09 (t, 1H, J= 2.4 Hz), 7.04-6.96 (m, 2H), 6.93 (d, 2H, J= 9.3 Hz), 6.40 (dt, 1H, J= 1.8 and 7.5 Hz), 4.15 (t, 2H, J= 5.4 Hz), 3.75-3.70 (m, 4H), 2.81 (t, 2H, J= 5.1 Hz), 2.63-2.59 (m, 4H); LCMS: ret. time: 14.16 min.; purity: 98 %; MS (m/e): 426 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.235	N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[4-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926711)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[4-[2-(N-morpholino)ethyleneoxy]phenyl]-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to yield N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.80 (d, 1H, J= 4.2 Hz), 7.56 (d, 2H, J= 8.7 Hz), 7.13 (d, 1H, J= 2.4 Hz), 6.91 (d, 2H, J= 9.6 Hz), 6.86 (dd, 1H, J= 2.4 and 9.0 Hz), 6.67 (d, 1H, J= 9.0 Hz), 4.23-4.18 (m, 4H), 4.14 (t, 3H, J= 5.4 Hz), 3.74-3.70 (m, 4H), 2.82 (t, 3H, J= 5.4 Hz), 2.64-2.59 (m, 4H); ^{19}F NMR ($CDCl_3$): - 47914; LCMS: ret. time: 15.97 min.; purity: 94 %; MS (m/e): 468 (MH^+).
7.3.236	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[4-(tetrahydro-(1H)-pyrrol-1-ylsulfonyl)phenyl]-2,4-pyrimidinediamine (R926716)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-(tetrahydro-(1H)-pyrrol-1-ylsulfonyl)aniline were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[4-(tetrahydro-(1H)-pyrrol-1-ylsulfonyl)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.11 (bs, 1H), 9.76 (bs, 1H), 8.19 (d, 1H, J= 3.9 Hz), 7.82 (d, 2H, J= 8.7 Hz), 7.62 (d, 2H, J= 8.7 Hz), 7.27 (d, 1H, J= 2.4 Hz), 7.08 (dd, 1H, J= 2.4 and 8.7 Hz), 6.85 (d, 1H, J= 8.7 Hz), 4.23 (s, 4H), 3.10-3.06 (m, 4H), 1.64-1.58 (m, 4H); LCMS: ret. time: 22.68 min.; purity: 93 %; MS (m/e): 472 (MH^+).
7.3.237	N2-[3-[4-(2-Chloro-6-fluorobenzyl)piperazino]propyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926717)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-[4-(2-chloro-6-fluorobenzyl)piperazino]propylamine were reacted to yield N2-[3-[4-(2-chloro-6-fluorobenzyl)piperazino]propyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.79 (d, 1H, J= 3.0 Hz), 7.37 (d, 1H, J= 2.4 Hz), 7.19-7.15 (m, 2H), 7.00-6.93 (m, 2H), 6.81 (d, 1H, J= 8.7 Hz), 6.56 (d, 1H, J= 2.7 Hz), 5.48 (bs, 1H), 4.27-4.21 (m, 4H), 3.70 (d, 2H, J= 1.8 Hz), 3.36 (q, 2H, J= 6.3 Hz), 2.68-2.35 (m, 10H), 1.75 (q, 2H, J= 6.3 Hz); ^{19}F NMR ($CDCl_3$): - 31693, - 48483; LCMS: ret. time: 18.20 min.; purity: 97 %; MS (m/e): 532 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.238	N2-(4-*tert*-Butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]- 2,4-pyrimidinediamine (R926719)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-(4-*tert* -butylphenyl]-2-chloro-5-fluoro-4-pyrimidineamine and 5-amino-2,3-dihydro-2-(methoxycarbonyl)benzofuran were reacted to yield N2-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.16 (bs, 1H), 9.84 (bs, 1H), 8.16 (d, 1H, J= 5.4 Hz), 7.56 (d, 2H, J= 8.1 Hz), 7.49 (s, 1H), 7.35 (d, 2H, J= 8.7 Hz), 7.13 (dd, 1H, J= 1.8 and 8.7 Hz), 6.78 (d, 1H, J= 8.7 Hz), 5.35 (dd, 1H, J= 6.6 and 10 5 Hz), 3.52 (dd, 1H, J= 10.5 and 16.5 Hz), 3.20 (dd, 1H, J= 6.6 and 16.5 Hz), 1 27 (s, 9H); LCMS: ret. time: 26.52 min.; purity: 96 %; MS (m/e): 437 (MH^+).
7.3.239	N4-[(5-Chloro-1-benzothiophen-3-yl)methyl]-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926721)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(5-chloro-1-benzothiophen-3-yl)methyl]-5-fluoro-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to yield N4-[(5-chloro-1-benzothiophen-3-yl)methyl]-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.08 (d, 1H, J= 1.8 Hz), 8.02 (d, 1H, J= 8.7 Hz), 7.97 (d, 1H, J= 4.8 Hz), 7.63 (s, 1H), 7.42 (dd, 1H, J= 1.8 and 9.3 Hz), 7.07 (bs, 1H), 6 85 (dd, 1H, J= 2.4 and 8.7 Hz), 6.56 (d, 1H, J= 8.7 Hz), 4.77 (s, 1H), 4.75 (s, 1H), 4.14 (s, 4H); LCMS: ret. time: 25.89 min.; purity: 97 %; MS (m/e): 444 (MH^+).
7.3.240	N4-[(5-Chloro-1-benzothiophen-3-yl)methyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926722)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(5-chloro-1-benzothiophen-3-yl)methyl]-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to yield N4-[(5-chloro-1-benzothiophen-3-yl)methyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.47 (bs, 1H), 9.33 (bs, 1H), 8.78 (bs, 1), 8.11 (d, 1H, J= 2.1 Hz), 8.02 (d, 1H, J= J= 8.7 Hz), 7.98 (d, 1H, J= 4.5 Hz), 7.69 (s, 1H), 7.41 (dd, 1H, J= 1.8, 8.1 Hz), 7.07 (bs, 1H), 6.92 (d, 1H, J= 8.4 Hz), 6.82 (t, 1H, J= 8.1 Hz), 6.34 (d, 1H, J= 6.9 Hz), 4.80 (s, 1H), 4.78 (s, 1H); LCMS: ret. time: 23.32 min.; purity: 93 %; MS (m/e): 402 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.241	N4-[2-[(2-Chloro-6-fluorobenzyl)thio]ethyl]-N2-(3,4-ethylenedioxy)-5-fluoro-2,4-pyrimidinediamine (R926723)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[2-[(2-chloro-6-fluorobenzyl)thio]ethyl]-5-fluoro-4-pyrimidineamine and 1,4-benzodioxan-6-amine were reacted to yield N4-[2-[(2-chloro-6-fluorobenzyl)thio]ethyl]-N2-(3,4-ethylenedioxy)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.09 (bs, 1H), 7.94 (bs, 1H), 7.87 (d, 1H, J= 4.2 Hz), 7.34-7.30 (m, 2H), 7.24-7.18 (m, 2H), 7.01 (dd, 1H, J= 2.4 and 8.7 Hz), 6.68 (d, 1H, J= 8.7 Hz), 4.11 (s, 4H), 3.83 (d, 2H, J= 1.2 Hz), 3.63-3.56 (m, 2H), 2.74 (t, 2H, J= 7.5 Hz); LCMS: ret. time: 25.17 min.; purity: 92 %; MS (m/e): 466 (MH^+).
7.3.242	N2-(2,3-Dihydro-1,4-benzodioxin-6-ylmethyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945168)	In a manner analogous to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 2,3-dihydro-1,4-benzodioxin-6-ylmethylamine gave N2-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$) δ 4.24 (s, 4 H), 4.45 (d, J= 6.0 Hz, 2 H), 6.55 (ddd, J= 0.9, 2.4 and 8.4 Hz, 1 H), 6.66 (d, 1 H), 6.84 (m, 4 H), 6.90 (m, 1 H), 7.14 (t, J= 8.1 Hz, 1 H), 7.30 (m, 1 H), 7.86 (d, J= 3.3 Hz, 1 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -170.44; LCMS: ret. time: 18.33 min.; purity: 96.75%; MS (m/e): 369.03 (MH^+).
7.3.243	N4-[2-[(2-Chloro-6-fluorobenzyl)thio]ethyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926724)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[2-[(2-chloro-6-fluorobenzyl)thio]ethyl]-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to yield N4-[2-[(2-chloro-6-fluorobenzyl)thio]ethyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (methyl sulfoxide-d_6): δ 9.76 (bs, 1H), 9.42 (bs, 1H), 8.70 (bs, 1H), 8.02 (d, 1H, J= 5.1 Hz), 7.33-7.30 (m, 2H), 7.24-7.18 (m, 1H), 7.08-6.96 (m, 2H), 6.42 (d, 1H, J= 4.6 Hz), 3.82 (d, 2H, J= 1.2 Hz), 3.68-3.61 (m, 2H), 2.77 (t, 2H, J= 7.2 Hz); LCMS: ret. time: 23.00 min.; purity: 93 %; MS (m/e): 424 (MH^+).
7.3.244	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3-phenyl-5-methylisoxazol-4-yl)-2,4-pyrimidinediamine (R926743)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 5-methyl-3-phenyl-4-isoxazolamine were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-phenyl-5-methylisoxazol-4-yl)-2,4-pyrimidinediamine. LCMS: ret. time: 20.90 min.; purity: 96 %; MS (m/e): 420 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.245	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3,5-dimethylisoxazol-4-yl)-2,4-pyrimidinediamine (R926744)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3,5-dimethyl-4-isoxazolamine were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3,5-dimethylisoxazol-4-yl)-2,4-pyrimidinediamine. LCMS: ret. time: 18.89 min.; purity: 98 %; MS (m/e): 358 (MH^+).
7.3.246	N2-[2-(Ethoxycarbonylmethylenethio)pyridin-5-yl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926727)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 5-amino-2-(ethoxycarbonylmethylenethio)pyridine were reacted to yield N2-[2-(ethoxycarbonylmethylenethio)pyridin-5-yl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.30 (s, 1H), 9.22 (s, 1H), 8.62 (d, 1H, J= 2.4 Hz), 8.06-8.01 (m, 2H), 7.25 (d, 1H, J= 2.4 Hz), 7.18-7.14 (m, 2H), 6.80 (d, 1H, J= 6 0 Hz), 4.22 (bs, 4H), 4.07 (q, 2H, J= 6.9 Hz), 3.95 (s, 2H), 1.14 (t, 3H, J= 6.9 Hz); LCMS: ret time: 21.60 min.; purity: 97 %; MS (m/e): 458(MH^+).
7.3.247	N2-[2-(Ethoxycarbonylmethyleneoxy)pyridin-5-yl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926740)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 5-amino-2-(ethoxycarbonylmethyleneoxy)pyridine were reacted to yield N2-[2-(ethoxycarbonylmethyleneoxy)pyridin-5-yl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.54 (bs, 1H), 9.14 (bs, 1H), 8.05 (s, 1H), 7.88 (d, 1H, J= 2.4 Hz), 7.54 (dd, 1H, J= 2.7 and 10.2 Hz), 7.22 (d, 1H, J= 1.8 Hz), 7.10 (dd, 1H, J= 1 8 and 8.7 Hz), 6.75 (d, 1H, J= 9.0 Hz), 6.40 (d, 1H, J= 9.9 Hz), 4.55 (s, 2H), 4.20 (bs, 4H), 4.10 (q, 2H, J= 7.2 Hz), 1.18 (t, 2H, J= 7.2 Hz).
7.3.248	5-Bromo-N2-(3,4-ethylenedioxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925797)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 5-bromo-2-chloro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to yield 5-bromo-N2-(3,4-ethylenedioxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 9.33 (s, 1H), 9.06 (s, 1H), 8.34 (s, 1H), 8.14 (s, 1H), 7.13-7.06-(m, 4H), 6.94 (bs, 1H), 6.61 (d, 1H, J= 8.7 Hz), 6.54-6.50 (m, 1H), 4.17-4.13 (m, 4H); LCMS: ret. time: 20.01 min.; purity: 93 %; MS (m/e): 416 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.249	N2-Allyl-5-bromo-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925822)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 5-bromo-2-chloro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and allylamine were reacted to yield N2-allyl-5-bromo-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.08 (s, 1H), 7.21 (t, 1H, J= 8.1 Hz), 7.02-6.97 (m, 2H), 6.71 (dd, 1H, J= 2.4 and 8.7 Hz), 5.91-5.77 (m, 1H), 5.19-5.09 (m, 2H), 3.94-3.89 (m, 2H); LCMS: ret. time: 18.33 min.; purity: 99 %; MS (m/e): 322 (MH^+).
7.3.250	5-Cyano-N2-(3,4-ethylenedioxyphenyl)-N4-(methoxycarbonylbenzyl)-2,4-pyrimidinediamine (R925820)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-cyano-N4-(methoxycarbonylbenzyl)-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to yield 5-cyano-N2-(3,4-ethylenedioxyphenyl)-N4-(methoxycarbonylbenzyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.23 (s, 1H), 7.41-7.32 (m, 5H), 7.01 (d, 1H, J= 3.0 Hz), 6.86-6.71 (m, 3H), 6.54 (bs, 1H), 5.48 (d, 1H, J= 6.3 Hz), 4.31 (bs, 4H), 3.68 (s, 3H); LCMS: ret. time: 25.53 min.; purity: 97 %; MS (m/e): 418 (MH^+).
7.3.251	(R935172): N4-[4-[Ethoxycarbonyl(dimethyl)methyl]phenyl]-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[4-[ethoxycarbonyl(dimethyl)methyl]phenyl]-5-fluoro-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to produce N4-[4-[ethoxycarbonyl(dimethyl)methyl]phenyl]-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.31 (s, 1H), 8.97 (s, 1H), 8.03 (d, 1H, J = 3.5 Hz), 7.70 (d, 2H, J = 8.8 Hz), 7.29 (d, 1H, J = 2.3 Hz), 7.23 (d, 2H, J = 8.8 Hz), 6.98 (dd, 1H, J = 2.1 and 8.8 Hz), 6.66 (d, 1H, J = 8.2 Hz), 4.19-4.15 (m, 4H), 4 07 (qt, 2H, J = 7.0 Hz), 1.48 (s, 6H), 1.10 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 24.51 min.; purity: 100%; MS (*m/e*): 453 (MH^+).
7.3.252	(R935173): N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-pyrimidine-2,4-diamine, N4-[4-[ethoxycarbonyl(dimethyl)methyl]phenyl]-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine was reduced with DIBALH to give N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.23 (s, 1H), 8.94 (s, 1H), 8.01 (d, 1H, J = 3.5 Hz), 7.63 (d, 2H, J = 8.8 Hz), 7.31-7.27 (m, 3H), 6.98 (dd, 1H, J= 2.9 and 8.8 Hz), 6.65 (d, 1H, J = 8.8 Hz), 4.65 (t, 1H, J = 5.3 Hz), 4.17-4.16 (m, 4H), 3.39 (d, 2H, J = 5.2 Hz), 1.20 (s, 6H). 8.9 Hz), LCMS: ret. time: 19.52 min.; purity: 100%; MS (*m/e*): 411 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.253	R935182: 5-Fluoro-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3,4-propylenedioxyphenyl)-4-pyrimidineamine and 4-(methoxycarbonylmethyleneoxy)aniline were reacted to produce 5-fluoro-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.16 (s, 1H), 9 01 (s, 1H), 8.10 (d, 1H, J= 4.1 Hz), 7.51 (d, 2H, J= 8.8 Hz), 7.37 (d, 1H, J= 2.9 Hz), 7.32 (dd, 1H, J= 2.9 and 8.8 Hz), 6.98 (d, 1H, J= 8.3 Hz), 6.80 (d, 2H, J= 8 3 Hz), 4.70 (s, 2H), 4.12-4 05 (app qt, 4H, J= 5.3 Hz), 3.68 (s, 3H), 2.07 (q, 2H, J= 5.3 Hz); LCMS: ret. time: 20.51 min.; purity: 97%; MS (*m/e*): 441 (MH^+)
7.3.254	R935185: 5-Fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3,4-propylenedioxyphenyl)-4-pyrimidineamine and 3-(methoxycarbonylmethyleneoxy)aniline were reacted to produce 5-fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.22 (s, 1H), 9.18 (s, 1H), 8.07 (d, 1H, J= 3.5 Hz), 7.41-7.35 (m, 2H), 7.32-7.28 (m, 2H), 7.09 (t, 1H, J= 8.2 Hz), 6.90 (d, 1H, J= 8.2 Hz), 6.43 (dd, 1H, J= 2.3 and 8.8 Hz), 4.65 (s, 2H), 4.11-4.04 (app q, 4H, J= 5.3 Hz), 3.67 (s, 3H), 2.06 (q, 2H, J= 5.3 Hz); LCMS: ret. time: 20.57 min.; purity: 97%; MS (*m/e*): 441 (MH^+).
7.3.255	R935187: N4-[3-(1-Bis(ethoxycarbonyl)ethoxy)phenyl]-5-fluoro-N2-[4-isopropoxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine and 3-[1-bis(ethoxycarbonyl)ethoxy]aniline were reacted to provide N4-[3-(1-bis(ethyloxycarbonyl)ethoxy)phenyl]-5-fluoro-N2-[4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.08 (s, 1H), 9.98 (s, 1H), 8.19 (d, 1H, J= 4.7 Hz), 7.55 (d, 2H, J= 8.8 Hz), 7.25 (d, 1H, J= 8.8 Hz), 7.15 (d 1H, J= 8.3 Hz), 7.13 (d, 1H, J= 8.3 Hz), 6.91 (d, 2H, J= 8.8 Hz), 6.51 (dd, 1H, J= 1.7 and 8.3 Hz), 4.56 (q, 1H, J= 5.8 Hz), 4.19 (qt, 4H, J= 7.0 Hz), 1.61 (s, 3H), 1.23 (d, 6H, J= 5.8 Hz), 1.14 (t, 6H, J= 7.0 Hz); LCMS: ret. time: 15.23 min.; purity: 94%; MS (*m/e*): 527 (MH^+).
7.3.256	R935190: N4-(3,4-Ethylenedioxyphenyl)-5-fluoro - N2-(indazolin-6-yl) - 2,4-pyrimidinediamine.	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 6-aminoindazole were reacted to produce N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(indazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.69 (s, 1H), 9.62 (s, 1H), 8.14 (d, 1H, J= 4.7 Hz), 7.93 (s, 1H), 7.92 (s, 1H), 7.60 (d, 1H, J= 8.8 Hz), 7.33-7.31 (m 1H), 7.24 (dd, 2H, J= 1.7 and 8.8 Hz), 6.79 (d, J= 8.8 Hz), 4.20 (s, 4H); LCMS: ret. time: 17.66 min.; purity: 99%; MS (*m/e*): 379 (MH^+)

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Section Number	Name of compound and reference number	Experimental
7.3.257	R935191: 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(indazolin-6-yl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine and 5-aminoindazole were reacted to give 5-fluoro N4-(3-hydroxyphenyl)-N2-(indazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.74 (s, 1H), 9.66 (s, 1H), 8.18 (d, 1H, J= 4.1 Hz), 7.95 (s, 1H), 7.93 (s, 1H), 7.59 (d, 1H, J= 8.8 Hz), 7.33-7.26 (m, 2H), 7.12-7.07 (m, 2H), 6.52 (dd, 1H, J= 2.3 and 8.2 Hz); LCMS: ret. time: 15.27 min.; purity: 99%; MS (*m/e*): 337 (MH^+)
7.3.258	R935193: N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(1-methyl-indazoline-5-yl)-2,4-imidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine and 1-methyl-5-aminoindazole were reacted to give N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.42 (s, 2H), 8.25 (d, 1H, J= 5.2 Hz), 7.92 (s, 1H), 7.86 (app s, 1H), 7.61 (d, 1H, J= 8.8 Hz), 7.38 (dd, 1H, J= 2.3 and 9.3Hz), 7.21 (d, 1H, J= 2.3 Hz), 7.09 (dd, 1H, J= 2.3 and 8.8 Hz): 6.79 (d, 1H, J= 8.8 Hz), 4.20 (s, 4H), 4.02 (s, 3H); LCMS: ret. time: 19.09 min.; purity: 99%; MS (*m/e*): 393 (MH^+).
7.3.259	R935194: 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(1-methy-indazoline-5-yl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 1-methyl-5-aminoindazole to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-(1-methy-indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.56 (s, 1H), 10.49 (s, 1H), 8.29 (d, 1H, J= 5.2 Hz), 7.98 (d, 1H, J= 1.7 Hz), 7.92 (s, 1H), 7.59 (d, 1H, J= 8.8 Hz), 7.36 (dd, 1H, J= 1.7 and 8.8 Hz), 7.10 (br m, 3H), 6.66 (td, 1H, J= 1.7 and 7.0 Hz), 4.01 (s, 3H). LCMS: ret. time: 16.62 min.; purity: 98%; MS (*m/e*): 351 (MH^+).
7.3.260	R935197: 5-Fluoro-N2-(indazoline-5-yl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine:	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 5-aminoindazoline to produce 5-fluoro-N2-(indazoline-5-yl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. . ^{1}H NMR (DMSO-d6): δ 9.96 (s, 1H), 9.76 (s, 1H), 8.12 (d, 1H, J= 4.6 Hz), 7.94 (s, 1H), 7.92 (s, 1H), 7.53 (d, 2H, J= 9.8 Hz), 7.46 (d, 1H, J= 8.8 Hz), 7.34 (dd, 1H, J= 1.7 and 9.8 Hz), 6.83 (d, 2H, J= 9.8 Hz), 4.55 (q, 1H, J= 5.8 Hz), 1.24 (d, 6H, J= 5.8 Hz). LCMS: ret. time: 18.96 min.; purity: 100%; MS (*m/e*): 379 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.261	R935198: N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3,4-ethylenedioxyphenyl)-4-pyrimidineamime and 5-aminoindazole were reacted to give N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.91 (s, 1H), 9.82 (s, 1H), 8.13 (d, 1H, J= 4.6 Hz), 7.94 (app s, 2H), 7.47 (d, 1H, J= 8.8 Hz), 7.36 (dd, 1H, J= 1.7 and 8.8 Hz), 7.23 (d, 1H, J= 2.3 Hz), 7.13(dd, 1H, J= 2.3 and 8.8 Hz), 6.76 (d, 1H, J= 8.8 Hz), 4.20 (s, 4H); LCMS: ret. time: 16.17 min.; purity: 99%; MS (*m/e*): 379 (MH^+).
7.3.262	R935199: 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(indazoline-5-yl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamime and 5-aminoindazole were reacted to give 5-fluoro-N4-(3-hydroxyphenyl)-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.78 (s, 1H), 9.68 (s, 1H), 9.49 (br s, 1H), 8.13 (d, 1H, J= 4.6 Hz), 8.06 (s, 1H), 7.93 (s, 1H), 7.50 (d, 1H, J= 8.8 Hz), 7.38 (dd, 1H, J= 1.7 and 8.8 Hz), 7.17 (d, 1H, J= 8.2 Hz), 7.11-7.06 (m, 2H), 6.57 (dd, 1H, J= 1.1 and 8.2 Hz). LCMS: ret. time: 13.79 min.; purity: 96%; MS (*m/e*): 337 (MH^+).
7.3.263	R935203: 5-Fluoro-N2-(4-isopropoxyphenyl)-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1-methyl-indazoline-5-yl)-4-pyrimidineamine and 4-isopropoxyaniline were reacted to produce 5-fluoro-N2-(4-isopropoxyphenyl)-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.57 (s, 1H), 10.12 (s, 1H), 8.24 (d, 1H, J= 5.3 Hz), 8.04 (s, 1H), 7.95 (s, 1H), 7.63 (d, 1H, J= 9.3 Hz), 7.55 (dd, 1H, J= 1.7 and 8.8 Hz), 7.30 (d, 2H, J= 9.4 Hz), 6.82 (d, 2H, J= 8.8 Hz), 4.53 (q, 1H, J= 6.4 Hz), 4.02 (s, 3H), 1.22 (d, 6H, J= 6.4 Hz). LCMS: ret. time: 20.56 min.; purity: 99%; MS (*m/e*): 393 (MH^+).
7.3.264	R935204: 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1-methyl-indazoline-5-yl)-4-pyrimidineamine and 3-aminophenol were reacted to produce 5-fluoro-N2-(3-hydroxyphenyl)-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine.. LCMS: ret. time: 15.55 min.; purity: 98%; MS (*m/e*): 351 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.265	R935207: N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-methoxycarbonyl-fur-4-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro- N-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 4-(4-aminophenoxymethyl)-2-methoxycarbonyl-furan to give N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-methoxycarbonyl-fur-4-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.48 (s, 1H), 9.41 (s, 1H), 8.08 (d, 1H, J= 3.4 Hz), 7.37-7.10 (m, 6H), 6.74 (d, 2H, J= 8.2 Hz), 6.61 (d, 1H, J= 8.2 Hz), 5.00 (s, 2H), 4.19 (br s, 4H), 3.79 (s, 3H). LCMS: ret. time: 22.85 min.; purity: 97%; MS (*m/e*): 493 (MH^+).
7.3.266	R935208: N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-(methoxycarbonyl)methyl-indazoline to produce N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.39 (s, 1H), 9.19 (s, 1H), 8.08 (d, 1H, J= 3.5 Hz), 7.95 (s, 1H), 7.91 (s, 1H), 7.56 (d, 1H, J= 8 2 Hz), 7.32 (d, 2H, J= 8.9 Hz), 7.22 (dd, 1H, J= 2.9 and 8.2 Hz), 6.78 (d, 1H, J= 8.8 Hz), 5.06 (s, 2H), 4.21 (s, 4H), 3.61 (s, 3H) LCMS: ret. time: 19.39 min.; purity: 93%; MS (*m/e*): 451 (MH^+).
7.3.267	R935209: 5-Fluoro-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1-methyl-indazoline-5-yl)-4-pyrimidineamine and 4-(methoxycarbonylmethyleneoxy)aniline were reacted to provide 5-fluoro-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.31 (s, 1H), 8.99 (s, 1H), 8.17 (s, 1H), 8.02 (d, 1H, J= 3.5 Hz), 7.92 (s, 1H), 7.59 (s, 2H), 7.50 (d, 2H, J= 8.8 Hz), 6.73 (d, 2H, J= 8.8 Hz), 4.69 (s, 2H), 4.03 (s, 3H), 3.68 (s, 3H). LCMS: ret. time: 17.60 min.; purity: 99%; MS (*m/e*): 423 (MH^+).
7.3.268	R935214: 5-Fluoro-N2-(3,5-dimethoxyphenyl)-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1-methyl-indazoline-5-yl)-4-pyrimidineamine and 3,5-dimethoxyaniline were reacted to produce 5-fluoro-N2-(3,5-dimethoxyphenyl)-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.34 (s, 1H), 9.09 (s, 1H), 8.20 (d, 1H, J= 5.3 Hz), 8.07 (d, 1H, J= 3.5 Hz), 7.90 (s, 1H), 7.63-7.55 (m, 2H), 6.89 (d, 2H, J= 1.7 Hz), 6.02 (t, 1H, J= 2.3 Hz), 4.02 (s, 3H), 3.54 (s, 6H). LCMS: ret. time: 18.81 min.; purity: 97%; MS (*m/e*): 395 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.269	R935215: 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-(methoxycarbonyl)methyl-indazoline to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 16.08 min.; purity: 90%; MS (*m/e*): 408 (MH^+).
7.3.270	R935218: 5-Fluoro-N2-(4-isopropoxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-4-pyrimidineamine was reacted with 4-isopropoxyaniline to provide 5-fluoro-N2-(4-isopropoxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 9.47 (s, 1H), 8.99 (s, 1H), 8.10 (s, 1H), 8.07 (d, 1H, J= 4.1 Hz), 8.02 (s, 1H), 7.68 (d, 1H, J= 8.8 Hz), 7.50-7.46 (m, 3H), 6.74 (d, 2H, 8.8 Hz), 5.26 (s, 2H), 4.47 (q, 1H, J= 5.8 Hz), 3.62 (s, 3H), 1.21 (d, 6H, J= 5.8 Hz). LCMS: ret. time: 21.76 min.; purity: 97%; MS (*m/e*): 451 (MH^+).
7.3.271	R935219: N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-4-pyrimidineamine was reacted with 3,4-ethylenedioxyaniline to provide N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 9.48 (s, 1H), 9.01 (s, 1H), 8.10 (s, 1H), 8.09 (d, 1H, J= 3.5 Hz), 8.01 (s, 1H), 7.68 (d, 1H, J= 8.8 Hz), 7.48-7.43 (m, 1H), 7.29 (d, 1H, J= 2.3 Hz), 6.99 (d, 1H, J= 2.3 and 8 2 Hz), 6.67 (dd, 1H, J= 2.3 and 8.8 Hz), 5.27 (s, 2H), 4.15 (s, 4H), 3.62 (s, 3H). LCMS: ret. time: 18.99 min.; purity: 93%; MS (*m/e*): 451 (MH^+).
7.3.272	R935220: 5-Fluoro-N2-(3-hydroxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-4-pyrimidineamine was reacted with 3-aminophenol to provide 5-fluoro-N2-(3-hydroxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 9.51 (s, 1H), 9.19 (s, 1H), 9.10(s, 1H), 8.21 (s, 1H), 8 12 (d, 1H, J= 3.5 Hz), 8.02 (s, 1H), 7.68 (d, 1H, J= 8.8 Hz), 7.49-7.45 (m 1H), 7 16 (s, 1H), 7.09 (d, 1H, J= 7.6 Hz), 6.95 (app t, 1H, J= 7.6 and 8.2 Hz), 6.31 (dd, 1H, J= 1.7 and 7.6 Hz), 5.29 (s, 2H), 3.62 (s, 3H). LCMS: ret. time: 16.16 min.; purity: 97%; MS (*m/e*): 409 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.273	N4-(3,4-Ethylenedioxyphenyl)-N2-(3-furanylmethylene)-5-fluoro-2,4-pyrimidinediamine (R950203)	In like manner to the preparation of N4-(3-aminophenyl)-N2-[2-(methoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-aminomethylenefurane were reacted to give N4-(3,4-ethylenedioxyphenyl)-N2-(3-furanylmethylene)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 19.99 min.; purity: 88.4%; MS (m/e): 343.07 (MH^+).
7.3.274	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[(4-methoxyphenyloxy)ethyl]-2,4-pyrimidinediamine (R950204)	In like manner to the preparation of N4-(3-aminophenyl)-N2-[2-(methoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 2-(4-methoxyphenyloxy)ethyl amine were reacted to give N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[(4-methoxyphenyloxy)ethyl]-2,4-pyrimidinediamine. LCMS: ret. time: 22.74 min.; purity: 91.9%; MS (m/e): 413.05 (MH^+).
7.3.275	N2-[2,3-Dihydrobenzo[b]furan-5-ylmethyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950205)	In like manner to the preparation of N4-(3-aminophenyl)-N2-[2-(methoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 2,3-dihydrobenzo[b]furan-5-ylmethylamine were reacted to give N2-[2,3-dihydrobenzo[b]furan-5-ylmethyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 21.43 min.; purity: 97.5%; MS (m/e): 395.05 (MH^+).
7.3.276	N2-(2,3-Dihydro-1,4-benzodioxin-2-ylmethyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950206)	In like manner to the preparation of N4-(3-aminophenyl)-N2-[2-(methoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 2,3-dihydro-1,4-benzodioxin-2-ylmethylamine were reacted to give N2-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 22.49 min.; purity: 87.6%; MS (m/e): 411.01 (MH^+).
7.3.277	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(methylthio)-1,3-benzothiaz-6-yl]-2,4-pyrimidinediamine (R950201)	In like manner to the preparation of N4-(3-aminophenyl)-N2-[2-(methoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 2-(methylthio)-1,3-benzothiazol-6-amine were reacted to give N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(methylthio)-1,3-benzothiaz-6-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 22.67 min.; purity: 76.9%; MS (m/e): 441.91 (MH^+).
7.3.278	N2-[2,3-Dihydrobenzo[b]furan-5-ylmethyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R950213)	In like manner to the preparation of N4-(3-aminophenyl)-N2-[2-(methoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 2,3-dihydrobenzo[b]furan-5-ylmethylamine were reacted to N2-[2,3-dihydrobenzo[b]furan-5-ylmethyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 17.80 min.; purity: 99.2%; MS (m/e): 353.08 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.279	N2-(2,3-Dihydro-1,4-benzodioxin-2-ylmethyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R950214)	In like manner to the preparation of N4-(3-aminophenyl)-N2-[2-(methoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 2,3-dihydro-1,4-benzodioxin-2-ylmethylamine were reacted to give N2-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 19.26 min.; purity: 96.2%; MS (m/e): 369.08 (MH^+).
7.3.280	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(methylthio)-1,3-benzothiaz-6-yl)-2,4-pyrimidinediamine (R950212)	In like manner to the preparation of N4-(3-aminophenyl)-N2-[2-(methoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 2-(methylthio)-1,3-benzothiazol-6-amine were reacted to give 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(methylthio)-1,3-benzothiaz-6-yl)-2,4-pyrimidinediamine. LCMS: ret. time: 19.83 min.; purity: 98.9%; MS (m/e): 399.98 (MH^+).
7.3.281	N2-(3-Aminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R950227)	In like manner to the preparation of N4-(3-aminophenyl)-N2-[2-(methoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 1,3-diaminobenzene were reacted to give N2-(3-aminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 11.89 min.; purity: 97.6%; MS (m/e): 312.05 (MH^+).
7.3.282	N2-(1,4-Benzoxazin-6-yl)]-5-fluoro-N4-(3-nitrophenyl)-2,4-pyrimidinediamine (R950253)	In like manner to the preparation of N4-(3-aminophenyl)-N2-[2-(methoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 6-amino-1,4-benzoxazine were reacted to give N2-(1,4-benzoxazin-6-yl)]-5-fluoro-N4-(3-nitrophenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 18.52 min.; purity: 99.5%; MS (m/e): 382.93 (MH^+).
7.3.283	N2-(Ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R950215)	In like manner to the preparation of N4-(3-aminophenyl)-N2-[2-(methoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-ethoxycarbonylmethyleneaminophenylaniline were reacted to N2-(ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 18.90 min.; purity: 83.4%; MS (m/e): 398 06 (MH^+).
7.3.284	N2-(Ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine (R950229)	In like manner to the preparation of N4-(3-aminophenyl)-N2-[2-(methoxycarbonyl)-benzofurane-5-yl]-5-fluoro-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-ethoxycarbonylmethyleneaminophenylaniline were reacted to N2-(ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 16.37 min.; purity: 78.3%; MS (m/e): 441.03 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.285	5-Cyano-N2-(3-hydroxyphenyl)-N4-(methoxycarbonylbenzyl)-2,4-pyrimidinediamine (R925821)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-cyano-N4-(methoxycarbonylbenzyl)-4-pyrimidineamine and 3-hydroxyaniline were reacted to yield 5-cyano-N2-(3-hydroxyphenyl)-N4-(methoxycarbonylbenzyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.27 (s, 1H), 7.38-7.28 (m, 5H), 7.19-7.07 (m, 2H), 6.98-6.91 (m, 2H), 6.64 (d, 1H, J= 6.6 Hz), 3.55 (s, 3H); LCMS: ret. time: 24.18 min.; purity: 98 %; MS (m/e): 376 (MH^+).
7.3.286	5-Fluoro-N4-[2-fluoro-4-(methoxymethyleneoxy)phenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926680)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(2-fluoro-4-methoxymethyleneoxyphenyl)-4-pyrimidineamine and 3-hydroxyaniline were reacted to yield 5-fluoro-N4-(2-fluoro-4-methoxymethyleneoxyphenyl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine.
7.3.287	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[(1H)-indol-5-yl]-2,4-pyrimidinediamine (R926748)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 5-aminoindole were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[(1H)-indol-5-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 20.37 min.; purity: 97 %; MS (m/e): 378 (MH^+).
7.3.288	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[(1H)-indol-5-yl]-2,4-pyrimidinediamine (R926749)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 5-aminoindole were reacted to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-[(1H)-indol-5-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 17.31 min.; purity: 94 %; MS (m/e): 366 (MH^+).
7.3.289	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[(1H)-indol-6-yl]-2,4-pyrimidinediamine (R926750)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 6-aminoindole were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[(1H)-indol-6-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 20.80 min.; purity: 91 %; MS (m/e): 378 (MH^+).
7.3.290	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[(1H)-indol-6-yl]-2,4-pyrimidinediamine (R926751)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 6-aminoindole were reacted to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-[(1H)-indol-6-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 18.13 min.; purity: 96 %; MS (m/e): 336 (MH^+).

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7.3.291	N4-[4-(Aminocarbonylmethyleneoxy)phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945063)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 3-hydroxyaniline (110 mg, 1 mmol) and N4-[4-(aminocarbonylmethyleneoxy)phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (80 mg, 0.27 mmol) gave N4-[4-(aminocarbonylmethyleneoxy)phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (75 mg, 76%). ^{1}H NMR (acetone-d_6): δ δ 4.51 (s, 2 H), 6.64 (dm, J= 8.4 Hz, 1 H), 7.06-7.14 (m, 5 H), 7.70 (dd, J= 2.4 and 9.0 Hz, 2 H), 8.27 (d, J= 6.0 Hz, 1 H); ^{19}F NMR (282 MHz, acetone-d_6): δ - 164.00; LCMS: ret. time: 14.66 min.; purity: 88.63%; MS (m/e): 370.00 (MH^+).
7.3.292	N4-[4-(Cyanomethyleneoxy)phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945071)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-hydroxyaniline (94 mg, 0.86 mmol) and 2-chloro-N4-[4-(cyanomethyleneoxy)phenyl]-5-fluoro-4-pyrimidineamine (80 mg, 0.29 mmol) gave N4-[4-(cyanomethyleneoxy)phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (65 mg, 64%) as a off-white solid. ^{1}H NMR (acetone-d_6): δ 5.16 (s, 2 H), 6.64 (ddd, J= 1.8, 2.4 and 7.5 Hz, 1 H), 7.03 (t, J= 2.1 Hz, 1 H), 7.08-7.16 (m, 2 H), 7.19 (d, J= 9.3 Hz, 2 H), 7.77 (d, J= 9.3 Hz, 2 H), 8.30 (d, J= 5 4 Hz, 1 H), 10.04 (s, 1 H, NH), 11.33 (s, 1 H, NH); ^{19}F NMR (282 MHz, acetone-d_6): δ - 163.52; LCMS: ret. time: 17.08 min.; purity: 100%; MS (m/e): 352.13 (MH^+).
7.3.293	N4-(3-Cyanophenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945109)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-aminobenzonitrile (142 mg, 1.2 mmol) and 2,4-dichloro-5-fluoropyrimidine (100 mg, 0.6 mmol) gave 2-chloro-N4-(3-cyanophenyl)-5-fluoro-4-pyrimidineamine (128 mg, 86%) as a white solid. The reaction of 2-chloro-N4-(3-cyanophenyl)-5-fluoro-4-pyrimidineamine (50 mg, 0.2 mmol) and 3-aminophenol (66 mg, 0.6 mmol) gave N4-(3-cyanophenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (40 mg, 62%). ^{1}H NMR (acetone-d_6): δ 6.48 (ddd, J= 0.9, 2.4 and 7.8 Hz, 1 H), 7.10 (t, J= 8.1 Hz, 1 H), 7.18 (ddd, J= 1.2, 2.1 and 8.1 Hz, 1 H), 7.33 (t, J= 2.1 Hz, 1 H), 7.45 (dt, J= 1.2 and 7.8 Hz, 1 H), 7.54 (t, J= 8.1 Hz, 1 H), 8.08 (d, J= 3.3 Hz, 1 H), 8.14 (ddd, J= 1.5, 2.7 and 8.4 Hz, 1 H), 8.39 (t, J= 2.1 Hz, 1 H), 8.58 (s, 1 H, NH), 8.84 (s, 1 H, NH); ^{19}F NMR (282 MHz, acetone-d_6): δ - 167.41; LCMS: ret. time: 17.75 min.; purity: 92.39%; MS (m/e): 322.59 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.294	N4-(3-Cyanophenyl)-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945110)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-cyanophenyl)-5-fluoro-4-pyrimidineamine (50 mg, 0.2 mmol) and 4-(methoxycarbonylmethyleneoxy)aniline (109 mg, 0.6 mmol) gave N4-(3-cyanophenyl)-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (30 mg, 38%). ^{1}H NMR (acetone-d_6): δ 3.74 (s, 3 H), 4.72 (s, 2 H), 6.93 (d, J= 9.0 Hz, 2 H), 7.46 (dt, J= 1.5 and 7.5 Hz, 1 H), 7.54 (t, J= 7.8 Hz, 1 H), 7.60 (dd, J= 1.8 and 9.0 Hz, 2 H), 8.03-8.07 (m, 2 H), 8.43 (m, 1 H), 8.48 (br, 1 H, NH), 8.80 (br, 1 H, NH); ^{19}F NMR (282 MHz, acetone-d_6): δ -168.2; LCMS: ret. time: 20.24 min.; purity: 94.79%; MS (m/e): 393.98 (MH^+).
7.3.295	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(indol-3-yl)ethyl]-2,4-pyrimidinediamine (R945117)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (50 mg, 0.21 mmol) and tryptamine (100 mg, 0.62 mmol) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(indol-3-yl)ethyl]-2,4-pyrimidinediamine (40 mg, 53%). ^{1}H NMR (CD_3OD): δ 3.01 (t, J= 7.2 Hz, 2 H), 3.61 (t, J= 7.2 Hz, 2 H), 6.51 (ddd, J= 0.9, 2.1 and 8.1 Hz, 1 H), 6.96 (td, J= 0.9 and 7.2 Hz, 1 H), 7.03-7.09 (m, 3 H), 7.22 (d, J= 7.5 Hz, 1 H), 7.28-7.32 (m, 2 H), 7.53 (d, J= 7.8 Hz, 1 H), 7.72 (d, J= 4.5 Hz, 1 H); ^{19}F NMR (282 MHz, CD_3OD): δ - 171.72; LCMS: ret. time: 20.17 min.; 95.66%; MS (m/e): 364.05 (MH^+).
7.3.296	5-Fluoro-N4-(3-hydroxyphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945118)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (80 mg, 0 33 mmol) and 3-methoxycarbonylmethyleneoxyaniline (180 mg, 0.99 mmol) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (130 mg). ^{1}H NMR (acetone-d_6): δ 3.74 (s, 3 H), 4.64 (s, 2 H), 6.71 (m, 1 H), 6.80 (m, 1 H), 7.23-7.32 (m, 6 H), 8.32 (d, J= 5.1 Hz, 1 H); LCMS: ret. time: 18.37 min.; purity: 100%; MS (m/e): 384.70 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.297	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945124)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (80 mg, 0.28 mmol) and 3-methoxycarbonylmethyleneoxyaniline (154 mg, 0.85 mmol) gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (90 mg, 74%). ^{1}H NMR ($CDCl_3$): δ 3.80 (s, 3H), 4.27 (q, J= 0.9 Hz, 4H), 4.58 (s, 2H), 6.54 (ddd, J= 0.9, 2.7 and 8.1 Hz, 1H), 6.65 (d, J= 2.7 Hz, 1H), 6.86 (d, J= 8.7 Hz, 1H), 6.98 (dd, J= 2.4 and 8.4 Hz, 1H), 6.98 (br, 1 H), 7.09 (ddd, J= 1.2, 2.1 and 8.1 Hz, 1H), 7.18 (t, J= 8.1 Hz, 1H), 7.24 (d, J= 2.4 Hz, 1H), 7.32 (t, J= 2.1 Hz, 1H), 7.92 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 167.52; LCMS: ret. time: 21.64 min.; purity: 98.07%; MS (m/e): 426.99 (MH^+).
7.3.298	5-Fluoro-N4-(4-isopropoxyphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945125)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(4-isopropoxyphenyl)-4-pyrimidineamine (80 mg, 0.28 mmol) and methyl 3-aminophenoxyacete (154 mg, 0.85 mmol) gave 5-fluoro-N4-(4-isopropoxyphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (80 mg, 66%). ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.35 (s, 3H), 3.80 (s, 3H), 4.52 (p, J= 6.0 Hz, 1H), 4.55 (s, 2H), 6.53 (ddd, J= 0.9, 2.4 and 8.1 Hz, 1H), 6.69 (d, J= 2.4 Hz, 1H), 6.90 (d, J= 9.0 Hz, 2H), 7.04-7.08 (m, 2H), 7.16 (t, J= 8.1 Hz, 1H), 7.32 (t, J= 2.1 Hz, 1H), 7.47 (d, J= 8.7 Hz, 2H), 7.92 (d, J= 3.0 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 167.64; LCMS: ret. time: 24.70 min.; purity: 100%; MS (m/e): 427.00 (MH^+).
7.3.299	N2-[4-(Aminocarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945064)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-N2-(3-hydroxyphenyl))-5-fluoro-2,4-pyrimidinediamine, 4-(aminocarbonylmethyleneoxy)aniline (198 mg, 1.2 mmol) and 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (95 mg, 0.4 mmol) gave N2-[4-(aminocarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (60 mg, 41%). ^{1}H NMR (CD_3OD): δ 4.55 (s, 2H), 6.75 (dm, J= 7.5 Hz, 1H), 7.08 (d, J= 9.3 Hz, 2H), 7.18 (m, 2H), 7.22 (d, J= 8.7 Hz, 1H), 7.46 (d, J= 9.0 Hz, 2H), 8.09 (d, 1H); LCMS: ret. time: 14.38 min.; purity: 100%; MS (m/e): 370.00 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.300	5-Fluoro-N2-(3-hydroxyphenyl)-N4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945132)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyaniline (490 mg, 2.4 mmol) and 2,4-dichloro-5-fluoropyrimidine (200 mg, 1.2 mmol) gave 2-chloro-5-fluoro-N4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-4-pyrimidineamine. The reaction of 2-chloro-5-fluoro-N4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-4-pyrimidineamine (40 mg, 0.12 mmol) and 3-aminophenol (40 mg, 0.36 mmol) gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (30 mg, 62%). ^{1}H NMR ($CDCl_3$): δ 2.61 (s, 3H), 5.21 (s, 2H), 6.50 (ddd, J= 0.9, 2.4 and 7.8 Hz, 1H), 6.76 (ddd, J= 0.6, 2.4 and 9.0 Hz, 1H), 6.80-6.85 (m, 3H), 7.12 (t, J= 8.1 Hz, 1H), 7.23 (t, J= 7.8 Hz, 1H), 7.50-7.52 (m, 2H), 7.94 (d, J= 3.3 Hz, 1H), 7.98 (t, J= 2.4 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 167.19; LCMS: ret. time: 18.88 min.; purity: 100%; MS (m/e): 408.97 (MH^+).
7.3.301	N2-[4-(Aminocarbonylmethoxy)phenyl]-5-fluoro-N4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945133)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-4-pyrimidineamine (30 mg, 0.09 mmol) and 4-(aminocarbonylmethyleneoxy)aniline (45 mg, 0.27 mmol) gave N2-[4-(aminocarbonylmethyleneoxy)phenyl]-5-fluoro-N4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (10 mg, 24%). ^{1}H NMR (acetone-d_6): δ 2.62 (s, 3H), 4.43 (s, 2H), 5.19 (s, 2H), 6.77 (ddd, J= 1.2, 2.4 and 8.1 Hz, 1H), 6.94 (d, J= 9.0 Hz, 2H), 7.25 (t, J= 8.1 Hz, 1H), 7.34 (ddd, J= 0.9, 1.8, 9.0 Hz, 1H), 7.68 (d, J= 9.0 Hz, 2H), 7.81 (t, J= 2.1 Hz, 1H), 7.99 (d, J= 3.6 Hz, 1H), 8.45 (br, 1H, NH), 8.57 (br, 1H, NH); ^{19}F NMR (282 MHz, acetone-d_6): δ - 168.20; LCMS: ret. time: 16.80 min.; purity: 84.91%; MS (m/e): 466.05 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.302	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945128)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (40 mg, 0.14 mmol) and 3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyaniline (87 mg, 0.42 mmol) gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (30 mg, 47%). ^{1}H NMR ($CDCl_3$): δ 2 62 (s, 3H), 4.26 (q, J= 2 1 Hz, 4H), 5.09 (s, 2H), 6.63-6 67 (m, 2H), 6.85 (d, J= 8.4 Hz, 1H), 6.95-6.99 (m, 2H), 7.09 (dt, J= 0.9 and 6.9 Hz, 1H), 7.19 (t, J= 8.4 Hz, 1H), 7.23 (d, J= 2.4 Hz, 1H), 7.42 (t, J= 2.4 Hz, 1H), 7.92 (d, J= 3.0 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ -167.47; LCMS: ret. time: 21.26 min.; purity: 96.72%; MS (m/e): 451.01 (MH^+).
7.3.303	5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945129)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(4-isopropoxyphenyl)-4-pyrimidineamine (40 mg, 0.14 mmol) and 3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyaniline (87 mg, 0.42 mmol) gave 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (40 mg, 63%). ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 3H), 1.34 (s, 3H), 2.61 (s, 3H), 4.52 (p, J= 6.0 Hz, 1H), 5.08 (s, 2H), 6.64 (ddd, J= 1.2, 2.7 and 8.1 Hz, 1 H), 6.70 (d, J= 2.4 Hz, 1H), 6.89 (d, J= 9.0 Hz, 2H), 7.07-7.11 (m, 2H), 7.16 (t, J= 8.1 Hz, 1H), 7.38 (t, J= 2.1 Hz, 1H), 7.46 (d, J= 9.0 Hz, 2H), 7.91 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 167.55; LCMS: ret. time: 24.49 min.; 96.15%; MS (m/e) 451.08 (MH^+).
7.3.304	N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945137)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-4-pyrimidineamine (40 mg, 0.12 mmol) and 3,4-ethylenedioxyaniline (55 mg, 0.36 mmol) reacted to give N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 2 60 (s, 3H), 4.24 (q, J= 2.7 Hz, 4H), 5.21 (s, 2H), 6.74-6.78 (m, 2H), 6.81 (d, J= 8.4 Hz, 1H), 6.90 (dd, J= 1.2, 7.8 Hz, 1H), 7.01 (dd, J= 2.4 and 8.4 Hz, 1H), 7.22 (t, J= 8.4 Hz, 1H), 7.30 (d, J= 2.4 Hz, 1H), 7.48 (br, 1H), 7.94 (d, J= 3.3 Hz, 1H), 7.98 (br, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ - 168.23; LCMS: ret. time: 21.20 min.; purity: 91.09%; MS (m/e): 450.99 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.305	5-Fluoro-N2-(4-isopropoxyphenyl)-N4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945138)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-4-pyrimidineamine (40 mg, 0.12 mmol) and 4-isopropoxyaniline (55 mg, 0.36 mmol) gave 5-fluoro-N2-(4-isopropoxyphenyl)-N4-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 1.31 (s, 3H), 1.33 (s, 3H), 2.60 (s, 3H), 4.48 (p, J= 6.0 Hz, 1H), 5.20 (s, 2H), 6.74-6.78 (m, 2H), 6.87 (d, J= 9.0 Hz, 2H), 6.92 (dd, J= 1.2 and 8.4 Hz, 1H), 7.22 (t, J= 8.4 Hz, 1H), 7.50 (m, 3H), 7.94 (d, J= 3.0 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$)· δ - 168.46; *LCMS· ret. time:* 24 95 min.; purity: 73.74%; MS (m/e): 451.06 (MH^+).
7.3.306	N4-(3,5-Dimethyl-4-hydroxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945139)	Using general hydrogenation conditions, 2,6-dimethyl-4-nitrophenol was reduced to 4-amino-2,6-dimethylphenol. In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 4-amino-2,6-dimethylphenol (823 mg, 6 mmol) and 2,4-dichloro-5-fluoropyrimidine (500 mg, 3 mmol) gave 2-chloro-N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-4-pyrimidineamine. Compound 2-chloro-N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-4-pyrimidineamine (500 mg, 1.87 mmol) and 3-(methoxycarbonylmethyleneoxy)aniline (500 mg, 2.76 mmol) reacted to give N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (500 mg, 65%). ^{1}H NMR (CD_3OD): δ 2.16 (s, 6H), 3.76 (s, 3H), 4.51 (s, 2H), 6.79 (ddd, J= 0.9, 2.4 and 8.1 Hz, 1H), 7.01-7.06 (m, 2H), 7.15 (s, 2H), 7.26 (t, J= 8.1 Hz, 1H), 7.93 (d, J= 5.7 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD): δ - 163.31; LCMS: ret. time: 20.44 min.; purity: 84.25%; MS (m/e): 413.03 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.307	N4-(Benzothiophen-3-ylmethyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945146)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of benzothiophen-3-ylmethylamine (244 mg, 1.5 mmol) and 2,4-dichloro-5-fluoropyrimidine (50 mg, 0.3 mmol) gave N4-(benzothiophen-3-ylmethyl)-2-chloro-5-fluoro-4-pyrimidineamine. The reaction of N4-(benzothiophen-3-ylmethyl)-2-chloro-5-fluoro-4-pyrimidineamine and 3-aminophenol (200 mg, 1.83 mmol) gave N4-(benzothiophen-3-ylmethyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. (40 mg, 36%). ^{1}H NMR ($CDCl_3$): δ 4.45 (br, 1H), 4.95 (dd, J= 1 2 and 5.4 Hz, 2H), 5.33 (br, 1H), 6.40 (ddd, J= 1.2, 2.4 and 8.1 Hz, 1H), 6.85 (ddd, J= 0.9, 2.1 and 8.1 Hz, 1H), 6.91 (br, 1H), 7.05 (t, J= 8.1 Hz, 1H), 7.26 (m, 1H), 7 39-7.47 (m, 3H), 7.81 (dd, J= 1.2 and 5.1 Hz, 1H), 7.84 (d, J= 3.3 Hz, 1H), 7.92 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ -168.89; LCMS: ret. time: 21.91 min.; purity: 99.34%; MS (m/e): 366.96 (MH^+).
7.3.308	5-Fluoro-N2-(3-hydroxyphenyl)-N4-(3-pyridylmethyl)-2,4-pyrimidinediamine (R945147)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of benzothiophen-3-ylmethylamine (244 mg, 1.5 mmol) and 2,4-dichloro-5-fluoropyrimidine (50 mg, 0.3 mmol) gave N4-(benzothiophen-3-ylmethyl)-2-chloro-5-fluoro-4-pyrimidineamine. The reaction of N4-(benzothiophen-3-ylmethyl)-2-chloro-5-fluoro-4-pyrimidineamine and 3-aminophenol (200 mg, 1.83 mmol) gave N4-(benzothiophen-3-ylmethyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. (40 mg, 36%). ^{1}H NMR ($CDCl_3$): δ 4.45 (br, 1H), 4.95 (dd, J= 1.2 and 5.4 Hz, 2H), 5.33 (br, 1H), 6.40 (ddd, J= 1.2, 2.4 and 8.1 Hz, 1H), 6.85 (ddd, J= 0.9, 2.1 and 8.1 Hz, 1H), 6.91 (br, 1H), 7.05 (t, J= 8.1 Hz, 1H), 7.26 (m, 1H), 7.39-7.47 (m, 3H), 7.81 (dd, J= 1.2 and 5.1 Hz, 1H), 7.84 (d, J= 3.3 Hz, 1H), 7.92 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ -168.89; LCMS: ret. time: 21.91 min.; purity: 99.34%; MS (m/e): 366.96 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.308	5-Fluoro-N2-(3-hydroxyphenyl)-N4-(3-pyridylmethyl)-2,4-pyrimidinediamine (R945147)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-pyridylmethylamine (162 mg, 1.5 mmol) and 2,4-dichloro-5-fluoropyrimidine (50 mg, 0.3 mmol) were reacted to give 2-chloro-5-fluoro-N4-(3-pyridylmethyl)-4-pyrimidineamine. Then 2-chloro-5-fluoro-N4-(3-pyridylmethyl)-4-pyrimidineamine and 3-aminophenol (200 mg, 1.83 mmol) reacted to give 5-fluoro-N2-(3-hydroxyphenyl)-N4-(3-pyridylmethyl)-2,4-pyrimidinediamine (40 mg, 43%). ^{1}H NMR (CD_3OD): δ 4.71 (s, 2H), 6.38 (ddd, J= 0.9, 2.4 and 8.1 Hz, 1H), 6.88 (ddd, J= 0.9, 2.1 and 8.1 Hz, 1H), 7.00 (t, J= 8.1 Hz, 1H), 7.14 (t, J= 2.4 Hz, 1H), 7.37 (dd, J= 4.8 and 7.8 Hz, 1H), 7.73 (d, J= 3.6 Hz, 1H), 7.87 (dt, J= 2.1 and 7.5 Hz, 1H), 8.39 (dd, J= 1.2 and 7.8 Hz, 1H), 8.57 (d, J= 2.1 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD): δ - 170.99; LCMS: ret. time: 8.82 min.; purity: 92.90%; MS (m/e): 312.05 (MH^+).
7.3.309	N4-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945148)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-amino-2-chloro-6-methylphenol and 2,4-dichloro-5-fluoropyrimidine resulted 2-chloro-N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-4-pyrimidineamine. The reaction of 2-chloro-N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-4-pyrimidineamine and 3-methoxycarbonylmethyleneoxyaniline (1.95 g, 11 mmol) gave N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (850 mg, 55%). ^{1}H NMR (CD_3OD): δ 2.22 (s, 3H), 3.76 (s, 3H), 4.52 (s, 2H), 6.50 (dt, J= 2.7 and 6.3 Hz, 1H), 7.09-7.14 (m, 2H), 7.24 (t, J= 1.8 Hz, 1H), 7.30 (t, J= 1.2 Hz, 1H), 7.49 (d, J= 2.4 Hz, 1H), 7.88 (d, J= 3.9 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD): δ - 168.70; LCMS: ret. time: 20.63 min.; purity: 98.56%; MS (m/e): 432.96 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.310	N4-[(2,5-Dimethyl-3-furyl)methyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945151)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of (2,5-dimethyl-3-furyl)methylamine (188 mg, 1.5 mmol) and 2,4-dichloro-5-fluoropyrimidine (50 mg, 0.3 mmol) gave 2-chloro-N4-[(2,5-dimethyl-3-furyl)methyl]-5-fluoro-4-pyrimidineamine. The reaction of 2-chloro-N4-[(2,5-dimethyl-3-furyl)methyl]-5-fluoro-4-pyrimidineamine and 3-aminophenol (200 mg, 1.83 mmol) gave N4-[(2,5-dimethyl-3-furyl)methyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (50 mg, 51%). ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 3H), 2.23 (s, 3H), 4.39 (d, J= 5.1 Hz, 2H), 5.24 (br, 1H), 5.90 (s, 1H), 6.52 (d, J= 6.6 Hz, 1H), 6.99 (d, J= 8.1 Hz, 1H), 7.13 (t, J= 8.1 Hz, 1H), 7.29 (s, 1H), 7.71 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 167.84; LCMS: ret. time: 19.83 min.; purity: 96.32%; MS (m/e): 329.05 (MH^+).
7.3.311	N4-(3,5-Dimethyl-4-methoxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945153)	In a manner analogous to the preparation of N2,N4-bis[3-methoxy-4-(methoxycarbonyl)phenyl]-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,6-dimethyl-4-nitrophenol (1.67 g, 10 mmol), potassium carbonate (13 g, 0.1 mol) and iodomethane (2.5 mL, 50 mmol) gave 2,6-dimethyl-1-methoxy-4-nitrobenzene. Hydrogenation of 2,6-dimethyl-1-methoxy-4-nitrobenzene gave 3,5-dimethyl-4-methoxyaniline. In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-N2-(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 3,5-dimethyl-4-methoxyaniline (400 mg, 2.6 mmol) and 2,4-dichloro-5-fluoropyrimidine (200 mg, 1.2 mmol) gave 2-chloro-N4-(3,5-dimethyl-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine. The reaction of 2-chloro-N4-(3,5-dimethyl-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 3-(methoxycarbonylmethyleneoxy)aniline (650 mg, 3.6 mmol) gave N4-(3,5-dimethyl-4-methoxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (180 mg, 35%). ^{1}H NMR (CD_3OD): δ 2.20 (s, 6H), 3.70 (s, 3H), 3.74 (s, 3H), 4.52 (s, 2H), 6.76 (ddd, J= 0.9, 2.4 and 8.4 Hz, 1H), 7.03-7.08 (m, 2H), 7 24 (m, 3H), 7.96 (d, J= 5.4 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD): δ - 162.92; LCMS: ret. time: 23.13 min.; purity: 100%; MS (m/e): 427.04 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.312	N4-[4-(N-Benzylpiperazino)phenyl]-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R945155)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-N2-(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of N4-[4-(N-benzylpiperazino)phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (50 mg, 0.12 mmol) and 3,4-ethylenedioxyaniline (0.045 mL, 0.36 mmol) gave N4-[4-(N-benzylpiperazino)phenyl)]-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (40 mg, 63%). ^{1}H NMR ($CDCl_3$): δ 2.64 (t, J= 4.8 Hz, 4H), 3.20 (t, J= 4.8 Hz, 4H), 3.59 (s, 2H), 4.24 (m, 4H), 6.61 (d, 1H, NH), 6.68 (br, 1H, NH), 6.76 (d, J= 8.7 Hz, 1H), 6.88 (dd, J= 2.4 and 8.7 Hz, 1H), 6.93 (d, J= 8.7 Hz, 2H), 7.19 (d, J= 2.4 Hz, 1H), 7.28-7.36 (m, 5H), 7.47 (d, J= 8.7 Hz, 2H), 7.87 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ -168.66; LCMS: ret. time: 18.05 min.; purity: 100%; MS (m/e): 513.10 (MH^+).
7.3.313	N2-[(2,5-Dimethyl-3-furyl)methyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945162)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (50 mg, 0.21 mmol) and (2,5-dimethyl-3-furyl)methylamine (80 mg, 0.63 mmol) gave N2-[(2,5-dimethyl-3-furyl)methyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (40 mg, 59%). ^{1}H NMR (acetone-d_6): δ 2.14 (s, 6H), 4.37 (d, J= 4.2 Hz, 2H), 5.96 (s, 1H), 6.77 (d, J= 6.6 Hz, 1H), 7.23-7.28 (m, 2H), 7.44 (s, 1H), 8.11 (d, J= 4.8 Hz, 1H), 9.05 (br, 1H), 9.75 (br, 1H); ^{19}F NMR (282 MHz, acetone-d_6): δ -165.77; LCMS: ret. time: 19.23 min.; purity: 94.89%; MS (m/e): 329.08 (MH^+).
7.3.314	N2-[4-(N-Benzylpiperazino)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R945163)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylendioxyphenyl)-5-fluoro-4-pyrimidineamine (50 mg, 0 18 mmol) and 4-(4-benzylpiperazino)aniline (142 mg, 0.53 mmol) resulted N2-[4-(N-benzylpiperazino)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (30 mg, 33%). ^{1}H NMR ($CDCl_3$): δ 2.63 (t, J= 4.8 Hz, 4H), 3.16 (t, J= 4.8 Hz, 4H), 3.58 (s, 2H), 4 27 (m, 4H), 6.56 (d, 1H, NH), 6.70 (br, 1H, NH), 6.82 (d, J= 8.7 Hz, 1H), 6.89 (d, J= 9.0 Hz, 2H), 6.96 (dd, J= 2.7 and 8.7 Hz, 1H), 7.28 (d, J= 2.7 Hz, 1H), 7.30-7.36 (m, 5H), 7.39 (d, J= 8.7 Hz, 2H), 7.88 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 168.94; LCMS: ret. time: 18.12 min.; purity: 98.42%; MS (m/e): 512.95 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.315	N2-(Benzothiophen-3-ylmethyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945164)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (50 mg, 0.21 mmol) and benzothiophen-3-ylmethylamine (100 mg, 0.61 mmol) gave N2-(benzothiophen-3-ylmethyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (40 mg, 53%). ^{1}H NMR ($CDCl_3$): δ 4.82 (d, J= 6.0 Hz, 2H), 6.45 (dd, J= 8.1 Hz, 1H), 6.70 (m, 1H), 6.80 (d, J= 8.4 Hz, 1H), 7.03 (t, J= 8.1 Hz, 1H), 7.22 (m, 1H), 7.34 (s, 1H), 7.39-7.46 (m, 2H), 7.82 (m, 1H), 7.89-7.92 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 170.02; LCMS: ret. time· 21.29 min.; purity: 92.97%; MS (m/e): 367.03 (MH^+).
7.3.316	5-Fluoro-N4-(3-hydroxyphenyl)-N2-(3-pyridylmethyl)-2,4-pyrimidinediamine (R945165)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (50 mg, 0.21 mmol) and 3-pyridylmethylamine (68 mg, 0.63 mmol) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-pyridylmethyl)-2,4-pyrimidinediamine (40 mg, 62%). ^{1}H NMR ($CDCl_3$): δ 4.40 (d, J= 6.3 Hz, 2H), 5.60 (br, 1H), 6.62-6.70 (m, 3H), 7.05 (br, 1H), 7.14 (t, J= 8.1 Hz, 1H), 7.30 (dd, J= 5.1 and 7.8 Hz, 1H), 7.73 (d, J= 7.5 Hz, 1H), 7.80 (d, J= 3.3 Hz, 1H), 8.49 (d, J= 4.5 Hz, 1H), 8.66 (s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ -169.52; LCMS: ret. time: 9.41 min.; purity: 99.25%; MS (m/e): 312.01 (MH^+).
7.3.317	5-Fluoro-N4-(3-hydroxyphenyl)-N2-(2-pyridylmethyl)-2,4-pyrimidinediamine (R945166)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (50 mg, 0.21 mmol) and 2-pyridylmethylamine (68 mg, 0.63 mmol) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-pyridylmethyl)-2,4-pyrimidinediamine (40 mg, 62%). ^{1}H NMR ($CDCl_3$): δ 4.73 (d, J= 6.3 Hz, 2H), 5.85 (t, J= 6.0 Hz, 1H, NH), 6.48 (d, J= 6.9 Hz, 1H), 6.61 (dd, J= 2.7 and 8.1 Hz, 1H), 6.67 (s, 1H), 7.13 (t, J= 8.1 Hz, 1H), 7.21 (dd, J= 5.1 and 7.5 Hz, 1H), 7.49 (d, J= 7.5 Hz, 1H), 7.69 (td, J= 1.8 and 7.8 Hz, 1H), 7.85 (d, J= 3.6 Hz, 1H), 8.38 (br, 1H), 8.56 (dd, J= 1.2 and 3.9 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ -170.49; LCMS: ret. time: 10.10 min.; purity: 100%; MS (m/e): 312.08 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.318	N4-(3,5-Dimethoxyphenyl)-N2-(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926802)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,5-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine with 3-hydroxyaniline gave N4-(3,5-dimethoxyphenyl)-N2-(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 18 98 min.; purity: 90%; MS (m/e): 357 (MH^+).
7.3.319	N4-(3,5-Dimethoxyphenyl)-N2-(2-ethoxycarbonylindol-7-yl)-5-fluoro-2,4-pyrimidinediamine (R926803)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,5-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine with 2-ethoxycarbonyl-7-aminoindole gave N4-(3,5-dimethoxyphenyl)-N2-(2-ethoxycarbonylindol-7-yl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 24.21 min.; purity: 91%; MS (m/e): 452 (MH^+).
7.3.320	N2-(3,4-Dimethoxyphenyl)-N4-(4-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926108)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(4-ethoxyphenyl)-5-fluoro-4-pyrimidineamine with 3,4-dimethoxyaniline gave N2-(3,4-dimethoxyphenyl)-N4-(4-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 7.89 (d, 1H, J= 3 Hz), 7.45 (bd, 2H, J= 9 Hz), 7.20 (d, 1H, J= 2.4 Hz), 6.96-6.77 (m, 5H), 6.63 (bs, 1H), 4.03 (q, 2H, J= 7.2 Hz), 3.86 (s, 3H), 3.72 (s, 3H), 1.42 (t, 3H, J= 7.2 Hz); ^{19}F NMR (CDCl3): - 47473.
7.3.321	N4-(4-Ethoxyphenyl)-N2-(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926146)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(4-ethoxyphenyl)-5-fluoro-4-pyrimidineamine with 3-hydroxyaniline gave N4-(4-ethoxyphenyl)-N2-(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.79 (d, 1H, J= 4.2 Hz), 7.54 (dd, 2H, J= 2.4 and 7.2 Hz), 7.05-6.97 (m, 3H), 6.87 (dd, 2H, J= 2.4 and 4.2 Hz), 6.41 (m, 1H), 4.02 (q, 2H, J= 6.6 Hz), 1.38 (t, 3H, J= 6.9 Hz); ^{19}F NMR (CD_3OD): - 47444; LCMS: ret. time: 21.15 min.; purity: 98%; MS (m/e): 341 (MH^+).
7.3.322	N4-(4-Ethoxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926213)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(4-ethoxyphenyl)-5-fluoro-4-pyrimidineamine with 3,4-ethylenedioxyaniline gave N4-(4-ethoxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 7.87 (d, 1H, J= 3Hz), 7.47 (dd, 2H, J= 2.4 and 5.1 Hz), 7.18 (d, 1H, J= 2.4 Hz), 6.91-6.85 (m, 3H), 6.79-6.73 (m, 2H), 6.64 (bs, 1H), 4.25 (bs, 4H), 4.05 (q, 2H, J= 6.9 Hz), 1.43 (t, 3H, J= 7.2 Hz); ^{19}F NMR ($CDCl_3$): - 47467; LCMS: ret. time: 24.32 min.; purity: 90%; MS (m/e): 383 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.323	N4-(3,4-Dimethoxyphenyl)-N2-(4-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926145)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine with 4-ethoxyaniline gave N4-(3,4-dimethoxyphenyl)-N2-(4-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.90 (bs, 1H), 7.37 (dd, 2H, J= 2.4 and 6.3 Hz), 7.21 (d, 1H, J= 2.4 Hz), 7.03 (dd, 1H, J= 2.4 and 8 1 Hz), 6.86-6.80 (m, 4H), 6.65 (bs, 1H), 4.00 (q, 2H, J= 7.2 Hz), 3.89 (s, 3H), 3.75 (s, 3H), 1.39 (t, 3H, J= 6.9 Hz); ^{19}F NMR ($CDCl_3$): -47501; LCMS: ret. time: 22.69 min.; purity: 98%, MS (m/e): 385 (MH^+).
7.3.324	N4-(3,4-Dimethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926147)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine with 3-hydroxyaniline gave N4-(3,4-dimethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.77 (d, 1H, J= 3.3 Hz), 7.15 (d, 1H, J= 2.4 Hz), 7.05 (dd, 1H, J= 2 4 and 8.4 Hz), 7.00-6.90 (m, 4H), 6.80 (d, 1H, J= 8.1 Hz), 6.40 (m, 1H), 4.05 (q, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 1.20 (t, 3H); ^{19}F NMR (CD_3OD): - 47223; LCMS: ret. time: 17.94 min.; purity: 99%; MS (m/e): 357 (MH^+).
7.3.325	N2-(3,4-Dimethoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926113)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3,4-dimethoxyaniline gave N2-(3,4-dimethoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.90 (d, 1H, J= 6.6 Hz), 7.59 (bs, 1H), 7.30 (s, 1H), 7.20-7.10 (m, 2H), 7.00-6.75 (m, 4H), 6.59 (bd, 1H, J= 7.8 Hz), 3.87 (s, 3H), 3.84 (s, 3H); ^{19}F NMR ($CDCl_3$): - 47229; LCMS: ret. time: 17.77 min.; purity: 78%; MS (m/e): 357 (MH^+).
7.3.326	N2-(4-Ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926395)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with ethyl-4-aminophenoxyacetate gave N2-(4-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.90 (d, 1H, J= 5.1 Hz), 7.35 (dd, 2H, J= 2.1 and 7.2 Hz), 7.13 (t, 1H, J= 7.2 Hz), 7.10 9d, 1H, J= 6.6 Hz), 6.96 (dd, 2H, J= 2.4 and 7.2 Hz), 6.67 (m, 1H), 4.72 (s, 2H), 4.25 (q, 2H, J= 7.2 Hz), 1.29 (t, 3H, J= 7.2 Hz); ^{19}F NMR (CD_3OD): - 21885, LCMS: ret. time: 20.18 min.; purity: 92%; MS (m/e): 399 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.327	5-Bromo-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926396)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with ethyl 4-aminophenoxyacetate gave 5-bromo-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 21.64 min.; purity: 92%; MS (m/e): 459 (MH^+).
7.3.328	N2-(4-Ethoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926211)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-ethoxyaniline were reacted to yield N2-(4-ethoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 7.88 (bs, 1H), 7.40 (bd, 2H, J= 8.7 Hz), 7.27 (bd, 2H, J= 6.3 Hz), 6.95 (dd, 1H, J= 3 and 9 Hz), 6.86-6.77 (m, 3H), 6.58 (s, 1H), 4.28 (bs, 4H), 4.01 (q, 2H, J= 6.9 Hz), 1.40 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 24.46 min.; purity: 90%, MS (m/e): 383 (MH^+).
7.3.329	N2-(3,4-Dimethoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926212)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3,4-dimethoxyaniline were reacted to yield N2-(3,4-dimethoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 20.98 min.; purity: 74%; MS (m/e): 399 (MH^+).
7.3.330	N2-(3-Chloro-4-fluorophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926218)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-chloro-4-fluoroaniline were reacted to yield N2-(3-chloro-4-fluorophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.75 (bd, 1H), 7.70 (bd, 1H), 7.18 (m, 1H), 7.10 (m, 1H), 6.90 (m, 2H), 6.75 (m, 1H), 4.20 (bs, 4H); LCMS: ret. time: 25.04 min.; purity: 99%, MS (m/e): 392 (MH^+).
7.3.331	N2-(4-tert-Butylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926219)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-tert-butylaniline were reacted to yield N2-(4-tert-butylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 7.85 (d, 1H, J= 3.6 Hz), 7.44 (bdd, 2H, J= 6.3 Hz), 7.35-7.31 (m, 3H), 6.93 (dd, 1H, J= 2.7 and 8.7 Hz), 6.83 (d, 1H, J= 9 Hz), 6.80 (bs, 1H), 4.23 (s, 4H), 1.28 (s, 9H); LCMS: ret. time: 27.67 min.; purity: 98%; MS (m/e): 395 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.332	N4-(3,4-Ethylenedioxyphenyl)-N2-(4-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine (R926220)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-fluoroaniline were reacted to yield N4-(3,4-ethylenedioxyphenyl)-N2-(4-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.92 (bs, 1H), 7.80 (bs, 1H), 7.60 (bd, 2H), 6.90 (m, 2H), 6.80 (bs, 1H), 6.65 (bs, 1H), 4.25 (s, 4H); LCMS: ret. time: 22.87 min.; purity: 97%; MS (m/e): 357 (MH^+).
7.3.333	N4-(3,4-Ethylenedioxyphenyl)-N2-(3-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine (R926221)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-fluoroaniline were reacted to yield N4-(3,4-ethylenedioxyphenyl)-N2-(3-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.76 (d, 1H, J= 5.6 Hz), 7.39 (m, 2H), 7.14 (d, 1H, J= 2.4 Hz), 6.94-6.85 (m, 3H), 6.75 (d, 1H, J= 9 Hz), 4.21 (s, 4H); LCMS: ret. time: 22.60 min.; purity: 100%; MS (m/e): 357 (MH^+).
7.3.334	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxyethyl)-2,4-pyrimidinediamine (R926229)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 2-methoxyethylamine were reacted to yield N4-(3,4-ethylenedioxyphenyl)--5-fluoro -N2-(2-methoxyethyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.81 (bs, 1H), 7.33 (d, 1H, J= 2.4 Hz), 6.93 (dd, 1H, J= 2.4 Hz and 9 Hz), 6.81 (d, 1H, J= 9 Hz), 6.53 (s, 1H), 4.25 (bs, 2H), 3.54 (bs, 2H), 3.36 (s, 3H); LCMS: ret. time: 18.01 min.; purity: 100%; MS (m/e): 321 (MH^+).
7.3.335	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(4-methoxybenzyl)-2,4-pyrimidinediamine (R926230)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-methoxybenzylamine were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(4-methoxybenzyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.81 (d, 1H, J= 2.7 Hz), 7.27 (m, 3H), 6.86 (m, 3H), 6.52 (s, 1H). 5.14 (s, 1H), 4.46 (d, 2H, J= 5.4 Hz), 4.24 (s, 4H), 3.78 (s, 3H); LCMS: ret. time: 23.06 min.; purity: 94%; MS (m/e): 383 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.336	N2-(2,2-Difluorobenzodioxol-5-yl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926386)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 2,2-difluoro-5-aminobenzodioxole were reacted to yield N2-(2,2-difluorobenzodioxol-5-yl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 9.39 (s, 1H), 9.24 (s, 1H), 8.06 (d, 1H, J= 5.6 Hz), 7.87 (d, 1H, J= 1.8 Hz), 7.27-7.19 (m, 3H), 7.08 (dd, 1H, J= 2.4 and 8.7 Hz), 6.80 (d, 1H, J= 9Hz), 4.21 (bs, 4H); ^{19}F NMR ($CDCl_3$): -14012 and - 46487; LCMS: ret. time: 25.32 min,; purity:100%; MS (m/e): 419 (MH^+).
7.3.337	N2-(2-Ethoxycarbonylindol-5-yl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926476)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 2-ethoxycarbonyl-5-aminoindole were reacted to yield N2-(2-ethoxycarbonylindol-5-yl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.84 (d, 1H, J= 5.4 Hz), 7.76 (d, 1H, J= 3.6 Hz), 7.50 (d, 1H, J= 9 Hz), 7.23-7.15 (m, 3H), 7.03 (bd, 1H, J= 8.7 Hz), 6.78 (d, 1H, J= 8.7 Hz), 4.38 (q, 2H, J= 7.2 Hz), 4.22 (s, 4H), 1.41 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 23.58 min; purity: 100%; MS (m/e): 451 (MH^+).
7.3.338	N2-(4-Cyanomethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926480)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-cyanomethyleneoxyaniline were reacted to yield N2-(4-cyanomethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 1H, J= 3.6 Hz), 7.52 (d, 1H, J= 8.7 Hz), 7.38 (bs, 1H), 7.28 (d, 1H, J= 2.4 Hz), 6.96-6.86 (m, 3H), 6.65 (bd, 1H), 4.73 (s, 2H), 4.29 (m, 4H); ^{19}F NMR ($CDCl_3$): -47416; LCMS: ret. time: 20.49 min.; purity: 100%; MS (m/e): 394 (MH^+).
7.3.339	N2-(3-Ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926482)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and ethyl-3-aminophenoxyacetate were reacted to yield N2-(3-ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 10.53 (s, 1H), 8.18 (s, 1H), 7.67 (d, 1H, J= 4.8 Hz), 7.19-7.02 (m, 5H), 6.86 (d, 1H, 9Hz), 6.71 (dd, 1H, J= 1.8 and 9 Hz), 4.51 (s, 2H), 4.25 (m, 6H), 1.29 (t, 3H, J= 7.5 Hz); ^{19}F NMR ($CDCl_3$): - 45640; LCMS: ret. time: 22.71 min.; purity: 99%; MS (m/e): 441 (MH^+).

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7.3.340	N2-(3-Ethoxycarbonylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R925745)	In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-ethoxycarbonylaniline gave N2-(3-ethoxycarbonylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8 04 (bs, 1H), 7.94 (bs, 1H), 7.90 (bd, 1H), 7.68 (bd, 1H, J= 7.5 Hz), 7.35 (t, 1H, J= 8.1 Hz), 7.28 (d, 1H, J= 2.4 Hz), 7.07 (s, 1H), 6.93 (dd, 1H, J= 3 and 8.7 Hz), 6.83 (d, 1H, J= 9 Hz), 6.64 (bs, 1H), 4.36 (q, 2H, J= 7.2 Hz), 4.26 9s, 4H), 1 35 (t, 3H, J= 7.5 Hz); ^{19}F NMR ($CDCl_3$): - 47247; LCMS· ret time: 15.88.; purity: 100%; MS (m/e): 411 (MH^+).
7.3.341	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-hydroxyethyl)-2,4-pyrimidinediamine (R925746)	In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamineand 2-hydroxyethylamine gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-hydroxyethyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.7 (bs, 1H), 7.32 (d, 1H, J= 2.4 Hz), 7.05 (dd, 1H, J= 2.4 and 9 Hz), 6.75 (d, 1H, J= 8.9 Hz), 4.21 (s, 4H), 3.67 (t, 2H, J= 5.7 Hz), 3.38 (t, 2H, J= 5.4 Hz); ^{19}F NMR (CD_3OD): - 48518; LCMD: ret. time: 15.54 min.; purity: 100%; MS (m/e): 307 (MH^+).
7.3.342	N2-(4-Ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R925747)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamineand ethyl-4-aminophenoxyacetate gave N2-(4-oxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.88 (bs, 1H), 7.42 (dd, 2H, J= 2.4 and 6.9 Hz), 7.28 (d, 1H, J= 3 Hz), 6.95-6.81 (m, 4H), 6.59 (s, 1H), 4.59 (s, 4H), 4.28 (q, 2H, J= 6.2 Hz), 1.30 (t, 3H, J= 6.1 Hz); 19F NMR (CDCl3): - 47570; LCMS: ret. time: 22.74 min.; purity: 100%, MS (m/e): 441 (MH^+).
7.3.343	N2-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R940233)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-chloro-4-hydroxy-5-methylaniline gave N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: retn, time: 19.20 min.; purity: 94%; MS (m/e): 360 (M^+); ^{1}H NMR ($CDCl_3$): δ 7.93 (1H, d, J= 3.1 Hz), 7.54 (1H, d, J= 2.6 Hz), 7.30 (1H, t, J= 2.1 Hz), 7.21 (1H, t, J= 7.9 Hz), 7.02 (3H, m), 6.78 (1H, s), 6.61 (1H, dd, J= 7.9 Hz, J= 2.1 Hz), 2.26 (3H, s).

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Section Number	Name of compound and reference number	Experimental
7.3.344	N4-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R940235)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-chloro-4-hydroxy-5-methylphenyl)-4-pyrimidineamine with 3-hydroxyaniline gave N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: retn, time: 18.20 min.; purity: 94%; MS (m/e): 360 (M^+); 1□□□□ (DMSO-d6): δ 9.26 (1H, s), 9.23 (1H, s), 9.16 (1H, s), 8.89 (1H, s), 8.14 (1H, d, J= 4.5 Hz), 7.66 (1H, d, J= 2.1 Hz), 7.60 (1H, d, J= 2.1 Hz), 7.29 (1H, d, J= 8.4 Hz), 7.11 (1H, s), 7.06 (1H, t, J= 8.4 Hz), 6.41 (1H, d, J= 8.4 Hz), 2.30 (3H, s).
7.3.345	N2-(3,4-Dimethoxyphenyl)-5-fluoro-N4-[4-[3-(N-morpholinyl)propyl]oxyphenyl]-2,4-pyrimidinediamine (R940250)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-[4-[3-(N-morpholinyl)propyl]oxyphenyl]-4-pyrimidineamine with 3,4-dimethoxyaniline gave N2-(3,4-dimethoxyphenyl)-5-fluoro-N4-[4-[3-(N-morpholinyl)propyl]oxyphenyl]-2,4-pyrimidinediamine. LCMS: retn, time: 14.72 min.; purity: 94%; MS (m/e). 484 (MH^+); ^{1}H NMR ($CDCl_3$): δ 7.89 (1H, d, J= 3.3 Hz), 7.47 (2H, d, J= 9 Hz), 7.22 (1H, d, J= 2.2 Hz), 6.93-6.76 (5H, m), 6.64 (1H, d, J= 2.2 Hz), 4.01 (2H, t, J= 5.6 Hz), 3.86 (3H, s), 3.72 (3H, s), 3.71 (4H, m), 2.58-2.44 (6H, m), 1.97 (2H, m).
7.3.346	N2-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-[4-[3-(N-morpholinyl)propyl]oxyphenyl]-2,4-pyrimidinediamine (R940251)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-[4-[3-(N-morpholinyl)propyl]oxyphenyl]-4-pyrimidineamine with 2-chloro-4-hydroxy-5-methylaniline gave N2-(2-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-[4-[3-(N-morpholinyl)propyl]oxyphenyl]-2,4-pyrimidinediamine. LCMS: retn, time: 15.19 min.; purity: 94%; MS (m/e): 488 (MH^+); ^{1}H NMR ($CDCl_3$): δ 7.89 (1H, d, J= 3.3 Hz), 7.52 (1H, d, J= 2.5 Hz), 7.44 (2H, d, 8.7 Hz), 6.97 (1H, d, J= 2.5 Hz), 6.91 (2H, d, 9 Hz), 6.71 (1H, s), 6.64 (1H, 2.5 Hz), 4.03 (2H, t, J= 6.03 Hz), 3.74 (4H, t, J= 4.65 Hz), 2.60-2.43 (6H, m), 2.23 (3H, s), 1.49 (2H, m).
7.3.347	N4-(3,5-Dimethyl-4-hydroxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R940253)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-4-pyrimidineamine with ethyl 3-aminophenoxyacetate gave N4-(3,5-dimethyl-4-hydroxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: retn, time: 21.79 min.; purity: 91 %; MS (m/e): 427 (MH^+); 1H NMR (DMSO-d6): δ 9.80 (1H, s), 8.30 (1H, s), 8.23 (1H, d, J= 4.5 Hz), 7.37-7.17 (5H, m), 6.66 (1H, d, J= 9 Hz), 4.73 (2H, s), 4.25 (2H, q, J= 7.2 Hz), 2.23 (6H, s), 1.29 (3H, t, J= 7.0 Hz).

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Section Number	Name of compound and reference number	Experimental
7.3.348	N2-(3-*tert*-Butylphenyl)-N4-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-4-pyrimidinediamine (R940266)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine with 3-*tert*-butylaniline gave N2-(3-*tert*-butylphenyl)-N4-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-4-pyrimidinediamine. LCMS: retn, time: 28.17 min.; purity: 96 %; MS (m/e): 439 (M^+), 440 (MH^+); ^{1}H NMR (DMSO-d6): δ 9.40 (1H, s), 9.19 (1H, s), 8.21 (1H, d, J= 3.6 Hz), 7.78 (1H, d, J= 8.5 Hz) 7.60 (2H, m), 7.48 (1H, t, J= 2 Hz), 7.31 (1H, t, J= 8.5 Hz), 7.25 (1H, t, J= 8.5 Hz), 7.02 (1H, d, J= 8.5 Hz), 6.70 (1H, dd, J= 8.5 and 2 Hz), 4.79 (2H, s), 4.26 (2H, q, J= 7.2 Hz), 1.33 (9H, s), 1.29 (3H, t, J= 7.2 Hz).
7.3.349	5-Fluoro-N4-(3-isopropylphenyl)-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine and 5-fluoro-N2-(2-ethoxoxycarbonylbenzofur-5-yl)-N4 -(3-isopropylphenyl)-2,4-pyrimidinediamine R940284	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hyroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-isopropylphenyl)-4-pyrimidineamine and ethyl 3-aminophenoxyacetate were reacted to give the mixture of 5-fluoro-N4-(3-isopropylphenyl)-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine and 5-fluoro-N2-(2-ethoxoxycarbonylbenzofur-5-yl)-N4 -(3-isopropylphenyl)-2,4-pyrimidinediamine. (R = CO_2Me). LCMS: retn, time: 25.41 min.; purity: 60.61 %; MS (m/e): 411 (MH^+); 1H NMR (DMSO-d6): δ 9.38 (1H, s), 9.29 (1H, s), 8.20 (1H, d, J= 3.9 Hz), 7.85 (1H, d, J= 9.3 Hz), 7.58 (1H, t, J= 1.6 Hz), 7.43-7.33 (3H, m), 7.18 (1H, t, J= 8.2 Hz), 7.05 (1H, d, J= 7.8 Hz), 6.53 (1H, dd, J= 8.4 Hz, J= 2.1 Hz), 4.72 (2H, s), 3.79 (3H, s), 2.95 (1H, quint, J= 7.2 Hz), 1.26 (6H, d, J= 7.2 Hz) (R = CO_2Et) LCMS: retn, time: 26.99 min.; purity: 39 %; MS (m/e): 425 (MH^+); 1H NMR (DMSO-d6): δ 9.38 (1H, s), 9.29 (1H, s), 8.20 (1H, d, J= 3.9 Hz), 7.85 (1H, d, J= 9.3 Hz), 7.58 (1H, t, J= 1.6 Hz), 7.43-7.33 (3H, m), 7.18 (1H, t, J= 8.2 Hz), 7.05 (1H, d, J= 7.8 Hz), 6.53 (1H, dd, J= 8.4 and 2.1 Hz), 4.71 (2H, s), 4.25 (2H, q, J= 7.2 Hz), 2.95 (1H, quint, J= 7.2 Hz), 1.31 (3H, t, J= 7.2 Hz), 1.26 (6H, d, J= 7.2 Hz).
7.3.350	N4-(3-*tert*-Butylphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine R940281	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hyroxyphenyl)-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-2-chloro-5-fluoro-4-pyrimidineamine and 2-methoxycarbonyl-5-aminobenzofuran were reacted to give N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine. LCMS: retn, time: 26.76 min.; purity: 97 %; MS (m/e): 435 (MH^+); 1H NMR (DMSO-d6): δ 9.41 (2H, sl), 8.27 (1H, s), 8.21 (1H, d, J 3.9 Hz), 7.98 (1H, m), 7.77-7.60 (3H, m), 7.37 (1H, t, J 8.1 Hz), 7.22 (1H, d, J 8.1 Hz), 3.98 (3H, s), 1.34 (9H, s).

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Section Number	Name of compound and reference number	Experimental
7.3.351	5-fluoro-N4-(3-isopropylphenyl)-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine R940283	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hyroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-isopropylphenyl)-4-pyrimidineamine and 2-methoxycarbonyl-5-aminobenzofuran were reacted to give 5-fluoro-N4-(3-isopropylphenyl)-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine. LCMS: retn, time: 26.05 min.; purity: 99 %; MS (m/e): 420 (M^+), 422 (MH^+), ^{1}H NMR (DMSO-d6): δ 10.00 (1H, s), 9.95 (1H, s), 8.31 (1H, d, J= 4.8 Hz), 8.11 (1H, s), 7.74 (3H, m), 7.35 (1H, s), 7 35 (1H, t, J= 7.2 Hz), 7.12 (1H, d, J= 7.2 Hz), 3.99 (3H, s), 2.83 (1H, sept, J= 6.9 Hz), 1.20 (6H, d, J= 6.9 Hz).
7.3.352	N2-(1,1-Dihydroisobenzofuran-1-one-6-yl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926786)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 6-amino-1,1-dihydroisobenzofuran-1-one gave N2-(1,1-dihydroisobenzofuran-1-one-6-yl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.20 (s, 1H), 9.85 (s, 1H), 8.22 (d, 1H, J= 4.8 Hz), 8.10 (d, 1H, J= 1.2 Hz), 7.86 (dd, 1H, J= 2.4 and 8.7 Hz), 7.54 (d, 1H, J= 8.4 Hz), 7.22 (d, 1H, J= 2.4 Hz), 7.13 (dd, 1H, J= 2.1 and 9 Hz), 6.81 (d, 1H, J= 8.7 Hz), 5.34 (s, 2H), 4.20 (s, 4H); LCMS: ret. time: 17.40 min.; purity: 83%; MS (m/e): 395 (MH^+).
7.3.353	N2-[3-(3-Acetamidophenoxy)propyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926787)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 3-N-acetamidophenoxy-3-propylamine gave N2-[3-(3-acetamidophenoxy)propyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.45 (bs, 1H), 10.07 (s, 1H), 8.42 (s, 1H), 8.20 (s, 1H), 7.37 (d, 1H, J= 3 Hz), 7.31 (s, 1H), 7.20-7.05 (m, 3H), 6.83 (d, 1H, J= 9Hz), 6.53 (d, 1H, J= 6.6 Hz), 4.18 (s, 4H), 3.95 (t, 2H, J= 6 Hz), 2.48 (m, 2H), 2.07 (s, 3H), 1.96 (t, 3H, J= 7.8 Hz); LCMS: ret. time: 19.58 min.; purity: 99%; MS (m/e): 454 (MH^+).
7.3.354	N2-[4-(4,5-Dichloro-1H-imidazol-1-yl)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926788)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 4,5-dichloro-1H-imidazoleamine gave N2-[4-(4,5-dichloro-1H-imidazol-1-yl)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.10 (s, 1H), 9.85 (s, 1H), 8.20 (d, 1H, J= 4.2 Hz), 8.01 (s, 1H), 7.78 (d, 1H, J= 8.7 Hz), 7.36 (d, 1H, J= 9 Hz), 7.25 (d, 1H, J= 3 Hz), 7.14 (dd, 1H, J= 2.1 and 9 Hz), 6.85 (d, 1H, J= 8.7 Hz); LCMS: ret. time: 23.59 min.; purity: 95%; MS (m/e): 474 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.355	N2-(2,4-Dimethoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926789)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 2,4-dimethoxyaniline gave N2-(2,4-dimethoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.35 (s, 1H), 8.14 (bd, 1H), 7.38 (d, 1H, J= 9 Hz), 7.23 (s, 1H), 7.09 (d, 1H, J= 8.7 Hz), 6.79 (d, 1H, J= 8.7 Hz), 6.66 (d, 1H, J= 2.4 Hz), 6.49 (dd, 1H, J= 2.4 and 9 Hz), 4.22 (s, 4H), 3.77 (s, 6H); LCMS: ret. time· 20.93 min.; purity: 98%; MS (m/e). 399 (MH^+).
7.3.356	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(4-isopropylphenyl)-2,4-pyrimidinediamine (R926790)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 4-isopropylaniline gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(4-isopropylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.30 (s, 1H), 10.50 (s, 1H), 8.22 (d, 1H, J= 5.4 Hz). 7.37 (d, 1H, J= 8.4 Hz), 7.26 (d, 1H, J= 3 Hz), 7.18 (s, 1H), 7.15 (s, 1H), 7.06 (dd, 1H, J= 3.3 and 8.7 Hz), 6.81 (d, 1H, J= 8.7 Hz), 4.23 (s, 4H), 2.85 (sept., 1H, J= 7.2 Hz), 1.17 (d, 6H, J= 6.9 Hz); LCMS: ret. time: 24.91 min.; purity: 95%; MS (m/e): 381 (MH^+).
7.3.357	N2-(3,5-Dimethoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926791)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 3,4-dimethoxyaniline gave N2-(3,5-dimethoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.08 (s, 1H), 9.99 (s, 1H), 8.19 (m, 1H), 7.21 (d, 1H, J= 2.4 Hz), 7.14 (dd, 1H, J= 2.1 and 8.7 Hz), 6.79 (d, 1H, J= 9 Hz), 6.72 (s, 1H), 6.20 (d, 1H, J= 1 8 Hz), 4.21 (s, 4H); LCMS: ret. time: 21.19 min.; purity: 93%; MS (m/e): 399 (MH^+).
7.3.358	N2-(2,5-Dimethyl-4-hydroxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926792)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 2,5-dimethyl-4-hydroxyaniline gave N2-(2,5-dimethyl-4-hydroxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.69 (d, 1H, J= 3.9 Hz), 7.16 (d, 1H, J= 2.4 Hz), 7.05 (d, 1H, J= 2.4 Hz), 7.02 (d, 1H, J= 1.2 Hz), 6.66 (s, 1H), 6.63 (s, 1H), 6.62 (s, 1H), 4.19 (s, 4H), 2.12 (s, 3H), 2.10 (s, 3H); LCMS: ret. time: 19.80 min.; purity: 90%; MS (m/e): 383 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.359	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(5-methyl-3-phenyl-4-oxazolyl)-2,4-pyrimidinediamine (R926793)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 5-methyl-3-phenyl-4-oxazolylamine gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(5-methyl-3-phenyl-4-oxazolyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.80-7.65 (m, 2H), 7.45 (bd, 1H), 7.20 (m, 1H), 7.00 (m, 1H), 6.65 (bd, 1H), 4.20 (s, 4H), 2.35 (s, 3H); LCMS: ret. time: 20.61 min.; purity: 78%; MS (m/e): 420 (MH^+).
7.3.360	N4-(3,5-Dimethoxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926795)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,5-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine with ethyl-3-aminophenoxyacetate gave N4-(3,5-dimethoxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 21.02 min.; purity: 84%; MS (m/e): 429 (MH^+).
7.3.361	N4-(3,4-Ethylenedioxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R926797)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-dimethoxyphenyl)-5-ethoxycarbonyl-4-pyrimidineamine with ethyl-3-aminophenoxyacetate gave N4-(3,4-ethylenedioxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine. LCMS: ret. time: 27.60 min.; purity: 82%; MS (m/e): 495 (MH^+).
7.3.362	N4-(3-Hydroxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R926798)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro- -5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-4-pyrimidineamine with ethyl-3-aminophenoxyacetate gave N4-(3-hydroxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine. LCMS: ret. time: 24.78 min.; purity: 85%; MS (m/e): 453 (MH^+).
7.3.363	5-Fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine (R926614)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 2-methoxycarbonyl-5-aminobenzofuran gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 9.42 (s, 1H), 9.33 (s, 1H), 9.23 (s, 1H), 8.26 (s, 1H), 8.09 (d, 1H, J= 3.6 Hz), 7.59 (m, 3H), 7.13 (m, 3H), 6.53 (d, 1H, J= 7.5 Hz), 3.87 (s, 3H), 3.87 (s, 3H).

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7.3.364	N2-(2-Ethoxycarbonylindol-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926615)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 2-ethoxycarbony-5-aminoindole gave N2-(2-ethoxycarbonylindol-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.95 (d, 1H), 7.84 (d, 1H, J= 3.9 Hz), 7.34 (s, 1H), 7.33 (d, 1H, J= 1.8 Hz), 7.22-7.19 (m, 2H), 7.11-7.05 (m, 2H), 6.55 (m, 1H), 4.62 (s, 2H), 4.38 (q, 1H, J= 6.9 Hz), 1.40 9t, 3H, J= 7.5 Hz).
7.3.365	N2-[4-(4,5-Dichloro-1H-imidazol-1-yl)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926777)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with (4,5-dichloro-1H-imidazol-1-yl)-4-aniline gave N2-[4-(4,5-dichloro-1H-imidazol-1-yl)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 22.09 min.; purity: 98%; MS (m/e): 431 (MH^+).
7.3.366	5-Fluoro-N4-(3-hydroxyphenyl)-N2-(4-isopropylphenyl)-2,4-pyrimidinediamine (R926778)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 4-isopropylaniline gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-(4-isopropylphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 23.08 min.; purity: 99%; MS (m/e): 439 (MH^+).
7.3.367	5-Fluoro N4-(3-hydroxyphenyl)-N2-(5-methyl-4-oxazolyl-2-phenyl)-2,4-pyrimidinediamine (R926779)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 5-methyl-4-oxazolyl-2-phenyl-1-amine gave 5-fluoro N4-(3-hydroxyphenyl)-N2-(5-methyl-4-oxazolylphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 23.08 min.; purity: 99%; MS (m/e): 439 (MH^+). LCMS: ret. time: 19.17 min.; purity: 81%; MS (m/e): 378 (MH^+).
7.3.368	N2-(3.5-Dimethoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926780)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3.5-dimethoxyaniline gave N2-(3.5-dimethoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 19.61 min.; purity: 97%; MS (m/e): 357 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.369	N4-(4-tert-Butoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl-2,4-pyrimidinediamine (R926572)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine with methyl 4-aminophenoxyacetate gave N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.49 (d, 2H, J= 8 7 Hz), 7.40 (d, 2H, J= 9.3 Hz), 6.89 (d, 2H, J= 9.3 Hz), 6.85 (d, 2H, J= 8.7 Hz), 4.62 (s, 2H), 4.52 (s, 2H), 3.81 (s, 3H), 1.49 (s, 9H); LCMS: ret. time. 24.68 min.; purity: 100%; MS (m/e): 499 (MH^+).
7.3.370	5-Fluoro-N4-(3-isopropoxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine (R926487)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-isopropoxyphenyl)-4-pyrimidinediamineamine with 2-methoxycarbonyl-5-aminobenzofuran gave 5-fluoro-N4-(3-isopropoxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.09 (d, 1H, J= 2.4 Hz), 7.96 (d, 1H, J= 3 Hz), 7.52 (s, 1H), 7.48 (t, 1H, J= 1.8 Hz), 7.40 (dd, 1H, J= 6.3 Hz), 7.24 9m, 2H), 7.10 (m, 1H), 6.97 (bs, 1H), 6.74 (d, 1H, J= 2.4 Hz), 6.68 (dd, 1H, J= 2.1 and 6.9 Hz), 4.49 (sept., 1H, J= 5.7 Hz), 3.98 (s, 3H), 1.30 (d, 6H, J= 5.7 Hz); LCMS: ret. time: 25.86 min.; purity: 94%; MS (m/e): 437 (MH^+).
7.3.371	N4-(4-tert-Butylphenyl)-N2-(2-ethoxycarbonylindol-5-yl)-5-fluoro-2,4-pyrimidinediamine (R926474)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of N4-(tert-butylcarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine with 2-ethoxycarbony-5-aminolindole gave N4-(4-tert-butylphenyl)-N2-(2-ethoxycarbonylindol-5-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.05 (d, 1H, J= 1.8 Hz), 7.85 (d, 1H, J= 3.9 Hz), 7.58 (d, 2H, J= 9 Hz), 7.36-7.10 (m, 4H), 7.03 (s, 1H), 6.95 (bd, 1H), 6.84 (dd, 1H, J= 7.2 Hz), 4.36 (q, 2H, J= 7.2 Hz), 1.40 (t, 3H, J= 7.5 Hz), 1.33 (s, 9H); LCMS: ret. time: 28.67 min.; purity: 100%; MS (m/e): 449 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.372	N4-(4-tert-Butylphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine (R926477)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of N4-(tert-butylcarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine with 2-methoxycarbonyl-5-aminobenzofuran gave N4-(4-tert-butylphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.6 (s, 1H), 8.09)d, 1H, J= 1.8 Hz), 7.86 (d, 1H, J= 3.3 Hz), 7.54-7.36 (m, 6H), 6.90 (m, 1H)3.97 (s, 3H), 1.36 (s, 9H), ^{19}F NMR ($CDCl_3$): - 47188, LCMS: ret. time: 29.69 min.; purity: 84%; MS (m/e): 393 (M-41).
7.3.373	N2-(3,4-Ethylenedioxyphenyl)-N4-(2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine (R926485)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidineamine with 2-methoxycarbonyl-5-aminobenzofuran gave N2-(3,4-ethylenedioxyphenyl)-N4-(2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.07 (s, 1H), 7.76 (s, 1H), 7.44 (m, 3H), 7.13 (m, 1H), 6.68 (m, 2H0, 4.18 (s, 4H), 3.95 (s, 3H); LCMS: ret. time: 26.63 min.; purity:100%; MS (m/e): 437 (MH^+).
7.3.374	N4-(3-Ethoxycarbonylmethyleneoxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926774)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidineamine with 3,4-ethylenedioxyaniline gave N4-(3-ethoxycarbonylmethyleneoxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.92 (d, 1H, J= 3.6 Hz), 7.67 (s, 1H), 7.40 (s, 1H), 7.28-7.21 (m, 2H), 7.01-6.96 (m, 2H), 6.80 (m, 2H), 6.68 (bd, 1H, 1H), 4.61 (s, 2H), 4.25 (m, 6H), 1.25 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 22.03 min.; purity: 84%; MS (m/e): 441 (MH^+).
7.3.375	N4-(3-Ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926775)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidineamine with 3-hydroxyaniline gave N4-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 19.50 min.; purity: 84%; MS (m/e): 399 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.376	N4-(4-Aminocarbonylmethyleneoxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R945171)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(4-aminocarbonylmethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine and 3,4-ethylenedioxyaniline gave N4-(4-aminocarbonylmethyleneoxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (acetone-d_6): δ δ 4.24-4.31 (m, 4H), 4.51 (s, 2H), 6.77 (d, J= 8.7 Hz, 1H), 6.95 (dm, J= 8.7 Hz, 1H), 7.06 (d, J= 9.3 Hz, 2H), 7.28 (m, 1H), 7.71 (d, J= 9.0 Hz, 2H), 8.15 (m, 1H); LCMS: 15.23 min, 97.05%; MS (m/e): 412.01 (MH^+).
7.3.377	(R935019): 5-Fluoro-N2-(3-hydroxyphenyl)-N4-[di-(4-chlorophenyl)methyl]-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-4-pyrimidinediamine, 3-aminophenol and N-(2-chloro-5-fluoro-pyrimidinyl)-1,1-di(4-chlorophenyl)methylamine produced 5-fluoro-N2-(3-hydroxyphenyl)-N4-[di-(4-chlorophenyl)methyl]-2,4-pyrimidinediamine. LCMS: ret. time: 25.59 min.; purity: 91%; MS (*m/e*): 421 (MH^+-Cl).
7.3.378	(R935020): N4-(Fluoren-9-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine:	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-4-pyrimidinediamine, 2-chloro-N-(fluoren-9-yl)-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to produce N4-(fluoren-9-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.85 (d, 1H, J= 2.9 Hz), 7.74 (d, 2H, J= 7.6 Hz), 7.64 (d, 2H, J= 7.6 Hz), 7.41-7.28 (m, 6H), 7.14-7.05 (m, 2H), 6.56 (d, 1H, J= 8.8 Hz), 5.28 (d, 1H, J= 8.8 Hz); LCMS: ret. time: 23.27 min.; purity: 89%; MS (*m/e*): 385 (MH^+).
7.3.379	(R935021): (±)-5-Fluoro-N4-[1-(4-fluorophenyl)ethyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-4-pyrimidinediamine, 3-aminophenol and (±)-N-(2-chloro-5-fluoropyrimidinyl)-1-(4-fluorophenyl)ethylamine were reacted to produce the desired (±)-5-fluoro- N4-[1-(4-fluorophenyl)ethyl]-N2-(3-hydroxyphenyl)-2, 4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.79 (d, 1H, J= 3.3 Hz), 7.38-7.34 (dd, 2H, J= 5.2 and 8.5 Hz), 7.14 (t, 1H, J= 4.5 Hz), 7.09 (d, 1H, J= 8.5 Hz), 7.03 (d, 1H, J= 8.5 Hz), 6.84 (br s, 1H), 6.84-6.78 (ddd, 1H, J= 0.8, 2.0, and 8.2 Hz), 6.46-6 42 (ddd, 1H, J= 0.8, 2.0 and 8.2 Hz), 5.26 (overlapped dq, 1H, J= 7.1 and 7.9 Hz), 5.18 (d, 1H, J=7.1 Hz), 1.59 (d, 3H, J= 7.1 Hz); LCMS: ret. time: 21.52 min.; purity: 92%; MS (*m/e*): 343 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.380	(R935023): (±)-5-Bromo-N4-[1-(4-fluorophenyl)ethyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-4-pyrimidinediamine, 3-aminophenol and (±)-5-bromo-2-chloro-N4-[1-(4-fluorophenyl)ethyl]-4-pyrimidineamine were reacted to produce (±)-5-bromo- N4-[1-(4-fluorophenyl)ethyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.97 (s, 1H), 7.36-7.31 (m, 2H), 7.17 (s, 1H), 7.09-7.01 (m, 4H), 6.82 (dd, 1H, J= 2.2 and 8.2 Hz), 6.46 (d, 1H, J= 2.2 and 8.2 Hz), 5.50 (br d, 1H, J= 7.0), 5.27 (overlapped dq, 1H, J= 7.1 and 7.9 Hz), 1.58 (d, 3H, J= 7.0 Hz); LCMS· ret. time: 22.64 min.; purity: 94%; MS (*m/e*): 404 (MH^+)
7.3.381	(R935025): 5-Bromo-N2-(3-hydroxyphenyl)-N4-(N-methyl-2-carbomethoxypyrrol-4-yl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-4-pyrimidinediamine, 3-aminophenol and 5-bromo-2-chloro-N-(N-methyl-2-carbomethoxypyrrol-4-yl)-4-pyrimidineamine were reacted to give 5-bromo-N2-(3-hydroxyphenyl)-N4-(N-methyl-5-carbomethoxypyrrol-4-yl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 7.92 (s, 1H), 7.58 (d, 1H, J= 8.0 Hz), 7.09 (d, 1H, J= 8 5 Hz), 7.04 (d, 1H, J= 8.5 Hz), 6.90 (d, 1H, J= 4.5 Hz), 6.81 (d, 1H, J= 1.8 Hz), 6.5 (m, 1H), 3.82 (s, 3H), 3.75 (s, 3H): LCMS: ret. time: 19.73 min.; purity: 90%; MS (*m/e*): 419 (MH^+)
7.3.382	(R935029): 4-Amino-5-bromo-N2-(3-hydroxyphenyl)-2-pyrimidineamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-4-pyrimidinediamine, 4-amino-5-bromo-2-chloropyrimidine and 3-aminophenol were reacted to give 4-amino-5-bromo-N2-(3-hydroxyphenyl)-2-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.33 (br s, 1H), 8.27 (s, 1H), 7.14-6.06 (m, 2H), 7.01 (d, 1H, J= 1.7 Hz), 6.54 (td, 1H, J= 1.7 Hz and 7.0 Hz).
7.3.383	R935134: 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	The reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 5-(4-aminophenoxymethyl)-3-phenyl-1,2-4-oxadiazole were reacted in microwave at 180 °C for 10-20 minutes at 20 bar. Upon concentration and addition of 2N HCl provided 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.21 (br s, 1H), 9.91 (br s, 1H), 8.18 (d, 1H, J= 5.2 Hz), 8.03-7.99 (m, 2H), 7.61-7.53 (m, 3H), 7.46 (br d, 2H, J= 7.9 Hz), 7.14-7.01 (m, 5H), 6.54 (app d, 1H, J= 7.96 Hz), 5.56 (s, 2H); LCMS: ret. time: 24.61 min.; purity: 100%; MS (*m/e*): 471 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.384	R935135: 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(4-isopropoxyphenyl)-4-pyrimidineamine and 5-(4-aminophenoxymethyl)-3-phenyl-1,2-4-oxadiazole were reacted to provide 5-fluoro- N4-(4-isopropyloxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine as fine flakes of the solid. ^{1}H NMR (DMSO-d6): δ 10.21 (br s, 1H), 9.93 (br s, 1H), 8.17 (d, 1H, J= 5.2 Hz), 8.02-7.98 (m, 2H), 7.60-7.49 (m, 5H), 7.42 (app d, 2H, J= 7.0 Hz), 7.04 (d, 2H, J= 9.4 Hz), 6.89 (app d, 2H, J= 9.4 Hz), 5.56 (s, 2H), 4.58 (septet, 1H, J= 6.4 Hz), 1.23 (app d, 6H, J= 6.4 Hz); LCMS: ret. time: 26.90 min.; purity: 97%; MS (*m/e*): 513 (MH^+).
7.3.385	R935136: N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxy)phenyl-4-pyrimidineamine and 5-(4-aminophenoxymethyl)-3-phenyl-1,2-4-oxadiazole were reacted provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine as fine flakes of the solid. ^{1}H NMR (DMSO-d6): δ 10.18 (br s, 1H), 9.12 (br s, 1H), 8.14 (d, 1H, 4.7 Hz), 8.02-7.97 (m, 2H), 7.65-7.52 (m, 3H), 7.44 (d, 2H, J= 8.8 Hz), 7.25-7.23 (m, 1H), 7.15-7.08 (m, 1H), 7.03 (d, 2H, J= 8.8 Hz), 6.81 (d, 1H, J= 8.8 Hz), 5.56 (s, 2H), 4.24-4.20 (m, 4H); LCMS: ret. time: 26.90 min.; purity: 97%; MS (*m/e*): 513 (MH^+).
7.3.386	R935137: 5-Fluoro-N4-(2-methoxycarbonylbenzofura-5-yl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(2-methoxycarbonylbenzofura-5-yl)-4-pyrimidineamine and 5-(4-aminophenoxymethyl)-3-phenyl-1,2-4-oxadiazole were reacted to provide 5-fluoro-N4-(2-methoxycarbonylbenzofura-5-yl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.21 (br s, 1H), 9.79 (br s, 1H), 8.19 (d, 1H, J= 4.7 Hz), 8.09 (br s, 1H), 7.99 (dd, 2H, J= 2.3 and 8.2 Hz), 7.76-7.67 (m, 2H), 7.59-7.52 (m, 4H), 7.44 (d, 2H, J= 8.8 Hz), 7 02 (d, 2H, J= 8.8 Hz), 5.55 (s, 2H), 3.85 (s, 3H); LCMS: ret. time: 27.61 min.; purity: 92%; MS (*m/e*): 553 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.387	R935138: 5-Fluoro-N2-(3-hydroxyphenyl)-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine and 3-aminophenol were reacted to provide 5-fluoro-N2-(3-hydroxyphenyl)-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine as fine flakes of the solid. ^{1}H NMR (DMSO-d6): δ 8.12 (d, 1H, J= 4.7 Hz), 8.03-7.99 (m, 2H), 7.69 (dd, 2H, J= 3.5 and 8.8 Hz), 7.61-7.53 (m, 3H), 7.06 (d, 2H, J= 9.9 Hz), 6.98 (m, 3H), 6.38 (br s, 1H), 5.58 (s, 2H). LCMS: ret. time. 24.83 min.; purity: 96%; MS (*m/e*): 471 (MH^+).
7.3.388	R935139: 5-Fluoro-N2-(4-isopropoxyphenyl)-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine and 4-isopropoxyaniline were reacted to provide 5-fluoro- N2-(4-isopropoxyphenyl)-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine as fine flakes of the solid. ^{1}H NMR (DMSO-d6): δ 10.21 (br s, 1H), 9.78 (br s, 1H), 8.13 (d, 1H, J= 4.7Hz), 8.02-7.98 (m 2H), 7.65-7.53 (m, 5H), 7.34 (d, 2H, J= 7.6 Hz), 7.07 (d, 2H, J= 9.3 Hz), 6.86 (d, 2H, J= 8.8 Hz), 5.59 (s, 2H), 4.54 (sept, 1H, J= 5.8 Hz), 1.22 (d, 6H, J= 5.8 Hz); LCMS: ret. time: 29.64 min.; purity: 97%; MS (*m/e*): 513 (MH^+).
7.3.389	R935140: N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to provide N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.31 (br s, 1H), 9.59 (br s, 1H), 8.11 (d, 1H, J= 4.7 Hz), 8.03-7.99 (m, 2H), 7.68-7.49 (m, 5H), 7.14-7.08 (m, 1H), 7.06 (d, 2H, J= 8.8 Hz), 6.90 (d, 1H, J= 8.8 Hz), 6.76 (d, 1H, J= 8.8 Hz), 5.59 (s, 2H), 4.22-4.17 (m, 4H); LCMS: ret. time: 21.35 min.; purity: 95%; MS (*m/e*): 513 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.390	R935141: 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine:	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 5-(4-aminophenoxymethyl)-3-methyl-1,2-4-oxadiazole were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine as fine flakes of the solid. ^{1}H NMR (DMSO-d6): δ 10.91 (br s, 1H), 9.91 (br s, 1H), 8.18 (d, 1H, J= 4.7 Hz), 7.43 (d, 2H, J= 8.8 Hz), 7.15-7 04 (m, 3H), 6.96 (d, 2H, J= 8.8 Hz), 6.58 (app d, 1H, J= 7.6 Hz), 5.43 (s, 2H), 2.34 (s, 3H), LCMS: ret. time: 18.68 min.; purity: 95%; MS (*m/e*): 409 (MH^+).
7.3.391	R935142: 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(4-isopropoxyphenyl)-4-pyrimidineamine and 5-(4-aminophenoxymethyl)-3-methyl-1,2-4-oxadiazole were reacted to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine as fine flakes of the solid. ^{1}H NMR (DMSO-d6): δ 8.16 (d, 1H, J= 5.2 Hz), 7.52 (dd, 2H, J= 3.5 Hz and 9.3 Hz), 7.40 (d, 2H, J= 8.8 Hz), 6.98 (d, 2H, J= 8.8 Hz), 6.88 (d, 2H, J= 9.3 Hz), 5.44 (s, 2H), 4.58 (sept, 1H, J= 5.8 Hz), 2.34 (s, 3H), 1.24 (d, 6H, J= 5.8 Hz); LCMS: ret. time: 24.47 min.; purity: 93%; MS (*m/e*): 451 (MH^+).
7.3.392	R935143: N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxy)phenyl-4-pyrimidineamine and 5-(4-aminophenoxymethyl)-3-methyl-1,2-4-oxadiazole were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine as fine flakes of the solid. ^{1}H NMR (DMSO-d6): δ 9.12 (br s, 1H), 9.04 (br s, 1H), 7.99 (d, 1H, J= 3.5 Hz), 7.55 (d, 2H, J= 1.7 and 8.8 Hz), 7.30 (d, 1H, J= 2.9 Hz), 7.17 (td, 1H, J= 2.9 and 8.8 Hz), 6.88 (d, 2H, J= 8.8 Hz), 6.77 (d, 1H, J= 8.8 Hz), 5.38 (s, 2H), 4.24-4.20 (m, 4H), 2.34 (s, 3H); LCMS: ret. time: 21.34 min.; purity: 97%; MS (*m/e*): 451 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.393	R935144: 5-Fluoro-N2-(4-isopropoxyphenyl)-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine and 4-isopropoxyaniline were reacted to provide 5-fluoro- N2-(4-isopropoxyphenyl)-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine as fine flakes of the solid. ^{1}H NMR (DMSO-d6): δ 10.11 (br s, 1H), 9.72 (br s, 1H), 8.12 (s, 1H, J= 5.3 Hz), 7.61 (dd, 2H, J= 8.8 Hz), 7.34 (d, 2H, J= 7.3 Hz), 7.01 (d, 2H, J= 8.8 Hz), 6.84 (d, 2H, J= 8.8 Hz), 5.47 (s, 2H), 4.54 (septet, 1H, J= 5.8 Hz), 2.34 (s, 3H), 1.23 (d, 6H, J= 6.4 Hz); LCMS: ret. time: 24.31 min.; purity: 96%; MS (*m/e*): 451 (MH^+).
7.3.394	R935145: N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to provide N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.81 (br s, 1H), 9.67 (br s, 1H), 8.13 (d, 1H, J= 4.7 Hz), 7.63 (dd, 2H, J= 4.1 and 8.8 Hz), 7.07 (m, 1H), 7.00 (d, 2H, J= 8.8 Hz), 6.89 (d, 1H, J= 8.8 Hz), 6.76 (d, 1H, J= 8.8 Hz), 5.46 (s, 2H), 4.22-4-18 (m, 4H), 2.34 (s, 3H); LCMS: ret. time: 21.54 min.; purity: 97%; MS (*m/e*): 451 (MH^+).
7.3.395	R935146: 5-Fluoro-N2-(2-methoxycarbonylbenzofura-5-yl)-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine and 2-methoxycarbonyl-5-aminobenzofuran were reacted to provide 5-fluoro-N2-(2-methoxycarbonylbenzofura-5-yl)-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.14 (d, 1H, J= 4.7 Hz), 8.02 (s, 1H), 7.63-7.56 (m, 5H), 7.02 (d, 2H, J= 8.8 Hz), 5.47 (s, 2H), 3.85 (s, 3H), 2.34 (s, 3H); LCMS: ret. time: 22.46 min.; purity: 97%; MS (*m/e*): 491 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.396	R935147: 5-Fluoro-N2-(3-hydroxyphenyl)-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine and 3-hydroxyaniline were reacted to provide 5-fluoro-N2-(3-hydroxyphenyl)-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine as fine flakes of the product. ^{1}H NMR (DMSO-d6): δ 8.11 (d, 1H, J= 4.6 Hz), 7.66 (d, 2H, J= 5.8 Hz), 7.06-6.97 (m, 5H), 6.42-40 (m, 1H), 5.46 (s, 2H), 2.35 (s, 3H); LCMS: ret. time: 19.00 min.; purity: 95%; MS (*m/e*): 409 (MH^+).
7.3.397	R935148: N2-(3,4-Ethylenedioxyphenyl)-N4-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-Chloro--[4-[ethoxycarbonyl(dimethyl)methyl]phenyl]-5-fluoro-2, 4-pyrimidine amine and 3,4-ethylenedioxyaniline were reacted to produe N2-(3,4-ethylenedioxyphenyl)-N4-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.31 (s, 1H), 8.97 (s, 1H), 8.03 (d, 1H, J= 3.5 Hz), 7 70 (d, 2H, J= 8.8 Hz), 7.29 (d, 1H, J= 2.3 Hz), 7.23 (d, 2H, J= 8.8 Hz), 6.98 (dd,, 1H, J= 2.1 and 8.8 Hz), 6.66 (d, 1H, 8.2 Hz); 4.19-4.15 (m, 4H), 4.07 (qt, 2H, J= 7.0 Hz), 1.48 (s, 6H), 1.10 (t, 3H, J= 7.0 Hz); LCMS: ret. time: 24.51 min.; purity: 100%; MS (*m/e*): 453 (MH^+).
7.3.398	R935150: N2-[4-[(1-Ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (or it can be be prepared similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine), 2-chloro-5-fluoro-N4-(4-isopropoxyphenyl)-4-pyrimidineamine and 4-[ethoxycarbonyl(dimethyl)methyl]aniline were reacted to produce N2-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.18 (br s, 1H), 9.11 (br s, 1H), 8.01 (d, 1H, J= 3.5 Hz), 7.56 (d, 2H, J= 8.8 Hz), 7.54 (d, 2H, J= 8.8 Hz), 7.09 (d, 2H, J= 8.8 Hz), 6.86 (d, 2H, J= 8.8 Hz), 4.56 (sept, 1H, J= 5 8 Hz), 4.02 (qt, 2H, J= 7.0 Hz), 1.43 (s, 6H), 1.26 (d, 6H, J= 7.0 Hz), 1.09 (t, 3H, J= 7.0 Hz); LCMS: ret. time: 28.49 min ; purity: 98%; MS (*m/e*): 453 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.399	R935179: N2-[4-(2,3-Dihydroxypropoxy)phenyl]-N4-(3,4-ethylenedioxypheny)-5-fluoro-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine and 4-(2,3-dihydroxypropoxy)aniline were reacted to produce N2-[4-(2,3-dihydroxypropoxy)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.09 (s, 1H), 8.95 (s, 1H), 7.98 (d, 1H, J= 3.5 Hz), 7.51 (d, 2H, J= 8.8 Hz), 7.32 (d, 1H, J= 2.3 Hz), 7.17 (dd, 1H, J= 2.3 and 8.8 Hz), 6.77 (dd, 3H, J= 8.8 Hz), 4.90 (d, 1H, J= 5.3 Hz), 4.64 (t, 1H, J= 5.8 Hz), 4.23-4.19 (m, 4H), 3.91-3.89 (m, 1H), 3.80-3.73 (m, 2H), 3.41 (t, 2H, J= 5.3 Hz); LCMS: ret. time: 15.04 min.; purity: 96%; MS (*m/e*): 429 (MH^+).
7.3.400	R935180: N2-[4-(2,3-Dihydroxypropoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine and 4-(2,3-dihydroxypropoxy)aniline were reacted to produce N2-[4-(2,3-dihydroxypropoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.38 (s, 1H), 9.18 (s, 1H), 8.98 (s, 1H), 8.12 (d, 1H, J= 3.5 Hz), 7.58 (d, 2H, J= 8.8 Hz), 7.22 (d, 1H, J= 2.3 Hz), 7.12 (dd, 2H, J= 2.3 and 8.8 Hz), 6.79 (d, 2H, J= 8.8 Hz), 6.45 (d, 1H, J= 8.8 Hz), 4.91 (d, 1H, J= 5.3 Hz), 4.65 (t, 1H, J= 5.8 Hz), 3.92-3.89 (m, 1H), 3.79-3.74 (m, 2H), 3.44 (t, 2H, J= 5.3 Hz); LCMS: ret. time: 12.79 min.; purity: 89%; MS (*m/e*): 387 (MH^+).
7.3.401	R935175: N2-[4-(2,3-Dihydroxypropoxy)phenyl]-5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isoproxyphenyl)-4-pyrimidineamine and 4-(2,3-dihydroxypropoxy)aniline were reacted to produce N2-[4-(2,3-dihydroxypropoxy)phenyl]-5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine: ^{1}H NMR (DMSO-d6): δ 9.12 (s, 1H), 8.91 (s, 1H), 7.97 (d, 1H, J= 3.5 Hz), 7.58 (d, 2H, J= 8.8 Hz), 7.49 (d, 2H, J= 8.8 Hz), 6.85 (d, 2H, J= 8.8 Hz), 6.76 (d, 2H, J= 8.8 Hz); 4.89 (d, 1H, J= 4.7 Hz), 4.63 (t, 1H, J= 5.2 Hz), 4.56 (septet, 1H, J= 5.8 Hz), 3.90-3.89 (m, 1H), 3.76-3.73 (m, 2H), 3.41 (t, 2H, J= 5.3 Hz), 1.25 (d, 6H, J= 5.8 Hz); LCMS: ret. time: 17.48 min.; purity: 98%; MS (*m/e*): 429 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.402	R935169: N4-[4-[(1-Ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to produce N4-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 7.87 (d, 1H, J= 3.5 Hz), 7.56 (d, 2H, J= 8.8 Hz), 7.35 (d, 2H, J= 8.8 Hz), 7.25-7.23 (m, 1H), 7.08 (t, 1H, J= 8.2 Hz), 6.91 (d, 1H, J= 2.3 Hz), 6.83 (d, 1H, J= 7.6 Hz), 6.50 (dd, 1H, J= 1.7 and 8.2 Hz), 4.13 (qt, 2H, J= 7.0 Hz), 1.58 (s, 6H), 1.19 (t, 3H, J= 7.0 Hz); LCMS: ret. time: 22.97 min.; purity: 98%; MS (*m/e*): 411 (MH^+).
7.3.403	R935164: 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[(N-methyl-2-methoxycarbonyl)pyrrol-4-yl]-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine, 2-chloro-5-fluoro-N4-(4-isopropoxyphenyl)-4-pyrimidineamine and and N-methyl-2-methoxycarbonyl-4-aminopyrrole hydrochloride with added diisopropylethylamine were reacted to produce the desired product 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[(N-methyl-2-carbomethoxy)pyrrol-4-yl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.87 (br s, 1H), 7.44 (d, 2H, J= 8.8 Hz), 7.08 (br s, 1H), 6.99-6.85 (m, 3H), 6.70 (d, 1H, J= 2.3 Hz), 6.63 (d, 1H, J= 1.7 Hz), 4.52 (septet, 1H, J= 5.8 Hz), 3.80 (s, 3H), 3.79 (s, 3H), 1.34 (d, 6H, J= 5.8 Hz); LCMS: ret. time: 23.89 min.; purity: 99%; MS (*m/e*): 400 (MH^+).
7.3.404	R935165: 5-Fluoro-N2-(4-isopropoxyphenyl)-N4-[(N-methyl-2-carbomethoxy)pyrrole-4-yl]-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-2-carbomethoxypyrrol-4-yl)-4-pyrimidineamine and 4-isopropoxyaniline were reacted to produce 5-fluoro-N2-(4-isopropoxyphenyl)-N4-[(N-methyl-5-carbomethoxy)pyrrol-4-yl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.84 (d, 1H, J= 2.3 Hz), 7.36 (d, 2H, J= 8.8 Hz), 7.22 (d, 1H, J= 1.1 Hz), 6.87 (d, 2H, J= 8.8 Hz), 6.84 (s, 1H), 6.77 (d, 1H, J= 1.7 Hz), 6.61 (br s, 1H), 4.49 (septet, 1H, J= 5.8 Hz), 3.82 (d, 3H), 3.81 (s, 3H), 1.33 (d, 6H, J= 5.8 Hz); LCMS: ret. time: 23.36 min.; purity: 96%; MS (*m/e*): 400 (MH^+).
7.3.405	R935166: N2-(3,4-Ethylenedioxyphenyl)- 5-fluoro-N4-[(N-methyl-2-methoxycarbonyl)pyrrol-4-yl]-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-2-methoxycarbonylpyrrol-2-yl)-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to produce 5-fluoro-N2-(3,4-ethylenedioxyphenyl)-N4-[(N-methyl-2-carbomethoxy)pyrrol-4-yl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.84 (d, 1H, J= 3.5 Hz), 7.34 (s, 1H), 7.21 (s, 1H), 6.82 (d, 2H, J= 8.8 Hz), 6.76 (d, 2H, J= 8.8 Hz), 6.58 (s, 1H), 4.27-4.18 (m, 4H), 3.90 (s, 3H), 3.81 (s, 3H); LCMS: ret. time: 20.02 min.; purity: 93%; MS (*m/e*): 400 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.406	R935167: N4-[4-[(1-Ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[4-[1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-4-pyrimidineamine and 4-isopropoxyaniline were reacted to produce N4-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.29 (s, 1H), 8.95 (s, 1H), 8.02 (d, 1H, J= 4.1 Hz), 7.68 (d, 2H, J= 8.8 Hz), 7.46 (d, 2H, J= 8.8 Hz), 7.22 (d, 2H, J= 8.8 Hz), 6.75 (d, 2H, J= 8.8 Hz), 4.48 (septet, 1H, J= 5.8 Hz), 4.04 (qt, 2H, J= 7.0 Hz), 1.47 (s, 6H), 1 22 (d, 6H, J= 5 8 Hz), 1.10 (t, 3H, J= 7.0 Hz); LCMS: ret. time: 28.11 min.; purity: 99%; MS (*m/e*): 453 (MH^+).
7.3.407	R935159: 5-Fluoro-N4-(4-isopropoxyphenyl)-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[3-hydroxyphenyl]-pyrimidine-2,4-diamine, 2-chloro-5-fluoro-N4-(4-isopropoxyphenyl)-4-pyrimidineamine and methl 4-aminophenoxyacetate were reacted to produce 5-fluoro-N4-(4-isopropoxyphenyl)-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1H, J= 3.5 Hz), 7.46 (d, 2H, J= 8.8Hz), 7.42 (d, 2H, J= 8.8 Hz), 6.88 (d, 2H, J= 9.3 Hz), 6.85 (d, 2H, J= 9.3 Hz), 6.78 (br s, 1H), 6.63 (br d, 1H, J= 2.3 Hz), 4.61 (s, 2H), 4.53 (septet, 1H, J= 6.4 Hz), 3.81 (s, 3H), 1.35 (d, 6H, J= 6.4 Hz); LCMS: ret. time: 23.19 min.; purity: 97%; MS (*m/e*): 427 (MH^+).
7.3.408	R935157: N4-[4-[(1-Ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[3-hydroxyphenyl]-pyrimidine-2,4-diamine, 2-chloro-N4-[4-[1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-4-pyrimidineamine was reacted with 4-(methoxycarbonylmethyleneoxy)aniline to produce N4-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.92 (s, 1H), 7.55 (d, 2H, J= 8.7 Hz), 7.43 (d, 2H, J= 9.3 Hz), 7.33 (d, 2H, J= 8.7 Hz), 6.87 (d, 2H, J= 9.3 Hz), 6.79 (s, 1H), 6.73 (d, 1H, J= 2.3 Hz), 4.62 (s, 2H), 4.13 (qt, 2H, J= 7.0 Hz), 3.81 (s, 3H), 1.59 (s, 6H), 1.20 (t, 3H, 7.0 Hz); LCMS: ret. time: 25.20 min.; purity: 97%; MS (*m/e*): 483 (MH^+).
7.3.409	R935152: N2-[4-[(1-Ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N2-[4-(1-ethoxycarbonyl-1-methyl)ethyl)phenyl]-5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 4-[1-ethoxycarbonyl-1-methyl)ethyl]aniline were reacted to give N2-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.89 (d, 1H, J= 2.9 Hz), 7.24-7.10 (m, 5H), 6.93 (d, 1H, J= 7.6 Hz), 6.68 (d, 2H, J= 8.2 Hz), 4.08 (qt, 2H, J= 7.0 Hz), 1.52 (s, 3H), 1.49 (s, 3H), 1.16 (t, 3H, J= 7.0 Hz); LCMS: ret. time: 22.15 min.; purity: 96%; MS (*m/e*): 411 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.410	N2-(3-*tert*-Butylphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R940257)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-*tert*-buthylaniline gave N2-(3-*tert*-butylphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 23.82 min.; purity: 100%; MS (m/e): 353 (MH^+); ^1H NMR ($CDCl_3$): δ 7.96 (1H, d, J= 3 Hz), 7.61 (1H, ddd, J= 7.5, 2.2 and 0.9 Hz), 7.49 (1H, t, J= 2.5 Hz), 7.27 (1H, m), 7.18 (1H, t, J= 8.1 Hz), 7.99 (1H, m), 6.94 (1H, s), 6.91 (1H, dd, J= 7.5 and 2.5 Hz), 6.80 (1H, d, J= 7.5 Hz), 6 72 (2H, m), 6.58 (1H, ddd, J= 7.5, 2.5 and 0.9 Hz), 6.52 (1H, ddd, J= 7.5, 2.5 and 0.9 Hz), 1.28 (9H, s).
7.3.411	N4-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and N4-(3-chloro-4-hydroxy-5-methylphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R940258)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-chloro-4-hydroxy-5-methylphenyl)-4-pyrimidineamine with ethyl 3-aminophenoxyacetate gave a mixture of N4-(3-chloro-4-hydroxy-5-methylphenyl)- 5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and N4-(3-chloro-4-hydroxy-5-methylphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 20.34 min. (CO_2Me); purity: 17%; MS (m/e): 432 (M^+); LCMS: ret. time: 21.83 min; purity 78%; MS (m/e): 446 (M^+).
7.3.412	N2-(3-*tert*-Butylphenyl)-N4-(3,4-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R940260)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-dimethoxyphenyl)-4-pyrimidineamine with ethyl 3-*tert*-buthylaniline gave N2-(3-*tert*-butylphenyl)-N4-(3,4-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 24.87 min.; purity: 99%; MS (m/e): 397 (MH^+); ^1H NMR ($CDCl_3$): δ 7.92 (1H, d, J= 3.4 Hz), 7.50 (1H, d, J= 8 Hz), 7.28 (1H, t, J= 2.3 Hz), 7.21 (1H, d, J= 8 Hz), 718 (1H, m), 7.08-7 01 (2H, m), 6.99 (1H, s), 6.84 (2H, d, J= 9.2 Hz), 6.65 (1H, s), 3.89 (3H, s), 3.72 (3H, s), 1.26 (9H, s).
7.3.413	N2-[2-(N-Benzylpiperazino)ethyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R940261)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 4-(N-benzylpiperazino)ethylamine gave N2-[2-(N-benzylpiperazino)ethyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 17.15 min.; purity: 90 %; MS (m/e): 422 (M^+), 423 (MH^+); ^1H NMR ($CDCl_3$): δ 8.42 (1H, s), 7.82 (1H, d, J= 3.9 Hz), 7.32-7.08 (6H, m), 6.73 (1H, s), 6.61 (1H, dd, J= 8.1 and 2.1 Hz), 6.51 (1H, d, J= 7.5 Hz), 5.18 (1H, s), 3.59 (2H, m), 3.02 (2H, m), 2.71-2.41 (3H, m), 2.10-1.16 (5H, m).

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Section Number	Name of compound and reference number	Experimental
7.3.414	N2-[2-(N-Benzylpiperazino)ethyl]-N4-(3,4-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R940262)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-dimethoxyphenyl)-4-pyrimidineamine with 4-(N-benzylpiperazino)ethylamine gave N2-[2-(N-benzylpiperazino)ethyl]-N4-(3,4-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 17.48 min.; purity: 99 %; MS (m/e): 466 (M^+), 467 (MH^+); ^{1}H NMR ($CDCl_3$): δ 7.82 (1H, d, J= 3.9 Hz), 7.44 (1H, s), 7.33-7.10 (6H, m), 7.04 (1H, dd, J= 8.9 and 2.5 Hz), 6.84 (1H, d, J= 8.9 Hz), 6.58 (1H, s), 5.40 (1H, s), 3.91 (3H, s), 3.87 (3H, s), 3.41 (2H, m), 2.87 (2H, m), 2.51 (3H, m), 1.80 (2H, m), 1.60 (4H, m), 1.30 (1H, m).
7.3.415	N2-[4-(N-Benzylpiperidino)]-N4-(3,4-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R940263)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-dimethoxyphenyl)-4-pyrimidineamine with N-benzyl-4-aminopiperidine gave N2-[4-(N-benzylpiperidino)]-N4-(3,4-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 15.52 min.; purity: 99 %; MS (m/e): 438 (MH^+); ^{1}H NMR ($CDCl_3$): δ 7.81 (1H, d, 3.3 Hz), 7.35-7.18 (5H, m), 7.10 (1H, dd, J= 8.7 and 2.6 Hz), 6.84 (1H, d, J= 8.7 Hz), 6.56 (1H, s), 4.73 (1H, d, J= 6.9 Hz), 3.89 (6H, s), 3.75 (1H, m), 3.51 (2H, m), 2.81 (2H, m), 2.15 (2H, m), 2 00 (2H, m), 1.66-1.44 (4H, m).
7.3.416	N2-[4-(N-Benzylpiperidino)]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R940264)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with N-benzyl-4-aminopiperidine gave N2-[4-(N-benzylpiperidino)]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 14.00 min.; purity: 96 %; MS (m/e): 394 (M^+), 395 (MH^+); ^{1}H NMR ($CDCl_3$): δ 7.81 (1H, d, J= 3.6 Hz), 7.40-7.28 (5H, m), 7.21-7.14 (2H, m), 6.69 (1H, m), 6.62 (1H, m), 6.59 (1H, m), 5.20 (1H, s), 3.65 (2H, s), 3.50 (1H, s), 3.03 (1H, m), 2.83 (1H, m), 2.13 (1H, m), 1.95-1.70 (1H, m), 1.58 (4H, m).
7.3.417	N4-(3-*tert*-Butylphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R940270)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of N4-(3-*tert*-butylphenyl)-2-chloro-5-fluoro-4-pyrimidineamine with ethyl 3-aminophenoxyacetate gave N4-(3-*tert*-butylphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 27.30 min.; purity: 98 %; MS (m/e): 439 (MH^+); ^{1}H NMR (DMSO-d6): δ 9.50 (1H, s), 9.33 (1H, s), 8.11 (1H, dd, J=4.2 and 1.8 Hz), 7.81 (1H, d, J= 7.2 Hz), 7.49 (1H, t, 2.4 Hz), 7.30-7.28 (3H, m), 7.14-7.03 (2H, m), 6.46 (1H, d, J= 7.8 Hz), 4.57 (2H, s), 4.13 (2H, q, J= 7.2 Hz), 1.23 (9H, s), 1.18 (3H, t, J= 7.2 Hz).

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Section Number	Name of compound and reference number	Experimental
7.3.418	N4-(3-*tert*-Butylphenyl)-N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R940271)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of N4-(3-*tert*-butylphenyl)-2-chloro-5-fluoro-4-pyrimidineamine with 3-chloro-4-hydroxy-5-methylaniline gave N4-(3-*tert*-butylphenyl)-N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 25.46 min.; purity: 100 %; MS (m/e): 400 (M^+); ^{1}H NMR (DMSO-d6): δ 9.63 (1H, s), 9.30 (1H, s), 8.82 (1H, s), 8.20 (1H, d, J= 3.9 Hz), 7.92 (1H, d, J= 8,8 Hz), 7.58 (2H, m), 7.40-7.20 (3H, m) 2.22 (3H, s), 1.35 (9H, s).
7.3.419	N2-(3-*tert*-Butylcarbonylaminophenyl)-N4-(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R940275)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-butylcarbonylaminoaniline gave N2-(3-*tert*-butylcarbonylaminophenyl)-N4-(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 20.19 min.; purity: 91 %; MS (m/e): 396 (MH^+); 1H NMR (DMSO-d6): δ 9.42 (1H, s), 9.28 (1H, s), 9.21 (1H, s), 9.18 (1H, s), 8.17 (1H, d, J= 3.9 Hz), 7.90 (1H, s), 7.55 (1H, dt, J= 6.9 and 2.1 Hz), 7.51 (1H, dd, J= 7.8 and 1.5 Hz), 7.26-7.13 (4H, m), 6.57 (1H, dd, J= 7.5 and 1.5 Hz), 1.30 (9H, s).
7.3.420	N4-(3,3-Dihydroisobenzofuranyl-1-one-6-yl)-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine R940294	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hyroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,3-dihydroisobenzofuranyl-1-one-6-yl)-5-fluoro-4-pyrimidineamine and 2-methoxycarbonyl-5-aminobenzofuran were reacted to give N4- (3,3-dihydroisobenzofuranyl-1-one-6-yl)-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine. LCMS: ret. time: 21.34 min.; purity: 97 %; MS (m/e): 434 (M^+); 1H NMR (DMSO-d6): δ 9.90 (1H, s), 9.61 (1H, s), 8.4-8.12 (4H, m), 7.35-7.67 (4H, m), 5.50 (2H, s), 3.98 (3H, s).
7.3.421	N2-[3-Ethoxycarbonylmethyleneoxyphenyl]-N4-(3,3-dihydroisobenzofuranyl-1-one-6-yl)-5-fluoro-2,4-pyrimidinediamine R940285	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hyroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,3-dihydroisobenzofuranyl-1-one-6-yl)-5-fluoro-4-pyrimidineamine and ethyl 3-aminophenoxyacetate were reacted to give N2-(3-ethoxycarbonylmethyleneoxyphenyl)-N4-(3,3-dihydroisobenzofuranyl-1-one-6-yl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 20.55 min.; purity: 76 %; MS (m/e): 438 (M^+), 440 (MH^+); 1H NMR (DMSO-d6): δ 9.70 (1H, s), 9.30 (1H, s), 8.23-8.06 (1H, m), 8.05 (1H, s), 7.63 (1H, d, J= 8.1 Hz), 7.30 (1H, s), 7.22 (1H, m), 7.08 (1H, t, J= 8.1 Hz), 6.43 (1H, d, J= 8.1 Hz), 5.37 (1H, s), 5.37 (2H, s), 4.60 (2H, s), 4.13 (2H, q, J= 7.2 Hz), 1.18 (3H, t, J= 7.2 Hz).

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Section Number	Name of compound and reference number	Experimental
7.3.422	N2-(3,5-Dimethoxyphenyl)-N4-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926804)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine with 3,5-dimethoxyaniline gave N2-(3,5-dimethoxyphenyl)-N4-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 24.12 min.; purity: 86%; MS (m/e): 443 (MH^+).
7.3.423	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3-trifluoromethylphenyl)]-2,4-pyrimidinediamine (R926805)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 3-trifluoromethylaniline gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-trifluoromethylphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 25.88 min.; purity: 89%; MS (m/e): 407 (MH^+).
7.3.424	N2-(2-Ethoxycarbonylindol-7-yl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine (R926808)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 2-ethoxycarbonyl-7-aminoindole gave N2-(2-ethoxycarbonylindol-7-yl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine. LCMS: ret. time: 24.11 min.; purity: 88%, MS (m/e): 450 (MH^+).
7.3.425	N4-[4-(4,5-Dichloro-1H-imidazol-1-yl)phenyl]-5-fluoro-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R926809)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of N-4-[4-(4,5-dichloro-1H-imidazol-1-yl)phenyl]-2-chloro-5-fluoro-4-pyrimidineamine with ethyl-3-aminophenoxyacetate gave N4-[4-(4,5-dichloro-1H-imidazol-1-ylphenyl)]-5-fluoro-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 25.22 min, purity: 77%; MS (m/e): 519 (MH^+).
7.3.426	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(1,3-oxazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926813)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 3-(1,3-oxazol-5-yl)aniline gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(1,3-oxazol-5-yl)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 20.25 min.; purity: 81%, MS (m/e): 406 (MH^+).
7.3.427	N2-(2-Ethoxycarbonylindol-7-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyridinediamine (R926814)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 2-ethoxycarbonyl-7-aminoindol gave N2-(2-ethoxycarbonylindol-7-yl)-5-fluoro N4-(3-hydroxyphenyl)-2,4-pyridinediamine. LCMS: ret. time: 25.94 min.; purity: 91%.

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Section Number	Name of compound and reference number	Experimental
7.3.428	N2-(3-Aminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950207)	N4-(3,4-Ethylenedioxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (50 mg, 0.18 mmol) was dissolved in dry MeOH (1 ml), to it was added 3-aminoaniline (163 mg, 1.2 mmol) and the mixture was refluxed for 4 days (70 °C oil-bath temperature). The mixture was cooled to 22 °C, concentrated to dryness under reduced pressure and subjected to column chromatography on silica gel ($CHCl_3$–Acetone, 9:1) to give N2-(3-aminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.66 (d, 1H, J= 3.6 Hz), 7.18 (d, 1H, J= 2.1 Hz), 7.09 (t, 1H, J= 2.1 Hz), 6.80-6.90, (m, 1H), 6.69 (d, 1H, J= 8.1 Hz), 6.57 (m, 1H), 6.20 (m, 1H), 6.60 (m, 1H), 4.10 (m, 4H); LCMS purity: 90.7%; MS (m/e): 354.13 (M^+, 100).
7.3.429	N4-(3,4-Ethylenedioxyphenyl)-N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine (R950186)	In like manner to the preparation of N2-(3-aminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine and 3-ethoxycarbonylmethyleneaminophenylaniline were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 23 29 min.; purity: 95.7%; MS (m/e): 440.41 (MH^+).
7.3.430	N4-(3,5-Dichloro-4-hydroxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950185)	In like manner to the preparation of N2-(3-aminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(3,5-dichlorophenyl-4-hydroxy)-5-fluoro-4-pyrimidineamine and ethyl 3-aminophenoxyacetate were reacted to prepare N4-(3,5-dichloro-4-hydroxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 22.51 min.; purity: 96.1%; MS (m/e): 466.88 (MH^+).
7.3.431	N4-(3-Aminophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofurane-5-yl)-2,4-pyrimidinediamine (R950162)	A mixture of N4-(3-aminophenyl)-2-chloro-5-fluoro-4-pyrimidineamine (10 mg, 0.06 mmol) and 2-methoxycarbonyl-5-aminobenzofuran (36 mg, 0.18 mmol) in dry MeOH (0.5 ml) was refluxed for 2 days (100 °C oil-bath temperature). The mixture was cooled to 22 °C, concentrated to dryness under reduced pressure and subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 9:1) to give N4-(3-aminophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofurane-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.24 (s, 1H), 7.96 (dd, 1H, J= 1.7, 3.5 Hz), 7.46-7.59 (m, 3H), 6.93-6.99 (m, 2H), 6.84 (d, 1H, J= 8.2 Hz), 6.35 (m, 1H), 3.84 (s, 3H); LCMS purity: 97.8%; MS (ES) m/e 394.02 (M^+, 70).

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Section Number	Name of compound and reference number	Experimental
7.3.432	N4-(3-Aminophenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R950163)	In like manner to the preparation of N4-(3-aminophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofurane-5-yl)-5-fluoro-2,4-pyrimidinediamine, N4-(3-aminophenyl)-2-chloro-5-fluoro-4-pyrimidineamine and 3-hydroxyaniline were reacted to prepare N4-(3-aminophenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 7.94 (d, 1H, J= 4.1 Hz), 7.20 (m, 2H), 6.89-7.00 (m, 4H), 6 30 (m, 2H); LCMS: ret. time: 11.92 min.; purity: 95.0%; MS (m/e): 312 09 (MH^+)
7.3.433	N4-(3-Aminophenyl)-5-fluoro-N2-(3-isopropoxyphenyl)-2,4-pyrimidinediamine (R950164)	In like manner to the preparation of N4-(3-aminophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofurane-5-yl)-5-fluoro-2,4-pyrimidinediamine, N4-(3-aminophenyl)-2-chloro-5-fluoro-4-pyrimidineamine and 3-isopropoxyaniline were reacted to prepare N4-(3-aminophenyl)-5-fluoro-N2-(3-isopropoxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 17.52 min.; purity: 98.9%; MS (m/e). 354.13 (MH^+).
7.3.434	N4-(3-Aminophenyl)-5-fluoro-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R950165)	In like manner to the preparation of N4-(3-aminophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofurane-5-yl)-5-fluoro-2,4-pyrimidinediamine, N4-(3-aminophenyl)-2-chloro-5-fluoro-4-pyrimidineamine and 4-isopropoxyaniline were reacted to prepare N4-(3-aminophenyl)-5-fluoro-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-D6–MeOD, 300 MHz): δ 7.90 (d, 1H, J= 4.1 Hz), 7.47 (m, 2H), 7.03 (t, 1H, J= 1.7 Hz), 6.60-6.95 (m, 5H), 6.29 (m, 1H), 4.43 (septett, 1H, J= 6.0 Hz), 1.18 (d, 6H, J= 6.0 Hz); LCMS: ret. time: 17.11 min.; purity: 88.4%; MS (m/e): 354.09 (MH^+).
7.3.435	N2-(3-Furylmethylene)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R950210)	In like manner to the preparation of N4-(3-aminophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofurane-5-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-furylmathylamine were reacted to prepare N2-(3-furylmethylene)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 16.03 min.; purity: 93.5%; MS (m/e): 301.10 (MH^+).
7.3.436	5-Fluoro-N4-(3-hydroxyphenyl)-N2-(4-methoxyphenyloxyethyleneamino)-2,4-pyrimidinediamine (R950211)	In like manner to the preparation of N4-(3-aminophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofurane-5-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 2-(4-methoxyphenyl)ethylamine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-(4-methoxyphenyloxyethyleneamino)-2,4-pyrimidinediamine. LCMS: ret. time: 18.88 min.; purity: 97.6%; MS (m/e): 371.09 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.437	N4-(3-Aminophenyl)-N2-[[N3-[N4-(3-aminophenyl)]-5-fluoro-2,4-pyrimidinediamine]aminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950137)	2,4-Dichloro-5-fluoropyrimidine and 3-aminoaniline were reacted to prepare N4-(3-aminophenyl)-N2-[[N3-[N4-(3-aminophenyl)]-5-fluoro-2,4-pyrimidinediamine]aminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 13.10 min.; purity: 96.4%; MS (m/e): 513.01 (MH^+).
7.3.438	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(hydroxyethyleneamino)phenyl]-2,4-pyrimidinediamine (R950208)	N2-(3-Aminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and 2-bromoethanol were reacted together to give N4-(3,4-ethylenedioxyphenyl)-N2-[3-(hydroxyethylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 15.44 min.; purity: 98.6%; MS (m/e): 398.05 (MH^+).
7.3.439	N2-[3-Bis(hydroxyethyl)aminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950209)	N2-(3-Aminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and 2-bromoethanol were reacted together to give N2-[3-bis(hydroxyethyl)aminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 15.64 min.; purity: 97.8%; MS (m/e): 442.06 (MH^+).
7.3.440	6-Ethoxycarbonyl-N4-(ethoxycarbonylmethyl)-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-5-nitro-2,4-pyrimidinediamine (R925858)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-hydroxyphenyl)-2,4-pyrimidinediamine, N-(2-chloro-6-ethoxycarbonyl-5-nitro-4-pyrimidinyl)glycine ethyl ester and ethyl 4-aminophenoxyacetate were reacted to yield 6-ethoxycarbonyl-N4-(ethoxycarbonylmethyl)-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-5-nitro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 9.00 (bs, 1H), 7.49 (bs, 1H), 7.41 (d, 2H, J= 9.0 Hz), 6.89 (d, 2H, J= 9.0 Hz), 4.62 (s, 2H), 4.46 (q, 2H, J=-7.2 Hz), 4.31-4 19 (m, 6H), 1.40 (t, 3H, J= 7.2 Hz), 1.33-1.25 (m, 6H); LCMS: ret. time: 30.00 min.; purity: 98 %; MS (m/e): 492 (MH^+).
7.3.441	N4-Benzyloxy-5-ethoxycarbonyl-N2-(3,4-ethylenedioxyphenyl)-2,4-pyrimidinediamine (R925837)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-benzyloxy-2-chloro-5-ethoxycarbonyl-4-pyrimidineamine and 1,4-benzodioxan-6-amine were reacted to yield N4-benzyloxy-5-ethoxycarbonyl-N2-(3,4-ethylenedioxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 8.55 (s, 1H), 7.49-7.44 (m, 3H), 7.39-7.34 (m, 4H), 7.30-7.22 (m, 1H), 6.67 (d, 1H, J= 8.4 Hz), 4.98 (s, 2H), 4.23-4.17 (m, 6H), 1.26 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 26.14 min.; purity: 95%; MS (m/e): 423 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.442	N4-Benzyloxy-5-ethoxycarbonyl-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925824)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-benzyloxy-2-chloro-5-ethoxycarbonyl-4-pyrimidineamine and 3-hydroxyaniline were reacted to yield N4-benzyloxy-5-ethoxycarbonyl-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 24.28 min.; purity: 88 %; MS (m/e): 381 (MH^+).
7.3.443	N2,N4-Bis[4-(aminocarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (R945025)	A mixture of 4-nitrophenol (7.65 g, 55 mmol), 2-bromoacetamide (6.90 g, 50 mmol) and K_2CO_3 (13.8 g, 0.1 mol) in acetone (50 mL) was stirred at room temperature for 24 h. The reaction mixture was diluted with water, and acetone was removed under reduced pressure. The formed light-yellow precipitate was collected by filtration, washed with water and dried to give 1-aminocarbonylmethyleneoxy-4-nitrobenzene (8.28 g, 84%). Hydrogenation of 1-aminocarbonylmethyleneoxy-4-nitrobenzene (3 g, 15 mmol) in methanol (50 mL) catalyzed by 10% Pd-C (500 mg) and Na_2SO_4 (500 mg) at 50 psi for 2h gave 4-(aminocarbonylmethyleneoxy)aniline (2.59 g, quant.). 4-(Aminocarbonylmethyleneoxy)aniline (500 mg, 3 mmol) and 2,4-dichloro-5-fluoropyrimidine (200 mg, 1.2 mmol) were dissolved in methanol (10 mL) and water (1 mL) and was stirred at 70 °C for 24 h. Then methanol was removed under reduced pressure. The remaining aqueous solution was acidified with 1 N HCl (80 mL). The formed white precipitate was collected by filtration to give N2,N4-bis[4-(aminocarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (370 mg, 72%). ^1H NMR (acetone-d_6): δ 4.46 (s, 2H), 4.50 (s, 2H), 6.81 (br, NH, 2H), 6.91 (d, J= 9.0 Hz, 2H), 6.98 (d, J= 9.0 Hz, 2H), 7.20 (br, 2H, NH), 7.63 (d, J= 9.3 Hz, 2H), 7.72 (d, J= 8.7 Hz, 2H), 7 93 (d, J=3.6 Hz, 1H), 8.27 (br, 1H, NH), 8.44 (br, 1H, NH); LCMS: ret. time: 13.91 min.; purity: 100%; MS (m/e): 427.02 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.444	N2,N4-Bis[4-(cyanomethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (R945032)	To a solution of N2,N4-bis[4-(aminocarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (200 mg, 0.47 mmol) in THF (10 mL) was added trifluoroacetic anhydride (0.33 mL, 2.35 mmol) and pyridine (0.38 mL, 4.7 mmol) at room temperature and was stirred at room temperature overnight. The mixture was diluted with ethyl acetate (80 mL) and 1 N HCl (80 mL). The organic layer was washed with 1 N HCl (2 x 60 mL), water (2 x 60 mL) and brine (60 mL). The ethyl acetate layer was dried and evaporated. The residue was recrystallized from ethyl acetate and hexanes to give N2,N4-bis[4-(cyanomethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (159 mg, 87%) as a white solid. ^{1}H NMR (acetone-d_6): δ 5.09 (s, 2H), 5.16 (s, 2H), 7.08 (d, J= 9.3 Hz, 2H), 7.17 (d, J= 9.0 Hz, 2H), 7.63 (d, J= 9.0 Hz, 2H), 7.77 (d, J= 9.3 Hz, 2H), 8.17 (d, J= 4.8 Hz, 1H), 9.55 (br, 1H, NH), 11.00 (br, 1H, NH); LCMS: 21.47 min.; 96.11%; MS (m/e): 391.20 (MH^+).
7.3.4456	N2,N4-Bis[4-(1H-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R945033)	To a solution of N2,N4-bis[4-(cyanomethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (100 mg, 0.26 mmol) in DMF (10 mL) was added NH_4Cl (136 mg, 2.54 mmol), sodium azide (100 mg, 1.54 mmol), and one drop of acetic acid and was stirred at 70 °C overnight. Then it was titrated with ethyl acetate (80 mL) to give precipitation. The precipitate was collected by filtration, washed with 1 N HCl and water to give N2,N4-bis[4-(1H-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (66 mg, 54%) as a white solid. ^{1}H NMR (CD_3OD): δ 5.31 (s, 2H), 5.34 (s, 2H), 6.93 (d, J= 9.0 Hz, 2H), 7.00 (d, J= 9.3 Hz, 2H), 7.04 (d, J= 9.0 Hz, 2H), 7.57 (d, J= 9.0 Hz, 2H), 7.81 (d, J= 4.2 Hz, 1H); LCMS: 16.54 min.; purity: 88.34%; MS (m/e): 477.02 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.446	N2,N4-Bis(4-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R945034)	A mixture of 4-Aminobenzoic acid (410 mg, 3 mmol) and 2,4-dichloro-5-fluoropyrimidine (100 mg, 0.6 mmol) in methanol (10 mL) and water (1 mL) was stirred at 100 °C for 24 h to yield N2,N4-bis(4-carboxyphenyl)-5-fluoro-2,4-pyrimidinediamine after methanol was removal. This residue was redissolved in DMF (10 mL) and to it was added potassium carbonate (1.65 g, 12 mmol) and iodomethane (0.37 mL, 6 mmol), stirred at room temperature overnight, and then diluted with 1 N HCl (80 mL) and ethyl acetate (80 mL). The ethyl acetate layer was washed with 1N HCl (60 mL) and water (60 mL). The organic layer was separated, dried, evaporated and the resulting residue was recrystallized from ethyl acetate/hexanes to give N2,N4-bis(4-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (150 mg, 63%). ^{1}H NMR (acetone-d_6): δ 3.85 (s, 3H), 3.88 (s, 3H), 7.88-7.97 (m, 4H), 7.98-8.05 (m, 4H), 8.18 (d, J= 3 0 Hz, 1H), 9.00 (br, 1H, NH), 9.04 (br, 1H, NH); LCMS: ret. time: 27.07 min.; purity: 95.54%; MS (m/e): 397.04 (MH^+).
7.3.447	N2,N4-Bis(3-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R945035)	In a manner analogous to the preparation of N2,N4-bis(4-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 3-aminobenzoic acid (410 mg, 3 mmol) and 2,4-dichloro-5-fluoropyrimidine (100 mg, 0.6 mmol) gave N2,N4-bis(3-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (180 mg, 76%) as a white solid. ^{1}H NMR (acetone-d_6): δ 3.81 (s, 3H), 3.83 (s, 3H), 7.37 (t, J= 8.1 Hz, 1H), 7.47 (t, J= 8.1 Hz, 1H), 7.60 (d, J= 7.8 Hz, 1H), 7.75 (d, J= 7.5 Hz, 1H), 8.02 (d, J= 6.3 Hz, 1H), 8.10 (d, J= 3.6 Hz, 1H), 8.24 (d, J= 8.4 Hz, 1H), 8.36 (d, J= 11.4 Hz, 2H), 8.74 (br, 1H, NH), 8.82 (br, 1H, NH); LCMS: ret. time: 22.77 min.; purity: 91.04%; MS (m/e): 397.00 (MH^+).
7.3.448	N2,N4-Bis(3-carboxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R945036)	A solution of N2,N4-bis(3-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (100 mg, 0.25 mmol) and NaOH (140 mg, 3.5 mmol) in THF:H_2O (5 mL, each) was stirred at room temperature overnight. The reaction mixture was diluted with water (60 mL) and ethyl acetate (60 mL). The aqueous layer was separated, acidified with 1N HCl solution to pH 3. The formed precipitate was collected by filtration and recrystallized from methanol to give N2,N4-bis(3-carboxyphenyl)-5-fluoro-2,4-pyrimidinediamine (54 mg, 58%) as a white solid. ^{1}H NMR (CD_3OD): δ 7.31 (t, J= 8.1 Hz, 1H), 7.42 (t, J= 8.1 Hz, 1H), 7.61 (dm, J= 7.8 Hz, 1H), 7.76 (dm, J= 8.4 Hz, 1H), 7.89 (dm, J= 7.2 Hz, 1H), 7.98 (d, J= 3.6 Hz, 1H), 8.01 (m, 1H), 8.20 (m, 1H), 8.37 (m, 1H); LCMS: ret. time: 15.77 min.; purity: 98.84%; MS (m/e): 369.03 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.449	N2,N4-Bis(4-carboxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R945037)	In a manner analogous to the preparation of N2,N4-bis(3-carboxyphenyl)-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis(4-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (100 mg, 0.25 mmol) and NaOH (200 mg, 5 mmol) gave N2,N4-bis(4-carboxyphenyl)-5-fluoro-2,4-pyrimidinediamine (55 mg, 59%) as a white solid. ^{1}H NMR (CD_3OD): δ 7.77 (d, J= 8.7 Hz, 2H), 7.92 (d, J= 8.7 Hz, 2H), 7.94 (d, J= 8.4 Hz, 2H), 8.02 (d, J= 8.7 Hz, 2H), 8.07 (d, J= 3.6 Hz, 1H); LCMS: ret. time: 16.34 min.; purity: 100%; MS (m/e): 368.87 (MH^+).
7.3.450	N2,N4-Bis(3-isopropylaminocarbonyloxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926412)	The reaction of 1 equivalent of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine with 3 equivalents of isopropyl isocyanate in the presence of pyridine in CH_2Cl_2 at room temperature for 24 h followed by extractive work up using CH_2Cl_2 gave the desired N2,N4-bis(3-isopropylaminocarbonyloxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 7.82 (d, 1H, J= 3.6 Hz), 7.66 (bd, 1H), 7.48 (bd, 1H). 7.15-7.02 (m, 2H), 6.76-6.76 (m, 2H), 6.56 (bd, 1H, J= 8.1 Hz), 6.45 (dd, 1H, J= 1.8 and 8.4 Hz), 4.70 (m, 2H), 1.05 (d, 12H, J= 6.3 Hz); ^{19}F NMR ($CDCl_3$ + CD_3OD): - 47206; LCMS: ret. time: 15.40 min.; purity: 90%.
7.3.451	N2,N4-Bis[4-(ethylaminocarbonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R945040)	A mixture of 1,4-diaminobenzene (4 g, 37 mmol), ethyl isocyanate (1 mL, 12.6 mmol) and potassium carbonate (8.72 g, 63 mmol) in THF (20 mL) was stirred at room temperature overnight. The reaction mixture was partitioned in 1N HCl solution (80 mL) and ethyl acetate (80 mL). The aqueous layer was extracted with ethyl acetate (4 x 80 mL). The combined organic layers was dried, evaporated, recrystallized from MeOH/CH_2Cl_2/hexanes to give 4-(ethylaminocarbonylamino)aniline (1.4 g, 62%) as a beige solid. In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 4-(ethylaminocarbonylamino)aniline (537 mg, 3 mmol) and 2,4-dichloro-5-fluoropyrimidine (100 mg, 0.6 mmol) gave N2,N4-bis[4-(ethylaminocarbonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (180 mg, 66%) as a white solid. ^{1}H NMR (CD_3OD): δ 1.16 (t, J= 7.2 Hz, 6H), 3.24 (q, J= 7.2 Hz, 4H), 7.29 (d, J= 9.0 Hz, 2H), 7.40 (t, J= 9.0 Hz, 4H), 7.55 (d, J= 9.0 Hz, 2H), 7.87 (s, 1H, NH), 7.89 (s, 1H, NH); LCMS: ret. time: 16.93 min.; purity: 93.43%; MS (m/e): 453.03 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.452	N2,N4-Bis[3-(ethylaminocarbonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R945045)	In a manner analogous to the preparation of N2,N4-bis[4-(ethylaminocarbonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine, the reaction of 1,3-diaminobenzene (2 g, 18.5 mmol), ethyl isocyanate (0.5 mL, 6.3 mmol) and potassium carbonate (4.36 g, 31.5 mmol) gave 3-(ethylaminocarbonylamino)aniline (940 mg, 83%). The reaction of 3-(ethylaminocarbonylamino)aniline (537 mg, 3 mmol) and 2,4-dichloro-5-fluoropyrimidine (100 mg, 0.6 mmol) gave N2,N4-bis[3-(ethylaminocarbonylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (180 mg, 66%) as a white solid. ^{1}H NMR (CD_3OD): δ 1.14 (t, J= 6.9 Hz, 3H), 1.15 (t, J= 7.5 Hz, 3H), 3.21 (q, J= 7.2 Hz, 2H), 3.22 (q, J= 7.5 Hz, 2H), 7.06 (ddd, J= 0.9, 2.1, 7.8 Hz, 1H), 7.10-7 28 (m, 5H), 7.53 (t, J= 2.1 Hz, 1H), 7.80 (m, 1H), 7.92 (d, J= 5.7 Hz, 1H); LCMS: ret. time: 17.17 min.; purity: 89.63%; MS (m/e): 453.38 (MH^+).
7.3.453	N2,N4-Bis(4-hydroxy-3-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R945043)	A solution of N2,N4-bis(3-carboxy-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (70 mg, 0.17 mmol) and thionyl chloride (0.04 mL, 0.55 mmol) in MeOH (10 mL) was refluxed overnight. Methanol was removed *in vacuo*. The residue was diluted with EtOAc (60 mL) and sodium hydrogen carbonate solution (60 mL). The EtOAc layer was washed with $NaHCO_3$ aqueous solution (60 mL) and water (60 mL). The organic layer was dried, evaporated and crystallized from MeOH/Et_2O to give N2,N4-bis(4-hydroxy-3-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (58 mg, 77%). ^{1}H NMR (DMSO-d6): δ 3.69 (s, 3H), 3.71 (s, 3H), 6.81 (d, J= 9.3 Hz, 1H), 6.92 (d, J= 9.0 Hz, 1H), 7.64 (dd, J= 2.7, 9.0 Hz, 1H), 7.84 (dd, J= 2.1 and 8.4 Hz, 1 H), 8.03-8.07 (m, 3 H), 9.14 (s, 1 H, NH), 9.34 (s, 1 H, NH), 10.16 (s, 1 H, OH), 10.29 (s, 1H, OH); ^{19}F NMR (282 MHz, DMSO-d6): δ - 165.60; LCMS: ret. time: 22.24 min.; purity: 100%; MS (m/e): 428.98 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.454	N2,N4-Bis[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine(R945046) 5-Fluoro-N2,N4-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl],[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945047) N2,N4-Bis[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R945048)	Compound N2,N4-bis[4-(1H-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (30 mg, 0.063 mmol), iodomethane (0.024 mL, 0.38 mmol) and K_2CO_3 (88 mg, 0.64 mmol) in DMF (5 mL) was stirred at room temperature overnight. Then it was diluted with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (50 mL) and brine (50 mL). After separation, the ethyl acetate layer was dried, evaporated and purified by flash column chromatography (EtOAc/hexanes = 2/1, 1/1, EtOAc) to give a mixture of following compounds: N2,N4-bis[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine **R945046** (6 mg, 19%), ^1H NMR ($CDCl_3$): δ 4 37 (s, 3H), 4.38 (s, 3H), 5.33 (s, 2H), 5.36 (s, 2H), 6.65 (d, J= 3.0 Hz, 1H), 6.76 (s, 1H), 6.98 (d, J= 9.0 Hz, 2H), 7.04 (d, J= 9.3 Hz, 2H), 7.42 (d, J= 9.0 Hz, 2H), 7.51 (d, J= 9.0 Hz, 2H), 7.90 (br, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 168.52; LCMS: ret. time: 20.44 min.; purity: 94.92%, MS (m/e) 505.02 (MH^+); 5-fluoro-N2,N4-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl],[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine **R945047** (8 mg, 25%), ^1H NMR ($CDCl_3$): δ 4.18 (s, 3H), 4.20 (s, 3H), 4.36 (s, 3H), 4.37 (s, 3H), 5 34 (s, 2H), 5.37 (s, 2H), 5.42 (s, 2H), 5.46 (s, 2H), 6.69 (br, 2H), 6.80 (s, 1H), 6.83 (s, 1H), 6.91 (d, J= 9.3 Hz, 2H), 6.98 (d, J= 9.0 Hz, 2H), 6.99 (d, J= 9.3 Hz, 2H), 7.04 (d, J= 9.0 Hz, 2H), 7.41 (d, J= 9.9 Hz, 2H), 7.44 (d, J= 9.3 Hz, 2H), 7.50 (d, J= 9.0 Hz, 2H), 7.54 (d, J= 9.0 Hz, 2H), 7.91 (br, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 168.39, - 168.16; LCMS: ret. time: 19 42 min.; purity: 91.18%; MS (m/e): 504.99 (MH^+), and N2,N4-bis[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine **R945048** (6 mg, 19%), ^1H NMR (CD_3OD + $CDCl_3$): δ 4.20 (s, 3H), 4.22 (s, 3H), 5.50 (s, 2H), 5.55 (s, 2H), 6.95 (d, J= 9.0 Hz, 2H), 7.02 (d, J= 9.3 Hz, 2H), 7.52 (d, J= 9.0 Hz, 2H), 7.66 (d, J= 9.3 Hz, 2H), 7.84 (d, J= 3.6 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD+$CDCl_3$): δ - 163.12; LCMS: ret. time: 18.32 min.; purity: 83.41%; MS (m/e): 504.99 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.455	N4-(4-Aminocarbonylmethyleneoxyphenyl)-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945052)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 4-(aminocarbonylmethyleneoxy)aniline (398 mg, 2.4 mmol) and 2,4-dichloro-5-fluoropyrimidine (200 mg, 1.2 mmol) gave N4-(4-aminocarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (270 mg, 76%). In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of methyl 4-aminophenoxyacetate (183 mg, 1 mmol) and N4-(4-aminocarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (100 mg, 0.34 mmol) gave N4-(4-aminocarbonylmethyleneoxyphenyl)-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (120 mg, 80%). ^{1}H NMR (acetone-d_6): δ 3.25 (s, 3H), 3.98 (s, 2H), 4.33 (s, 2H), 6.45 (d, J= 8.7 Hz, 2H), 6.49 (d, J= 9.3 Hz, 2H), 6.93 (d, J= 8.7 Hz, 2H), 7.13 (d, J= 9.0 Hz, 2H), 7.71 (d, J= 5.1 Hz, 1H), 9.46 (br, 1H, NH), 9.78 (br, 1H, NH); LCMS: ret. time: 16.65 min.; purity: 100%; MS (m/e): 442.01 (MH^+).
7.3.456	N4-(4-Cyanomethyleneoxyphenyl])5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945053)	In a manner analogous to the preparation of N2,N4-bis(4-cyanomethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of N4-(4-aminocarbonylmethyleneoxyphenyl)-5-fluoro-N2-(4-methoxycarbonylmethylene oxyphenyl)-2,4-pyrimidinediamine (80 mg, 0.18 mmol), trifluoroacetic anhydride (0.13 mL, 0.92 mmol) and pyridine (0.15 mL, 1.84 mmol) gave N4-(4-cyanomethyleneoxyphenyl)-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (52 mg, 68%) as a white solid. ^{1}H NMR (DMSO-d6): δ 3.24 (s, 3H), 4.26 (s, 2H), 4.71 (s, 2H), 6.36 (d, J= 9.3 Hz, 2H), 6.59 (d, J= 9.0 Hz, 2H), 7.06 (d, J= 9.0 Hz, 2H), 7.28 (d, J= 9.0 Hz, 2H), 7 58 (d, J= 3.6 Hz, 1H), 8.59 (br, 1H, NH), 8.85 (br, 1H, NH); ^{19}F NMR (282 MHz, DMSO-d6): δ - 166.26; LCMS: ret. time: 21.37 min.; purity: 100%; MS (m/e): 424.01 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.457	N2,N4-Bis[3-hydroxy-4-(methoxycarbonyl)phenyl]-5-fluoro-2,4-pyrimidinediamine (R945056)	A solution of 4-amino-2-hydroxybenzoic acid (1 g, 6.5 mmol) in MeOH (15 mL) and concentrated sulfonic acid (1 mL) was refluxed overnight. The reaction mixture was quenched with $NaHCO_3$ aqueous solution (60 mL) and EtOAc (60 mL). The organic layer was separated, dried, evaporated to give 3-hydroxy-4-methoxycarbonylaniline. In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 3-hydroxy-4-methoxycarbonylaniline (500 mg, 3 mmol) and 2,4-dichloro-5-fluoropyrimidine (100 mg, 0.6 mmol) gave N2,N4-bis-[3-hydroxy-4-(methoxycarbonyl)phenyl]-5-fluoro-2,4-pyrimidinediamine (105 mg, 41%). ^{1}H NMR (DMSO-d6): δ 3.90 (s, 3H), 3.93 (s, 3H), 7.31 (dd, J= 2.4, 9.0 Hz, 1H), 7.56 (dd, J= 2.1, 8.7 Hz, 1H), 7.63 (d, J= 2.1 Hz, 1H), 7.67 (d, J= 2.1 Hz, 1H), 7.67 (d, J= 9.0 Hz, 1H), 7 79 (d, J= 9.0 Hz, 1H), 8.28 (d, J= 3.6 Hz, 1H), 9.72 (s, 1H, NH), 9 82 (s, 1H, NH), 10.77 (s, 1H, OH), 10 80 (s, 1H, OH); ^{19}F NMR (282 MHz, DMSO-d6): δ - 161.74; LCMS: ret. time: 31.47 min.; purity: 96.03%; MS (m/e): 428.99 (MH^+).
7.3.458	N2-(4-Aminocarbonylmethyleneoxyphenyl)-5-fluoro-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945060)	In a manner analogous to the preparation of N4-(4-aminocarbonylmethyleneoxyphenyl)-5-fluoro-N2-(4-methoxycarbonylmethylene oxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(4-methoxycarbonylmethyleneoxyphenyl)-4-pyrimidineamine (150 mg, 0.48 mmol) and 4-(aminocarbonylmethyleneoxy)aniline (240 mg, 1.44 mmol) gave N2-(4-aminocarbonylmethyleneoxyphenyl)-5-fluoro-N4-(4-methoxycarbonylmethylene oxyphenyl)-2,4-pyrimidinediamine (145 mg, 68%). ^{1}H NMR (DMSO-d6): δ 3.70 (s, 3H), 4.40 (s, 2H), 4.81 (s, 2H), 6.91 (d, J= 8.4 Hz, 2 H), 6.93 (d, J= 8.4 Hz, 2H), 7.36 (d, J= 8.4 Hz, 2H), 7.54 (d, J= 8.7 Hz, 2H), 8.21 (d, J= 4.8 Hz, 1H), 10.13 (br, 1H, NH), 10.39 (br, 1H, NH); ^{19}F NMR (282 MHz, DMSO-d6): δ - 162.26; LCMS: ret. time: 15.37 min.; purity: 78.49%; MS (m/e): 442.07 (MH^+).
7.3.459	N2,N4-Bis(3-hydroxy-4-carboxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R945061)	In a manner analogous to the preparation of N2,N4-bis(3-carboxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of N2,N4-bis[3-hydroxy-4-(methoxycarbonyl)phenyl]-5-fluoro-2,4-pyrimidinediamine (70 mg, 0.16 mmol) and NaOH (100 mg, 2.5 mmol) gave N2,N4-bis(3-hydroxy-4-carboxyphenyl)-5-fluoro-2,4-pyrimidinediamine (50 mg, 77%) as a white solid. ^{1}H NMR (DMSO-d6): δ 7.21 (dd, J= 1.5 and 8.7 Hz, 1H), 7.46-7.52 (m, 3H), 7.63 (d, J= 8.7 Hz, 1H), 7.72 (d, J= 8.7 Hz, 1H), 8.28 (d, J= 3.3 Hz, 1H), 9.71 (s, 1H, NH), 9.79 (s, 1H, NH), 11.34 (br, 2H); ^{19}F NMR (282 MHz, DMSO-d6): δ - 161.10; LCMS: ret. time: 20.76 min.; purity: 84.65%; MS (m/e): 400.95 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.460	N2-(4-Cyanomethyleneoxyphenyl)-5-fluoro-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945062)	In a manner analogous to the preparation of N2,N4-bis(4-cyanomethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine, N2-(4-aminocarbonylmethyleneoxyphenyl)-5-fluoro-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (100 mg, 0.23 mmol), trifluoroacetic anhydride (0.16 mL, 1.13 mmol) and pyridine (0.18 mL, 2.21 mmol) gave N2-(4-cyanomethyleneoxyphenyl)-5-fluoro-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (66 mg, 69%) as a white solid. ^{1}H NMR (acetone-d_6): δ 3.75 (s, 3H), 4.67 (s, 2H), 4.89 (s, 2H), 6.88 (d, J= 9.0 Hz, 2H), 6.90 (d, J= 9.3 Hz, 2H), 7.48 (d, J= 9.0 Hz, 2H), 7.54 (d, J= 9.0 Hz, 2H), 7.84 (d, J= 4.2 Hz, 1H), 9.17 (br, 1H, NH), 10.59 (br, 1H, NH); ^{19}F NMR (282 MHz, acetone-d_6): δ - 164.65; LCMS: ret. time: 20.69 min.; purity: 94.35%; MS (m/e): 424.02 (MH^+).
7.3.461	N2,N4-Bis(3-methoxy-4-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R945065)	In a manner analogous to the preparation of N2,N4-bis[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine, 2-methoxy-4-nitrobenzoic acid (1 g, 5 mmol), potassium carbonate (1.4 g, 10 mmol) and iodomethane (0.47 mL, 7.5 mmol) gave methyl 2-methoxy-4-nitrobenzoate (820 mg, 77%) as a white solid. The hydrogenation of methyl 2-methoxy-4-nitrobenzoate (700 mg, 3.3 mmol) in methanol (10 mL) catalyzed by 5% Pd-C (100 mg) and Na_2SO_4 (100 mg) at 50 psi for 1h gave methyl 4-amino-2-methoxybenzoate (600 mg, quant.) as a white solid. In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, methyl 4-amino-2-methoxybenzoate (542 mg, 3 mmol) and 2,4-dichloro-5-fluoropyrimidine (100 mg, 0.6 mmol) gave N2,N4-bis(3-methoxy-4-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (180 mg, 66%) as a white solid. ^{1}H NMR (acetone-d_6): δ 3.76 (s, 3H), 3.77 (s, 3H), 3.81 (s, 6H), 7.36 (dd, J= 1.8, 8.7Hz, 1H), 7.57 (s, 1H), 7.58 (dd, J= 2.1 and 7.2 Hz, 1H), 7.69 (d, J= 2.1 Hz, 1H), 7.73 (d, J= 8.4 Hz, 1H), 7.75 (d, J= 9.0 Hz, 1H), 8.17 (d, J= 3.3 Hz, 1H), 8.89 (s, 2H, NH); ^{19}F NMR (282 MHz, acetone-d_6): δ - 165.18; LCMS: ret. time: 23.17 min.; purity: 100%; MS (m/e): 456.96 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.462	N2,N4-Bis(4-methoxy-3-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R945066)	In a manner analogous to the preparation of N2,N4-bis(3-methoxy-4-methoxycarbonyl)phenyl)-5-fluoro-2,4-pyrimidinediamine, 2-hydroxy-5-nitrobenzoic acid (1 g, 5.5 mmol), potassium carbonate (3 g, 22 mmol) and iodomethane (1 mL, 16 mmol) gave methyl 2-hydroxy-5-nitrobenzoate (880 mg, 77%). The hydrogenation of methyl 2-hydroxy-5-nitrobenzoate (700 mg, 3.3 mmol) using 10% Pd-C (100 mg) and Na_2SO_4 (100 mg) in MeOH at 50 psi gave methyl 5-amino-2-methoxybenzoate (600 mg). In a manner analogous to the preparation of N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine, methyl 5-amino-2-methoxybenzoate (542 mg, 3 mmol) and 2,4-dichloro-5-fluoropyrimidine (100 mg, 0.6 mmol) gave N2,N4-bis(4-methoxy-3-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (170 mg, 62%) as a pink solid. ^{1}H NMR (acetone-d_6): δ 3.76 (s, 3H), 3.77 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 7.08 (dd, J= 0.8, 9.0 Hz, 1H), 7.18 (d, J= 9.0 Hz, 1H), 7.66 (dd, J= 3.0 and 8.7 Hz, 1H), 7.78 (dd, J= 1.5 and 3.0 Hz, 1H), 7.86 (dt, J= 2.7 and 9.0 Hz, 1H), 7.98 (t, J= 2.7 Hz, 1H), 8.32 (d, J= 5.1 Hz, 1H); ^{19}F NMR (282 MHz, acetone-d_6): δ -163.88; LCMS: ret. time: 19.07 min.; purity: 98.17%; MS (m/e): 456.94 (MH^+).
7.3.463	N2,N4-Bis(3-carboxy-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R945067)	In a manner analogous to the preparation of N2,N4-bis(3-carboxyphenyl)-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis[4-methoxy-3-(methoxycarbonyl)phenyl]-5-fluoro-2,4-pyrimidinediamine (80 mg, 0.18 mmol) and NaOH (200 mg, 5 mmol) gave N2,N4-bis(3-carboxy-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (80 mg). ^{1}H NMR (DMSO-d6): δ 3.75 (s, 3H), 3.80 (s, 3H), 6.94 (d, J= 9.6 Hz, 1H), 7.05 (d, J= 9.3 Hz, 1H), 7.78-7.80 (m, 3H), 7.94 (dd, J= 9.3 Hz, 1H), 8.04 (d, J= 3.6 Hz, 1H), 9.10 (s, 1H, NH), 9.30 (s, 1H, NH); ^{19}F NMR (282 MHz, DMSO-d6): δ - 165.56; LCMS: ret. time: 14.65 min.; purity: 100%; MS (m/e): 428.83 (MH^+).
7.3.464	N2,N4-Bis(4-carboxy-3-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R945068)	In a manner analogous to the preparation of N2,N4-bis(3-carboxyphenyl)-5-fluoro-2,4-pyrimidinediamine, N2,N4-bis(3-methoxy-4-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (30 mg, 0.06 mmol) and NaOH (200 mg, 5 mmol) gave N2,N4-bis(4-carboxy-3-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (18 mg, 64%) as a white solid. ^{1}H NMR (DMSO-d6): δ 3.66 (s, 3H), 3.73 (s, 3H), 7.37 (d, J= 8.4 Hz, 1H), 7.47 (s, 1H), 7.49 (s, 1H), 7.61-7.71 (m, 3H), 8.25 (d, J= 3.6 Hz, 1H), 9.65 (s, 1H, NH), 9.70 (s, 1H, NH); ^{19}F NMR (282 MHz, DMSO-d6): δ - 162.11; LCMS: ret. time: 17.25 min.; purity: 100%; MS (m/e): 429.04 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.465	N2-(4-Cyanomethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945070)	In a manner analogous to the preparation of N2,N4-bis(4-cyanomethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine, N2-(4-(aminocarbonylmethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (60 mg, 0.16 mmol), trifluoroacetic anhydride (0.11 mL, 0.8 mmol) and pyridine (0.13 mL, 1.6 mmol) gave N2-(4-cyanomethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (30 mg, 53%). ^{1}H NMR (acetone-d_6): δ 5.04 (s, 2H), 6.60 (ddd, J= 0.9, 2.4 and 8.1 Hz, 1H), 7.02 (d, J= 9.3 Hz, 2H), 7.15 (t, J= 8.1 Hz, 1H), 7.31 (ddd, J= 1.2, 2.1 and 8.1 Hz, 1H), 7.38 (t, J= 2.1 Hz, 1H), 7.78 (d, J= 9.3 Hz, 2H), 7.98 (d, J= 3.6 Hz, 1H), 8.34 (s, 1H, NH), 8.42 (s, 1H, NH); ^{19}F NMR (282 MHz, acetone-d_6): δ - 168.06; LCMS: ret. time: 18.17 min.; purity: 97.47%; MS (m/e): 352.05 (MH^+).
7.3.466	N4-(4-Cyanomethyleneoxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R945172)	In a manner analogous to the preparation of N2,N4-bis(4-cyanomethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine, N4-(4-aminocarbonylmethyleneoxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, trifluoroacetic anhydride and pyridine in THF gave N4-(4-cyanomethyleneoxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 4.27 (m, 4H), 4.82 (s, 2H), 6.70 (dd, J= 2.4 and 8.4 Hz, 1H), 6.75 (d, J= 2.4 Hz, 1H), 6.86 (d, J= 8.4 Hz, 1H), 7.02 (d, J= 9.0 Hz, 2H), 7.32 (d, J= 9.0 Hz, 2H), 8.64 (d, J= 1.8 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 135.58; LCMS: ret. time: 19.92 min.; purity: 98.02%; MS (m/e): 393.98 (MH^+).
7.3.467	N2,N4-Bis[4-[2-methoxyimino(amino)ethyleneoxy]phenyl]-5-fluoro-2,4-pyrimidinediamine (R945096)	N2,N4-Bis(4-cyanomethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (50 mg, 0.13 mmol), methoxyamine HCl salt (54 mg, 0.65 mmol) and sodium bicarbonate (54 mg, 0.65 mmol) were dissolved in methanol (5 mL). The reaction solution was stirred at 70 °C for 7 days. Then methanol was removed under reduced pressure. The residue was partitioned in EtOAc (60 ml) and water (60 mL). The ethyl acetate layer was washed with water (2 x 60 mL), dried, evaporated and purified by flash column chromatography (EtOAc/hexanes; 1:1; EtOAc) to give N2,N4-bis[4-[2-methoxyimino(amino)ethyleneoxy]phenyl]-5-fluoro-2,4-pyrimidinediamine (30 mg, 48%). ^{1}H NMR (acetone-d_6): δ 3.70 (s, 3H), 3.71 (s, 3H), 4.44 (s, 2H), 4.49 (s, 2H), 5.43 (br, 2H), 5.47 (br, 2H), 6.93 (d, J= 9.0 Hz, 2H), 7.00 (d, J= 9.0 Hz, 2H), 7.62 (d, J= 9.0 Hz, 2H), 7.71 (d, J= 9.0 Hz, 2H), 7.93 (d, J= 3.6 Hz, 1H), 8.26 (br, 1H, NH), 8.40 (br, 1H, NH); ^{19}F NMR (282 MHz, acetone-d_6): δ - 169.08; LCMS: ret. time: 14.41 min.; purity: 100%; MS (m/e): 484.97 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.468	N2-(4-Carboxymethyleneoxyphenyl)-N4-(4-cyanomethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R945097)	In a manner analogous to the preparation of N2,N4-bis(3-carboxyphenyl)-5-fluoro-2,4-pyrimidinediamine, N4-(4-cyanomethyleneoxyphenyl)-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (10 mg, 0.024 mmol) and LiOH (2 mg, 0.048 mmol) gave N2-(4-carboxymethyleneoxyphenyl)-N4-(4-cyanomethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (5 mg, 52%) as a white solid. ^{1}H NMR (CD_3OD): δ 4.60 (s, 2H), 4.99 (s, 2H), 6.88 (d, J= 9.0 Hz, 2H), 7.02 (d, J= 9.0 Hz, 2H), 7.39 (d, J= 8.7 Hz, 2H), 7.65 (d, J= 9.0 Hz, 2H), 7.84 (d, J= 3.9 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD): δ - 168.81; LCMS: ret. time: 17.95 min.; purity: 86.04%; MS (m/e): 409.99 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.469	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945127)	A mixture of 3-nitrophenol (4 g, 29 mmol), bromoacetonitrile (2.5 mL, 36 mmol) and K_2CO_3 (8 g, 58 mmol) in acetone (20 mL) was stirred at room temperature overnight. The reaction mixture was diluted with water (80 mL) and acetone was removed under reduced pressure. The light-yellow precipitate was collected by filtration, washed with water and dried to give 1-cyanomethyleneoxy-3-nitrobenzene. 1-Cyanomethyleneoxy-3-nitrobenzene (2 g, 11 mmol) was dissolved in methanol (20 mL) and to the solution was added hydroxyamine HCl salt (1 g, 14 mmol) and triethylamine (3 mL, 22 mmol). The reaction mixture was refluxed for 2 h and the solvent was removed under reduced pressure. The residue was redissolved in THF (30 mL). To the solution was added acetyl chloride (4 mL, 56 mmol) and pyridine (9 mL, 0.11 mol). The reaction mixture was stirred at room temperature overnight, then added THF (10 mL), water (10 mL) and NaOH (3 g, 75 mmol). The reaction solution was refluxed overnight, diluted with water (80 mL). The aqueous solution was extracted with EtOAc (3 x 60 mL). After separation, the combined EtOAc layers was dried, evaporated to give 1-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxy-3-nitrobenzene. 1-(5-Methyl-1,2,4-oxadiazol-3-yl)methyleneoxy-3-nitrobenzene was dissolved in THF (10 mL) and water (10 mL) and to it were added sodium bisulfite (1 g, 5.7 mmol) and sodium bicarbonate (1 g, 12 mmol). The resulting mixture was stirred at room temperature for 30 min, then diluted with EtOAc (80 mL) and water (80 mL). The aqueous solution was extracted with EtOAc (80 mL). The organic layers were combined, dried, evaporated to give 3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyaniline (500 mg, 22% in four steps). The reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (40 mg, 0.17 mmol) and 3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyaniline (102 mg, 0.50 mmol) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (35mg, 51%). ^{1}H NMR ($CDCl_3$): δ 2.61 (s, 3H), 5.09 (s, 2H), 6.58-6.62 (m, 2H), 6.76 (dt, J= 1.2, 8.1 Hz, 1H), 6.84 (dt, J= 1.2 and 7.8 Hz, 1H), 6.92 (d, J= 3.0 Hz, 1H), 7.139 (t, J= 8.1 Hz, 1H), 7 145 (t, J= 8.1 Hz, 1H), 7.25 (m, 1H), 7.54 (dt, J= 2.1, 8.7 Hz, 2H), 7.88 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): -166.52; LCMS: ret. time: 19.33 min.; purity: 84.80%; MS (m/e): 409.35 (MH^+).
7.3.470	5-Fluoro-N2-(3-hydroxyphenyl)-N4-[3-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945130)	1-Methoxycarbonylmethyleneoxy-3-nitrobenzene (2 g, 9.5 mmol) was dissolved in THF (10 mL) and water (10 mL). To the solution was added NaOH (1 g, 25 mmol). The reaction mixture was stirred at room temperature overnight. The solution was diluted with water (60 mL) and EtOAc (60 mL). After extraction, the aqueous layer was separated, acidified with 1N HCl to

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Section Number	Name of compound and reference number	Experimental
		pH 3. The formed white precipitate was collected by filtration, washed with water, dried to give 1-carboxymethyleneoxy-3-nitrobenzene. Acetonitrile (2.25 mL, 43 mmol) was dissolved in methanol (10 mL) and to the solution was added hydroxyamine HCl salt (2 g, 29 mmol) and triethylamine (8 mL, 57 mmol). The reaction mixture was refluxed for 2 days and the solvent was removed under reduced pressure to give acetamide oxime as white solid. Acetamide oxime (0.75 g, 10 mmol), 1-carboxymethyleneoxy-3-nitrobenzene (1 g, 5 mmol), EDC HCl (1.45 g, 7.5 mmol) and diisopropylethylamine (2.65 mL, 15 mmol) were dissolved in THF (15 mL) and refluxed for 4h. The reaction mixture was diluted with EtOAc (60 mL) and water (60 mL). The EtOAc layer was washed with sodium bicarbonate aqueous solution (2 x 60 mL), 1N HCl (2 x 60 mL) and water (60 mL). After separation, the EtOAc layer was dried, evaporated to give 1-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxy-3-nitrobenzene. Sodium bisulfite (1.5 g, 8.6 mmol), sodium bicarbonate (1.5 g, 18 mmol) and 1-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxy-3-nitrobenzene (1 g, 4 mmol) were dissolved in THF (15 mL) and water (15 mL). It was stirred at room temperature for 20 min, diluted with EtOAc (60 mL) and water (60 mL). The aqueous solution was extracted with EtOAc (2 x 60 mL). The organic layers were combined, dried, evaporated to give 3-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyaniline. In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of 3-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyaniline (369 mg, 1.8 mmol) and 2,4-dichloro-5-fluoropyrimidine (150 mg, 0.9 mmol) gave 2-chloro-5-fluoro-N4-[3-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine. The reaction of 2-chloro-5-fluoro-N4-[3-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine (20 mg, 0.06 mmol) and 3-hydroxyaniline (20 mg, 0.18 mmol) gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-[3-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (10 mg, 42%). ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H), 5.28 (s, 2H), 6.49 (ddd, J= 0.9, 2.7 and 8.4 Hz, 1H), 6.73 (ddd, J= 0.9, 2.7 and 8 4 Hz, 1H), 6.81-6.84 (m, 2H), 6.88 (ddd, J= 0.6, 2.1 and 8.1 Hz, 1H), 7.13 (t, J= 8.1 Hz, 1H), 7.26 (t, J= 8.1 Hz, 1H), 7.40 (br, 1H), 7.49 (t, J= 2.1 Hz, 1H), 7.94-7.97 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 167.11; LCMS: ret. time: 18.80 min.; purity: 92.01%; MS (m/e): 409.01 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.471	5-Fluoro-N4-(2-methoxycarbonylbenzofuran-5-yl)-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945131)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, the reaction of N4-(2-carboxybenzofuran-5-yl)-2-chloro-5-fluoro-4-pyrimidineamine (50 mg, 0.16 mmol) and 3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyaniline (100 mg, 0.49 mmol) gave N4-(2-carboxybenzofuran-5-yl)-5-fluoro-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine. In a manner analogous to the preparation of N2,N4-bis[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine, the reaction of N4-(2-carboxybenzofuran-5-yl)-5-fluoro-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, potassium carbonate (100 mg, 0.7 mmol) and iodomethane (0.03 mL, 0.5 mmol) gave 5-fluoro-N4-(2-methoxycarbonylbenzofuran-5-yl)-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (40 mg, 50%). ^{1}H NMR (acetone-d_6): δ 2.63 (s, 3H), 3.94 (s, 3H), 5.04 (s, 2H), 6.65 (ddd, J= 0.9, 2.4 and 7.8 Hz, 1H), 7.16 (t, J= 7.8 Hz, 1H), 7.24 (ddd, J= 1.2, 1.8 and 8.1 Hz, 1H), 7.58 (d, J= 1.2 Hz, 1H), 7.64 (d, J= 9.3 Hz, 1H), 7.67 (t, J= 2.1 Hz, 1H), 7.88 (dd, J= 2.1 and 9.0 Hz, 1H), 8.04 (d, J= 3.6 Hz, 1H), 8.26 (d, J= 1.8 Hz, 1H), 8.47 (br, 1H, NH), 8.71 (br, 1H, NH); ^{19}F NMR (282 MHz, acetone-d_6): δ -167.73; LCMS: ret. time: 22.55 min.; purity: 85.43%; MS (m/e): 490.97 (MH^+).
7.3.472	N4-(2-Carboxybenzofuran-5-yl)-5-fluoro-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945134)	In a manner analogous to the preparation of N2,N4-bis(3-carboxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(2-methoxycarbonylbenzofuran-5-yl)-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (20 mg, 0.04 mmol) and NaOH (10 mg, 0.25 mmol) gave N4-(2-carboxybenzofuran-5-yl)-5-fluoro-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (acetone-d_6): δ 2.63 (s, 3H), 5.04 (s, 2H), 6.64 (d, J= 8.1 Hz, 1H), 7.17 (t, J= 8.1 Hz, 1H), 7.26 (d, J= 7.8 Hz, 1H), 7.56 (s, 1H), 7.62 (d, J= 9.3 Hz, 1H), 7.67 (t, 1H), 7.86 (dd, J= 1.8 and 9.0 Hz, 1H), 8.04 (d, J= 3.3 Hz, 1H), 8.26 (d, 1H), 8.48 (br, 1H, NH), 8.71 (br, 1H, NH); LCMS: ret. time: 18.00 min.; purity: 75.13%; MS (m/e): 476.70 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.473	N4-(2-Aminocarbonylbenzofuran-5-yl)-5-fluoro-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945135)	A mixture of 5-fluoro-N4-(2-methoxycarbonylbenzofuran-5-yl)-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (20 mg, 0.04 mmol) and concentrated NH_4OH (5 mL) in methanol (5 mL) was stirred at room temperature overnight. The solvent was evaporated to give N4-[2-(aminocarbonyl)benzofuran-5-yl]-5-fluoro-N2-[3-(5-methyl-1,2,4-oxadiazol-3-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (acetone-d_6): δ 2.61 (s, 3H), 5.04 (s, 2H), 6.64 (ddd, J= 0.9, 2.4 and 8.1 Hz, 1H), 7.16 (t, J= 8.1 Hz, 1H), 7.27 (ddd, J= 0.9, 1.8 and 8.4 Hz, 1H), 7.44 (d, J= 0.6 Hz, 1H), 7.55 (dd, J= 0.6 and 8.1 Hz, 1H), 7.64 (t, J= 2.4 Hz, 1H), 7.79 (dd, J= 2.4 and 9.0 Hz, 1H), 8.03 (d, J= 3.6 Hz, 1H), 8.24 (d, J= 2.4 Hz, 1H), 8.48 (br, 1H, NH), 8.68 (br, 1H, NH); ^{19}F NMR (282 MHz, acetone-d_6): δ - 167.80; LCMS: ret. time: 17.43 min.; purity: 100%; MS (m/e): 475.62 (MH^+).
7.3.474	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(2-methoxyimino(amino)ethyleneoxy)phenyl]-2,4-pyrimidinediamine (R945167)	In a manner analogous to the preparation of N2,N4-bis[4-(2-methoxyimino(amino)ethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine, the reaction of N2-(4-cyanomethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (50 mg, 0.14 mmol), methoxyamine HCl salt (0.71 mmol) and triethylamine (0.2 mL, 1.4 mmol) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(2-methoxyimino(amino)ethyleneoxy)phenyl]-2,4-pyrimidinediamine (40 mg, 70%). ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 3H), 4.50 (s, 2H), 4.87 (br, 2H, NH), 6.60 (ddd, J= 0.9, 2.4 and 8.1 Hz, 1H), 6.79-6.84 (m, 2H), 6.86 (d, J= 8.7 Hz, 2H), 7.00 (s, 1H), 7.14 (t, J= 8.1 Hz, 1H), 7.34 (d, J= 9.0 Hz, 2H), 7.47 (t, J= 2.1 Hz, 1H), 7.87 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 167.67; LCMS: ret. time: 13.69 min.; purity: 92.51%; MS (m/e): 399.01 (MH^+).
7.3.475	N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[4-methoxyimino(amino)ethyleneoxyphenyl]-2,4-pyrimidinediamine (R945175)	In a manner analogous to the preparation of N2,N4-bis[4-(2-methoxyimino(amino)ethyleneoxyphenyl)]-5-fluoro-2,4-pyrimidinediamine, N4-(4-cyanomethyleneoxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, methoxyamine hydrochloride salt and triethylamine gave N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-methoxyimino(amino)ethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (acetone-d_6): δ 3.70 (s, 3H), 4.21-4.28 (m, 4H), 4.48 (s, 2H), 5.46 (br, 2H), 6.71 (d, J= 8.7 Hz, 1H), 6.99 (d, J= 9.0 Hz, 2H), 7.06 (dd, J= 2.4 and 8.7 Hz, 1H), 7.42 (d, J= 2.4 Hz, 1H), 7.72 (d, J= 9.3 Hz, 2H), 7.93 (d, J= 3.3 Hz, 1H), 8.22 (br, 1H, NH), 8.40 (br, 1H, NH); ^{19}F NMR (282 MHz, acetone-d_6): δ - 169.05; LCMS: ret. time: 16.49 min.; purity: 96.47%; MS (m/e): 440.96 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.476	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926495)	A mixture of N2-(3-ethoxy/or methoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (19.8g, 45 mmol), methylamine hydrochloride (30.63g, 450 mmol) and diisopropylethylamine (78.07 mL, 450 mmol) in MeOH (450 mL) was stirred in a pressure bottle at 100 °C for 8h (followed by TLC). The reaction was cooled to room temperature, diluted with H_2O (6 lit), the solid obtained was filtered, washed with H_2O and dried to obtain 18 g of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxyphenyl)]-2,4-pyrimidinediamine. Alternatively, the reaction of equimolar amount of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-aminopyridine with 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110 °C for 24h and or in EtOH using microwave at 175 °C for 10-20 min followed by aqueous work up gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.90 (s, 1H), 7.89 (bs, 1H), 7.38 (d, 1H, J= 2.4 Hz), 7.28 (d, 1H, J= 2.4 Hz), 7.17-7.09 (m, 2H), 6.79 (d, 1H, J= 9 Hz), 6.57 (m, 1H), 4.38 (s, 2H), 4.24 (s, 4H), 2.81 (s, 3H); LCMS: ret. time: 18.20 min.; purity: 98%; MS (m/e): 426 (MH^+).
7.3.477	N4-(1,4-Benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl] -2,4-pyrimidinediamine (R921219)	In like manner to N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(1,4-benzoxazin-6-yl)-N2-(3-ethoxyocarbonylmethyleneoxyphenyl)-5-fluoro-pyrimidinediamine and methylamine hydrochloride were reacted to yield N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.8 (d, 1H), 7.4 (m, 1H), 7.05 (m, 2H), 7.0 (s, 1H), 6.8 (dd, 1H), 6.66 (d, 1H), 6.56 (dd, 1H), 4.35 (s, 2H), 4.18 (m, 2H), 3.25 (m, 2H), 2.8 (s, 3H); LCMS: ret time: 18.0 min. purity: 97 %; MS (m/e): 425 (MH^+).
7.3.478	N4-(3,4-Ethylendioxyphenyl)-5-fluoro-N2-[4-(N-2-hydroxyethylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R909239)	In like manner to N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and 2-hydroxyethylamine were reacted to yield N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[4-(N-2-hydroxyethylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (D_2O): δ 8.02 (d, 1H, J= 4 Hz), 7.40 (m, 2H), 7.28 (m, 1H), 7.05 (m, 5H), 4.83 (s, 2H), 4.5 (m, 2H), 4.23 (m, 2H), 4.03(m, 2H), 3.87 (m, 2H); LCMS: ret. time: 17.17 min.; purity: 94%; MS (m/e): 456 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.479	N4-(3,4-Ethylendioxyphenyl)-5-fluoro-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R909240)	In like manner to N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-(N-methylamino)carbonylmethyleneoxyaniline were reacted to yield N4-(3,4-ethylendioxyphenyl)-5-fluoro-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (D_2O): δ 8.02 (d, 1H, J= 4 Hz), 7.40 (m, 2H), 7.28 (m, 1H), 7.05 (m, 5H), 4.83 (s, 2H), 4.5 (m, 2H), 4.23 (m, 2H), 3 87 (s, 3H); LCMS: ret. time: 18 43 min.; purity· 94%; MS (m/e): 426 (MH^+)
7.3.480	N4-(1,4-Benzoxazin-6-yl)-5-fluoro-N2-[3-(N-2-hydroxypropylamino)carbonylmethyleneoxyphenyl] -2,4-pyrimidinediamine (R909251)	In like manner to N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(1,4-benzoxazin-6-yl)-N2-(3-ethoxyocarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine and 2-hydroxypropylamine were reacted to yield N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-2-hydroxypropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ□□□(d, 1H, J= 4 Hz), 7.25 (m, 2H), 7.04 (m, 1H), 6.82 (m, 2H), 6.58 (m, 1H), 6.45 (m, 1H) 4.36 (s, 2H), 4.02 (m, 2H), 3.75 (m, 1H), 3.31 (m, 2H), 3.00 (m, 2H), 1.00 (m, 3H); LCMS: ret. time: 17.33 min.; purity: 97 %; MS(m/e): 469 (MH^+).
7.3.481	N4-(1,4-Benzoxazin-6-yl)-5-fluoro-N2-[3-(N-3-hydroxypropylamino)carbonylmethyleneoxyphenyl] -2,4-pyrimidinediamine (R909252)	In like manner to N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(1,4-benzoxazin-6-yl)-N2-[3-ethoxyocarbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine and 3-hydroxypropylamine were reacted to yield N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-3-hydroxypropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ □□□ (d, 1H, J= 4 Hz), 7.39 (m, 2H), 7.04 (m, 1H), 6.87 (m, 2H), 6.55 (m, 1H), 6.41 (m, 1H), 4.29 (s, 2H), 4.02 (m, 2H), 3.35 (m, 2H), 3.31 (m, 2H), 3.09 (m, 2H), 1.50 (m, 3H); LCMS: ret. time: 17.11 min.; purity: 94 %; MS (m/e): 469 (MH^+).
7.3.482	N4-(1,4-Benzoxazin-6-yl)-N2-[3-(N-isopropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R909254)	In like manner to N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(1,4-benzoxazin-6-yl)]-N2-(3-ethoxyocarbonylmethyleneoxyphenyl)-5-fluoro-pyrimidinediamine and isopropylamine were reacted to yield N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-isopropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ□□□(d, 1H, J= 4 Hz), 7.25 (m, 1H), 7.14 (m, 1H), 7.02 (m, 1H), 6.85 (m, 3H), 6.63 (m, 1H), 4.39 (s, 2H), 4.12 (m, 2H), 4.05 (m, 1H), 3.38 (m, 2H), 1.20 (m, 6H); LCMS: ret. time: 20.83 min.; purity: 96 %; MS (m/e): 453 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.483	5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[2-(N-pyrrolidino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926703)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine and pyrrolidine were reacted to yield 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[2-(N-pyrrolidino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.83 (s, 1H), 7.79 (d, 1H, J= 5.4 Hz), 7.42 (bs, 1H), 7.39 (d, 2H, J= 8.7 Hz), 7.28-7.24 (m, 2H), 6.81 (d, 2H, J= 8.7 Hz), 4.52 (2q, 1H, J= 6.0 Hz), 3.92 (t, 2H, J= 6.9 Hz), 3.67 (t, 2H, J= 6.9 Hz), 2.05-1.90 (m, 4H), 1.32 (d, 6H, J= 6.6 Hz); ^{19}F NMR ($CDCl_3$): - 24000; LCMS: ret. time: 23.49 min.; purity: 97 %; MS (m/e): 476 (MH^+).
7.3.484	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926708)	In a manner similar to the preparation of N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.10 (bs, 1H), 9.88 (bs, 1H), 8.15 (t, 1H, J= 4.5 Hz), 8.05 (bs, 1H), 7.40 (d, 2H, J= 8.7 Hz), 7.23 (d, 1H, J= 2.1 Hz), 7.11 (dd, 1H, J= 2.4 and 8.7 Hz), 6.89 (d, 2H, J= 8.7 Hz), 6.81 (d, 1H, J= 8.7 Hz), 4.42 (s, 2H), 4.23 (s, 4H), 2.64 (d, 3H, J= 4.5 Hz); LCMS: ret. time: 17.60 min.; purity: 96 %; MS (m/e): 426 (MH^+).
7.3.485	N4-(4-tert-Butylphenyl)-5-fluoro-N2-[2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926494)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(4-tert-butylphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine with methylamine hydrochloride gave N4-(4-tert-butylphenyl)-5-fluoro-N2-[2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.04 (d, 1H, J= 2.4 Hz), 7.88 (d, 1H, 4.2 Hz), 7.58-7.30 (m, 7H), 2.94 (s, 3H), 1.33 (s, 9H); LCMS: ret. time: 22.86 min.; purity: 94%; MS (m/e): 434 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.486	N4-(4-*tert*-Butylphenyl)-5-fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926712)	In a manner similar to the preparation of N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[4-(*tert*-butyl)phenyl]-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.92 (d, 1H, J= 5.4 Hz), 7.53 (d, 2H, J= 8.7 Hz), 7.40 (d, 2H, J= 8.7 Hz), 7.34 (d, 2H, J= 8.7 Hz), 7.03 (d, 2H, J= 8.7 Hz), 4.52 (s, 2H), 2.82 (s, 3H), 1.35 (s, 9H); ^{19}F NMR (CD_3OD): -46174; LCMS: ret. time: 23.34 min.; purity: 94 %; MS (m/e): 424 (MH^+).
7.3.487	N4-(3-*tert*-Buthylpheny)-5-fluoro-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine R940295	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and 2-hydroxyethylamine were reacted to give N4-(3-tert-butylpheny)-5-fluoro-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 21.34 min.; purity: 97 %; MS (m/e): 453 (M^+); 454 (MH^+); ^{1}H NMR ($CDCl_3$): δ 10.34 (1H, s), 7.76 (1H, m), 7.52 (1H, m), 7.4-7.1 (5H, m), 6.98 (1H, m), 6.7 (1H, m), 4.36 (2H, s), 3.77 (2H, t, J 5 Hz), 3.51 (2H, m), 1.27 (9H, s).
7.3.488	N2,N4-Bis[4-(N-pyrrolidino)carbonylmethyleneoxyphenyl]-5-ethoxycarbonyl-2,4-pyrimidinediamine (R926562)	In like manner of the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine with pyrrolidine gave N2,N4-bis[4-(N-pyrrolidino)carbonylmethyleneoxyphenyl]-5-ethoxycarbonyl-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.17 (s, 1H), 8.73 (bs, 1H), 7.50(bd, 2H, J= 9.0 Hz), 7.43 (d, 2H, J= 2.4 and 6.9 Hz), 6.91 (m, 4H), 4.64 (s, 2H), 4.62 (s, 2H), 4.34 (q, 2H, J= 7.2 Hz), 3.53 (m, 8H), 1.95 (m, 4H), 1.86 (m, 4H), 1.38 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 22.54 min.; purity: 100%; MS (m/e): 590 (MH^+).
7.3.489	N2,N4-Bis(4-N-pyrrolidinocarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926563)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with pyrrolidine gave N2,N4-bis[4-(N-pyrrolidino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.90 (s, 1H), 7.50 (bd, 2H, J= 7.8 Hz), 7.41 (bd, 2H, J= 7.2 Hz), 6.93 (m, 4H), 6.73 (s, 1H), 6.64 (s, 1H), 4.65 (s, 1H), 4.65 (s, 1H), 3.54 (m, 8H), 1.96 (m, 4H), 1.87 (m, 4H).

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Section Number	Name of compound and reference number	Experimental
7.3.490	N4-(3-*tert*-Butylpheny)-N2-[3-(N-1,3-dihydroxypropyl-2-amino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R940296)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and 2-amino-1,3-propanediol were reacted to give N4-(3-*tert*-butylpheny)-N2-[-3-(1,3-dihydroxypropyl-2-amino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 20.26 min.; purity: 97.67 %; MS (m/e): 484 (M^+); 485 (MH^+); 1H NMR (DMSO-d6): δ 9.75 (1H, s), 9.57 (1H, s), 8.25 (1H, m), 7.92 (1H, m), 7.62 (2H, m), 7 37 (3H, m), 7.23 (1H, m), 6.66 (1H, m), 4.46 (2H, s), 3.87 (1H, m), 3.55 (4H, m), 1.36 (9H, s).
7.3.491	N2-[3-(N-2,3-Dihydroxypropylamino) carbonylmethyleneoxyphenyl]-5-fluoro-N4-(3-isopropylphenyl)-2,4-pyrimidinediamine R940290	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-isopropylphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and 3-amino-1,2-propanediol were reacted to give N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl)-5-fluoro-N4-(3-isopropylphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 20.04 min.; purity: 98 %; MS (m/e): 470 (MH^+); ^1H NMR (DMSO-d6): δ 9.54 (1H, s), 9.41 (1H, s), 8.22 (1H, m), 7.95 (1H, m), 7.85 (1H, d, J= 10 Hz), 7.58 (1H, s), 7.43-7.32 (3H, m), 7.25 (1H, t, J= 7.75 Hz), 7.06 (1H, d, J= 7.75 Hz), 6.64 (1H, d, J= 10 Hz), 4.47 (2H, s), 3.38 (4H, m), 3.16 (1H, m), 2.96 (1H, m), 1.28 (6H, d, J=6.9 Hz).
7.3.492	5-Fluoro-N4-(3-isopropylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine R940288	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-isopropylphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to give 5-fluoro-N4-(3-isopropylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 23.43 min.; purity: 99 %; MS (m/e): 409 (M^+), 411 (MH^+); ^1H NMR (DMSO-d6): δ 9.90 (1H, s), 9.74 (1H, s), 8.28 (1H, d, J= 4.8 Hz), 8.06 (1H, m), 7.78 (1H, d, J= 7.2 Hz), 7.58 (1H, s), 7.4-7.3 (3H, m), 7.24 (1H, t, J= 8.4 Hz), 7.00 (1H, d, J= 7.25 Hz), 6.70 (1H, d, J= 7.25 Hz), 4.44 (2H, s), 2.93 (1H, sept, J= 6.9 Hz), 2.74 (3H, d, J= 4.8 Hz), 1.27 (6H, d, J= 6.9 Hz).

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Section Number	Name of compound and reference number	Experimental
7.3.493	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-dimethylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926718)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and dimethylamine were reacted to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-dimethylamino)carbonylbenzofuran-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.06 (d, 1H, J= 2.1 Hz), 7.91 (d, 1H, J= 3.6 Hz), 7.57 (t, 1H, J= 2.4 Hz), 7.37 (d, 1H, J= 9.0 Hz), 7.28 (s, 1H), 7.19 (t, 1H, J= 7.8), 7.06 (s, 1H), 6.82-6.76 (m, 2H), 6.71 (dd, 1H, J= 2.4 and 7.8 Hz), 3.31 (s, 3H), 3.09 (s, 3H); ^{19}F NMR ($CDCl_3$): - 47292; LCMS: ret. time: 17.29 min.; purity: 92 %; MS (m/e): 408 (MH^+).
7.3.494	N4-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R945149)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (700 mg, 1.6 mmol) and piperazine (4 g, 46 mmol) gave N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (520 mg, 66%). ^{1}H NMR (CD_3OD): δ δ 2.22 (s, 3H), 2.75 (t, J= 5.4 Hz, 4H), 3.40 (t, J= 4.8 Hz, 2H), 3.54 (t, J= 5.1 Hz, 2H), 4.62 (s, 2H), 6.57 (ddd, J= 1.5, 2.7 and 7.5 Hz, 1H), 7.09 (dt, J= 1.5 and 8.1 Hz, 1H), 7.14 (t, J= 7.8 Hz, 1H), 7.28 (t, J= 2.1 Hz, 1H), 7.31 (dd, J= 0.9 and 2.7 Hz, 1H), 7.50 (d, J= 2.7 Hz, 1H), 7.88 (d, J= 3.9 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD): δ - 168.63; LCMS: ret. time: 14.99 min.; 93.88%; MS (m/e): 486.96 (MH^+).
7.3.495	N4-(4-*tert*-Butylphenyl)-5-fluoro-N2-[2-(N-methylamino)carbonylbenzofuran-5-yl]- 2,4-pyrimidinediamine (R926713)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2-(N-methylaminocarbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.05 (d, 1H, J= 2.4 Hz), 7.88 (d, 1H, J= 4.2 Hz), 7.57 (d, 2H, J= 8.7 Hz), 7.51-7.41 (m, 2H), 7.34-7.31 (m, 3H), 2.94 (s, 3H), 1.33 (s, 9H); ^{19}F NMR (CD_3OD): - 47682; LCMS: ret. time: 23.02 min.; purity: 90 %; MS (m/e): 434 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3496	N4-(3,5-Dimethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926796)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,5-dimethoxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyridinediamine with methylamine hydrochloride gave N4-(3,5-dimethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.92 (d, 1H, J= 4.2 Hz), 7.42 (t, 1H, J= 1.8 Hz), 7.12 (m, 2H), 6.91 (d, 1H, J= 2.4 Hz), 6.59 (m, 1H), 6.22 (t, 1H, J= 1.8 Hz), 4.35 (s, 2H), 3.69 (s, 6H), 2.81 (s, 3H); LCMS: ret. time: 18.35 min.; purity: 93%; MS (m/e): 428 (MH^+).
7.3.497	5-Ethoxycarbonyl-N4-(3,4-ethylenedioxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926800)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-ethoxycarbonyl-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-2,4-pyridinediamine with methylamine hydrochloride gave 5-ethoxycarbonyl-N4-(3,4-ethylenedioxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.05 (s, 1H), 9.34 (s, 1H), 8.69 (s, 1H), 7.95 (d, 1H, J= 4.8 Hz), 7.34 (dd, 1H, J= 1.2 and 7.8 Hz), 7.25 (bs, 2H), 7.13 (t, 1H, J= 8.1 Hz), 7.00 (bd, 1H, J= 9Hz), 6.81 (d, 1H, J= 8.7 Hz), 6.59 (dd, 1H, J= 1.5 and 8.4 Hz), 4.32 (s, 2H), 4.30 (q, 2H, J= 7.2 Hz), 4.21 (s, 4H), 2.63 and 2.62 (2s, 3H), 1.31 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 24.12 min.; purity: 91%; MS (m/e): 481 (MH^+).
7.3.498	N4-(3,5-Dimethoxyphenyl)-5-ethoxycarbonyl-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926801)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxyphenyl)]-2,4-pyrimidinediamine, the reaction of N4-(3,5-dimethoxyphenyl)-5-ethoxycarbonyl-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-2,4-pyridinediamine with methylamine hydrochloride gave N4-(3,5-dimethoxyphenyl)-5-ethoxycarbonyl-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.20 (s, 1H), 9.96 (s, 1H), 8.73 (s, 1H), 7.90 (bs, 1H), 7.36 (d, 1H, J= 8.7 Hz), 7.28 (bs, 1H), 7.12 (t, 1H, J= 7.5 Hz), 6.84 (s, 2H), 6.59 (dd, 1H, J= 1.8 and 8.1 Hz), 6.25 (t, 1H, J= 2.4 Hz), 4.31 (m, 4H), 3.67 (s, 6H), 2.63 and 2.62 (2s, 3H), 1.31 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 25.50 min.; purity: 96%; MS (m/e): 482 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.499	N4-(4-*tert*-Butylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926714)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.90 (d, 1H, J= 3.3 Hz), 7.61 (d, 2H, J= 8.7 Hz), 7.40-7.33 (m, 3H), 7.14-7.11 (m, 2H), 6.62-6.57 (m, 1H), 4.36 (s, 2H), 2.79 (s, 3H), 1.31 (s, 9H); ^{19}F NMR (CD_3OD): - 47514; LCMS: ret. time: 23.70 min.; purity: 93 %; MS (m/e): 424 (MH^+).
7.3.500	N4-(3-Hydroxyphenyl)-5-trifluoromethyl-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926742)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3-hydroxyphenyl)-5-trifluoromethyl-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield N4-(3-hydroxyphenyl)-5-trifluoromethyl-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 19.11 min.; purity: 99 %; MS (m/e): 434 (MH^+).
7.3.501	5-Fluoro-N4-[(1H)-indol-6-yl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926745)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)-indol-6-yl]-4-pyrimidineamine and 3-(N-methylamino)carbonylmethyleneoxyaniline were reacted to yield 5-fluoro-N4-[(1H)-indol-6-yl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time. 17.41 min.; purity: 93 %; MS (m/e): 407(MH^+).
7.3.502	N4-(3,5-Dimethyl-4-methoxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R945156)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,5-dimethyl-4-methoxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethylene oxyphenyl)-2,4-pyrimidinediamine and piperazine gave N4-(3,5-dimethyl-4-methoxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 2.23 (s, 6H), 3.24 (m, 4H), 3.71 (s, 3H), 3.72-3.81 (m, 4H), 4.75 (s, 2H), 6.81 (dt, J= 1.2 and 8.1 Hz, 1H), 7.10-7.13 (m, 2H), 7.24 (d, J= 8.7 Hz, 1 H), 7.29 (s, 2H), 7.98 (d, J= 4.8 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD): δ - 163.88; LCMS: ret. time: 15.94 min.; purity: 100%; MS (m/e): 481.12 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.503	N4-(3-*tert*-Butylphenyl)-5-fluoro-N2-[2-(N-methylamino)carbonylbenzofur-5-yl]-2,4-pyrimidinediamine R940291	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to give N4-(3-*tert*-butylphenyl)-5-fluoro-N2-[2-(N-methylamino)carbonylbenzofur-5-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 23.05 min.; purity: 100 %; MS (m/e): 434 (MH^+); ^{1}□□□□ (DMSO-d6): δ 9.6 (1H, s), 9.57 (1H, s), 8.75 (1H, m), 8.25 (1H, s), 8.15 (1H, s), 7.93 (1H, d, J= 8.5 Hz), 7.47 (3H, m), 7.44 (1H, s), 7 36 (1H, t, J= 8.5 Hz), 7.25 (1H, d, J= 8.5 Hz), 2.89 (3H, d, J= 4.5 Hz), 1.33 (9H, s).
7.3.504	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-hydroxyethylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926505)	In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxy)phenyl)-2,4-pyrimidinediamine and 2-hydroxyethylamine gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-hydroxyethylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.87 (d, 1H, J= 3.6 Hz), 7.37 (t, 1H, J= 1.8 Hz), 7.24 (d, 1H, J= 2.4 Hz), 7.13 (m, 2H), 7.08 (dd, 1H, J= 2.1 and 8.1 Hz), 6.77 (m, 1H), 4.38 (s, 2H), 4,22 (s, 3H), 3.63 (t, 2H), 3.40 (t, 2H, J= 6 Hz); LCMS: ret. time: 16.72 min.; purity: 98%; MS (m/e): 456 (MH^+).
7.3.505	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926746)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and 3-amino-1,2-propanediol were reacted to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.84 min.; purity: 96 %; MS (m/e): 444 (MH^+).
7.3.506	5-Fluoro-N2-[2-(2-hydroxy-1,1-dimethylethylamino)carbonylbenzofuran-5-yl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926715)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and 2-amino-2-methylpropanol were reacted to yield 5-fluoro-N2-[2-(2-hydroxy-1,1-dimethylethylamino)carbonylbenzofuran-5-yl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.41 (s, 1H), 9.28 (s, 1H), 9.22 (s, 1H), 8.18 (t, 1H, J= 2.4, Hz), 8.09 (d, 1H, J= 3.6 Hz), 7.56 (dd, 1H, J= 2.4 and 8.7 Hz), 7.47 (d, 1H, J= 8.7 Hz), 7.32 (s, 1H), 7.26-7.21 (m, 1H), 7.13- 7.07 (m, 2H), 6.53 (d, 1H, J= 8.7 Hz), 5.05 (t, 1H, J= 5.7 Hz), 3.46 (d, 2H, J= 5.7 Hz), 1.32 (s, 6H); LCMS: ret. time: 17.93 min.; purity: 97 %; MS (m/e): 452 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.507	5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926730)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.93 (d, 1H, J= 3.0 Hz), 7.47 (d, 2H, J= 9.3 Hz), 7.42 (t, 1H, J= 1.8 Hz), 7.17 (t, 1H, J= 8.1 Hz), 7.10 (bs, 1H), 7.00 (dd, 1H, J= 1.8 and 9.3 Hz), 6.89 (d, 2H, J= 9.3 Hz), 6.80 (d, 1H, J= 1.8 Hz), 6 58 (bs, 1H), 6.50 (dd, 1H, J= 1.5 and 8.1 Hz), 4.51 (2q, 1H, J= 5.7 Hz), 4.44 (s, 2H), 2.88 (d, 3H, J= 4.5 Hz), 1.33 (d, 6H, J= 5.7 Hz); ^{19}F NMR ($CDCl_3$): - 47198; LCMS: ret. time: 19.66 min.; purity: 97 %; MS (m/e): 426 (MH^+).
7.3.508	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R945170)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)methyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-(4-cyanomethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 2.91 (d, J= 5.1 Hz, 3H), 4.48 (s, 2H), 6.61 (ddd, J= 0.9, 2.7 and 8.1 Hz, 1H), 6.63 (br, 1H), 6.76 (d, J= 3.0 Hz, 1H), 6.84-6.89 (m, 4H), 7.18 (t, J= 8.1 Hz, 1H), 7.44 (d, J= 8.7 Hz, 2H), 7.51 (t, J= 2.1 Hz, 1H), 7.92 (d, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ -167.70; LCMS: ret. time: 14.32 min.; purity: 100%; MS (m/e): 383.98 (MH^+).
7.3.509	5-Fluoro-N4-(3-isopropoxyphenyl)-N2-[2-(N-morpholino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926489)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-isopropoxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidineamine with morpholine gave 5-fluoro-N4-(3-isopropoxyphenyl)-N2-[2-(N-morpholino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.01 (d, 1H, J= 1.2 Hz), 7.95 (bs, 1H), 7.43-7.38 (m, 2H), 7.29 (s, 1H), 7.25-7.11 (m, 4H), 6.97 (bs, 1H), 6.73 (m, 1H), 6.67 (bdd, 1H), 4.48 (sept, 1H, J= 5.7 Hz), 3.87 (m, 4H), 3.79 (m, 4H), 1.30 (d, 6H, J= 5.7 Hz), LCMS: ret. time: 22.12 min.; purity: 98%; MS (m/e): 492 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.510	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926772)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine with piperazine gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.91 (d, 1H, J= 3.6 Hz), 7.42 (t, 1H, J= 2.4 Hz), 7.20-7.07 (m, 5H), 6.55 (m, 2H), 4.63 (s, 2H), 3.54 (t, 2H, J= 6 Hz), 3.40 (t, 2H, J= 5.1 Hz), 2.76 (t, 4H, J= 5.4 Hz); LCMS: ret. time: 12.98 min.; purity: 92%; MS (m/e): 439 (MH^+).
7.3.511	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926506)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with 2-hydroxyethylamine gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 14.95 min.; purity: 96%; MS (m/e): 414 (MH^+).
7.3.512	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926508)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-ethoxy or methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with methylamine hydrochloride gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.64 (bs, 1H), 9.58 (bs, 1H), 8.15 (d, 1H, J= 4.2 Hz), 7.95 (bd, 1H), 7.25 (bd, 2H, J= 6.6 Hz), 7.16-7.07 (m, 4H), 6.53 (m, 2H), 4.35 (s, 2H), 2.64 and 2.62 (2s, 3H); LCMS: ret. time: 15.66 min.; purity: 98%; MS (m/e): 384 (MH^+).
7.3.513	5-Fluoro-N4-[3,4-(1,1,2,2-tetrafluoroethylendioxy)phenyl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926732)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[3,4-(1,1,2,2-tetrafluoroethylendioxy)phenyl]-4-pyrimidineamine and methylamine hydrochloride were reacted to yield 5-fluoro-N4-[3,4-(1,1,2,2-tetrafluoroethylendioxy)phenyl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine . ^{1}H NMR (DMSO-d6): δ 9.65 (s, 1H), 9.37 (s, 1H), 8.16 (d, 1H, J= 3.6 Hz), 8.14 (d, 1H, J= 2.4 Hz), 7.97 (d, 1H, J= 4.8 Hz), 7.65 (dd, 1H, J= 2.4 and 8.7 Hz), 7.41 (d, 1H, J= 9.3 Hz), 7.34 (t, 1H, J= 2.4 Hz), 7.27 (d, 1H, J= 8.1 Hz), 7.13 (t, 1H, J= 8.1 Hz), 6.51 (dd, 1H, J= 2.1 and 7.5 Hz), 4.36 (s, 2H), 2.63 (d, 3H, J= 4.8 Hz); ^{19}F NMR (DMSO-d6): - 25765 (pent, 2F), - 25830 (pent, 2F), - 46309; LCMS: ret. time: 24.85 min.; purity: 95 %; MS (m/e): 497 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.514	N4-(3,5-Dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R940254)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,5-dimethyl-4-hydroxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with morpholine gave N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-(N-morpholinocarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 18.38 min.; purity: 92 %; MS (m/e): 468 (MH^+); 1H NMR (DMSO-d6): δ 9 20 (1H, s), 9.10 (1H, s), 8.15 (1H, s), 8.11 (1H, d, J= 3.9 Hz), 7 43 (1H, d, J= 8.1 Hz), 7.32 (3H, m), 7.14 (1H, t, J= 8 1 Hz), 6.54 (1H, dd, J= 8.1 and 2.0 Hz), 4.77 (2H, s), 3.64 (4H, m), 3.54-3.45 (4H, m), 2.24 (6H, s).
7.3.515	N4-(3-*tert*-Butylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R940276)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3-*tert*-butylphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with methylamine hydrochloride gave N4-(3-*tert*-butylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 22.90 min.; purity: 99 %; MS (m/e): 424 (MH^+); 1H NMR (DMSO-d6): δ 9.46 (1H, s), 9.34 (1H, s), 8.08 (1H, d, J= 3.9 Hz), 7.90 (1H, m), 7.30 (1H, d, J= 8.1 Hz), 7.46 (1H, m), 7.26 (1H, m), 7.20 (2H, m), 7.10-7.03 (2H, m), 6.47 (1H, d, J= 8.1 Hz), 4.26 (2H, s), 2.59 (3H, d, J= 4.5 Hz), 1.20 (9H, s).
7.3.516	N4-(3-*tert*-Butylphenyl)-N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R940277)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3-*tert*-butylphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with 2,3-dihydroxypropylamine gave N4-(3-*tert*-butylphenyl)-N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS. retn. time: 20.46 min ; purity: 100 %; MS (m/e): 484 (MH^+); 1H NMR (DMSO-d6): δ 9.38 (1H, s), 9.29 (1H, s), 8.20 (1H, d, J= 3.9 Hz), 8.00 (1H, d, J= 8.3 Hz), 7.93 (1H, t, J= 5.5 Hz), 7.60 (1H, m), 7.47 (1H, m), 7.41-7.17 (4H, m), 6.59 (1H, dd, J= 8.3 and 2 Hz), 3.43 (2H, s), 3.39 (4H, m), 3.16 (1H, m), 1.36 (9H, s).

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Section Number	Name of compound and reference number	Experimental
7.3.517	N4-(3,3-Dihydroisobenzofuran-1-one-6-yl)-N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine R940293	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-[3-(ethoxycarbonylmethyleneoxy)phenyl]-N4-(3,3-dihydroisobenzofuran-1-one-6-yl)-5-fluoro-2,4-pyrimidinediamine and 3-amino-1,2-propanediol were reacted to N4-(3,3-dihydroisobenzofuran-1-one-6-yl)-N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 13.92 min.; purity: 92 %; MS (m/e): 483 (M^+); 1H NMR (DMSO-d6): δ 9.80 (1H, s), 9.46 (1H, s), 8.37-8.27 (2H, m), 8.21 (1H, s), 7.96 (1H, t, J= 4.6Hz), 7.24 (1H, d, J= 9Hz), 7.44 (1H, s), 7.37 (1H, d, J= 9 Hz), 7.23 (1H, t, J= 8 Hz), 6.60 (1H, dd, J= 7 and 3.75 Hz) 5.49 (2H, s), 4.46 (2H, s), 3.38 (4H, m), 3.2-3.1 (1H, m).
7.3.518	N4-(3,4-Dimethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926733)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-dimethoxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield N4-(3,4-dimethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.95 (d, 1H, J= 3.6 Hz), 7.45 (t, 1H, J= 1.8 Hz), 7.21-7.17 (m, 2H), 7.05 (dd, 1H, J= 2.7 and 8.7 Hz), 6.96-6.90 (m, 2H), 6.87 (d, 1H, J= 9.0 Hz), 6.72 (d, 1H, J= 2.4 Hz), 6.67-6.58 (m, 1H), 6.52 (dd, 1H, J= 3.6 and 8.1 Hz), 4.39 (s, 2H), 3.89 (s, 3H), 3.78 (s, 3H), 2.90 (d, 3H, J= 4.8 Hz); LCMS: ret. time: 17.09 min.; purity: 98 %; MS (m/e): 428 (MH^+).
7.3.519	N2-[3-(N-2,3-Dihydroxypropylamino) carbonylmethyleneoxyphenyl]-N4-(3,4-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926734)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-dimethoxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and 3-amino-1,2-propanediol were reacted to yield N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.05 (d, 1H, J= 4.2 Hz), 7.38-7.34 (m, 2H), 7.31-7.26 (m, 2H), 7.07 (t, 1H, J= 8.4 Hz), 6.89 (d, 1H, J= 8.7 Hz), 6.46 (dd, 1H, J= 2.4 and 8.4 Hz), 4.36 (s, 2H), 3 72 (s, 3H), 3.68 (s, 3H), 3.32-3.24 (m, 3H), 3.03 (dd, 1H, J= 6.9 and 13.5 Hz); ^{19}F NMR (DMSO-d6): - 46574; LCMS: ret. time: 14.85 min.; purity: 94 %; MS (m/e) 488 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.520	5-Fluoro-N4-(3-methoxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926738)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-methoxyphenyl)-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield 5-fluoro-N4-(3-methoxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 18.40 min.; purity: 98 %; MS (m/e): 398 (MH^+).
7.3.521	N2-[3-(N-2,3-Dihydroxypropylamino) carbonylmethyleneoxyphenyl]-5-fluoro-N4-(3-methoxyphenyl)-2,4-pyrimidinediamine (R926739)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-N4-(3-methoxyphenyl)-2,4-pyrimidinediamine and 3-amino-1,2-propanediol were reacted to yield N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N4-(3-methoxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 16.66 min.; purity: 99 %; MS (m/e): 458 (MH^+).
7.3.522	N4-(3,5-Dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R945140)	In a manner analogous to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethylene oxyphenyl)-2,4-pyrimidinediamine and piperazine gave N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 2.18 (s, 6H), 2.72 (q, J= 5.1 Hz, 4H), 3.32 (t, 2H), 3.52 (t, J= 5.1 Hz, 2H), 4.55 (s, 2H), 6.56 (ddd, J= 1.2, 2.4 and 8.1 Hz, 1 H), 7.03 (ddd, J= 1.2, 1.8 and 8.1 Hz, 1H), 7.11 (t, J= 8.1 Hz, 1H), 7.20 (s, 2H), 7.35 (t, J= 2.1 Hz, 1H), 7.84 (d, J= 3.9 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD): δ - 168.78; LCMS: ret. time: 14.32 min.; purity: 88.37%; MS (m/e): 467.06 (MH^+).
7.3.523	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-morpholino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926488)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine with morpholine gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-morpholino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 8.19 (t, 1H, J= 1.5 Hz), 7 90 (d, 1H, J= 3.9 Hz), 7.44 (d, 2H, J= 0.9 hz), 7.28 (s, 1H), 7.21 (t, 1H, J= 2.4 Hz), 7.15 (t, 1H, J= 7.5 Hz), 7.08 (m, 1H), 7.61 (bd, 1H, J= 6.9 Hz), 3.8 (m, 4H), 3.65 (m, 4H); LCMS: ret. time: 17.21 min.; purity: 83%; MS (m/e): 450 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.524	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926493)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine with methylamine hydrochloride gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD). δ 8.71 (d, 1H, J= 4.8 Hz), 8.00-7.92 (m, 2H), 7.56-7.52 (m, 1H), 7.44-7.39 (m, 2H), 7.12 (m, 2H), 6.69 (bdd, 1H), 2.96 and 2.94 (2s, 3H).
7.3.525	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-2-hydroxyethylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926497)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine with 2-hydroxyethylamine gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-2-hydroxyethylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.18 (d, 1H, J= 1.8 Hz), 7.80 (bs, 1H), 7.60 (m, 1H), 7.34-7.16 (m, 3H), 7.10 9t, 1H, 8.4 Hz), 6.85 (bdd, 1H), 6.62 (dd, 1H, J= 1.5 and 8.1 Hz), 3.70 (t, 2H, J= 4.8 Hz), 3.52 (t, 2H, J= 4.0 Hz); LCMS: ret. time: 14.49 min.; purity: 97%; MS (m/e): 424 (MH^+).
7.3.526	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926500)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine with piperazine gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.19 (t, 1H, J= 1.2 Hz), 7.90 (d, 1H, J= 3.9 Hz), 7.43 (d, 2H, J= 1.2 Hz), 7.25-7.06 (m, 4H), 6.59 (m, 1H), 3.80 (m, 4H), 2.95 (m, 4H); LCMS: ret. time: 12.97 min.; purity: 79%; MS (m/e): 449 (MH^+).
7.3.527	5-Cyano-N4-(3-hydroxyphenyl)-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R925844)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-N-methylaminocarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-cyano-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine with methylamine hydrochloride gave 5-cyano-N4-(3-hydroxyphenyl)-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 18.83 min.; purity: 96 %; MS (m/e): 391 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.528	5-Cyano- N4-[4-(N-cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925845)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-cyano-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine reacted with cyclopropylmethylamine to give 5-cyano-N4-[4-(N-cyclopropylmethylamino) carbonylmethyleneoxyphenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 22.47 min.; purity: 100 %; MS (m/e): 431 (MH^+).
7.3.529	5-Cyano-N4-(3-hydroxyphenyl)-N2-[4-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R925846)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-cyano-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine reacted with 2,3-dihydroxypropylamine to give 5-cyano-N4-(3-hydroxyphenyl)-N2-[4-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.84 min.; purity: 100 %; MS (m/e): 451 (MH^+).
7.3.530	5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3-trifluoromethylphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-N4-(3-trifluoromethylphenyl)-2,4-pyrimidineamine with methylamine hydrochloride gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)]-N4-(3-trifluoromethylphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 21.98 min., purity: 86%, MS (m/e): 436 (MH^+).
7.3.531	N4-[4-(4,5-Dichloro-1H-imidazol-1-ylphenyl)]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926812)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N-4-[4-(4,5-dichloro-1H-imidazol-1-ylphenyl)]-5-fluoro-N2-(3-ethoxycarbonylmethylene oxyphenyl)-2,4-pyrimidinediamine with methylamine hydrochloride gave N4-[4-(4,5-dichloro-1H-imidazol-1-ylphenyl)]-5-fluoro N2-(3-[N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 21.02 min., purity: 100%, MS (m/e): 502 (MH^+).
7.3.532	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-methylaminocarbonyllindol-7-yl)- 2,4-pyridinediamine (R926815)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-N4-(3-trifluorophenyl)-2,4-pyrimidineamine with methylamine hydrochloride gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-methylaminocarbonyllindol-7-yl)- 2,4-pyridinediamine. LCMS: ret. time: 17.97 min., purity: 97%, MS (m/e): 435 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.533	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926484)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-(3-ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and morpholine gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.94 (bs, 1H), 7.35 (t, 1H, J= 2.4 Hz), 7.24 (m, 1H), 7.19 (t, 1H, J= 8.1 Hz), 7.10 (bdd, 1H, J= 6.9 Hz), 6.95 (m, 2H), 6.85 (d, 1H, J= 8.1 Hz), 6.94 (s, 1H), 6.58 (dd, 1H, J= 1.8 and 2.8 Hz), 4.64 (s, 2H), 4.27 9s, 4H), 3.62 (m, 4H), 3.55 (m, 4H); LCMS: ret. time: 18.45 min.; purity: 100%; MS (m/e): 482 (MH^+).
7.3.534	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-morpholino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926492)	In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuron-5-yl)-2,4-pyrimidinediamine with morpholine gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-morpholino)carbonylbenzofuron-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.27 (s, 1H), 9.17 (s, 1H), 8.14 (d, 1H, J= 2.4 Hz), 8.05 (d, 1H, J= 5.6 Hz), 7.58-7.46 (m, 2H), 7.27 (m, 1H), 7.15 (dd, 1H, J= 2.4 and 9 Hz), 6.80 9m, 1H), 4.24 (s, 4H), 3.80-3.45 (m, 8H); LCMS: ret. time: 19.97 min.; purity: 76%; MS (m/e): 492 (MH^+).
7.3.535	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926496)	In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and methylamine hydrochloride gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.06 (s, 1H), 7.85 (d, 1H, J= 3.3 Hz), 7.42 (d, 2H, J= 1.2 Hz), 7.35 (s, 1H), 7.29 (d, 1H, J= 2.4 Hz). 6.99 (dd, 1H, J= 3.3 and 8.7 Hz), 6.78 (d, 1H, J= 8.7 Hz), 4.24 (s, 4H), 2.94 (s, 3H); LCMS: ret. time: 18.05 min.; purity: 99%; MS (m/e): 436 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.536	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-2-hydroxyethylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926498)	In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine with 2-hydroxyethylamine yielded N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-2-hydroxyethylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.07 (d, 1H, J= 1.2 Hz), 7.86 (d, 1H, J= 3.9 Hz), 7.43 (d, 2H, J= 1.5 Hz), 7.38 (s, 1H), 7.29 (d, 1H, J= 2.4 Hz). 6.98 (dd, 1H, J= 2.1 and 9 Hz), 6.78 (d, 1H, J= 8.7 Hz), 4.23 (s, 4H), 3.72 (t, 2H, J= 5.7 Hz), 3.53 (t, 2H, J= 6.0 Hz); LCMS: ret. time· 16.21 min.; purity: 97%; MS (m/e): 466 (MH^+).
7.3.537	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926499)	In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and piperazine yielded N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.26 (s, 1H), 9.16 (s, 1H), 8.12 (d, 1H, J= 1.8 Hz), 8.04 (d, 1H, J= 3.6 Hz), 7.49 (d, 2H), 7.30 (d, 1H, J= 2.4 Hz), 7.20 (s, 1H), 7.15 (bdd, 1H, J= 3 Hz), 6.79 (d, 1H, J= 8.7 Hz), 4.22 (s, 4H), 2.48 (s, 3H); LCMS: ret. time: 14.61 min.; purity: 94%; MS (m/e): 491 (MH^+).
7.3.538	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926503)	In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonymethyleneoxyphenyl)-2,4-pyrimidinediamine and piperazine were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 9.14 (bs, 2H), 8.04 (d, 3.6 Hz), 7.32-7.20 (m, 4H), 7.06 (t, 1H, J= 8.1 Hz), 6.79 (d, d, 1H, J= 9 Hz), 6.43 (bd, 1H, J= 9.9 Hz), 4.64 (s, 2H), 4.20 (bs, 4H), 3.29 (m, 4H), 2.59 (m, 4H); LCMS: ret. time: 14.92 min.; purity: 99%; MS (m/e): 481 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.539	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxy-1,1-dimethylethylamino)carboxymethyleneoxyphenyl]-2,4-pyrimidinediamine (R926764)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and 2-amino-2-methylpropanol gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxy-1,1-dimethylethylamino)carboxymethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.95 (d, 1H, J= 2.7 Hz), 7.47 (t, 1H, J= 2.4 Hz), 7.20 (t, 1H, J= 8.1 Hz), 7.03 (dd, 1H, J= 1.2 and 8.1 Hz), 6.98 (dd, 1H, J= 3 and 8.2 Hz), 6.93 (s, 1H), 6.84 (d, 1H, J= 8.7 Hz), 6.66 (d, 1H, J= 3 Hz), 6.57 (bs, 1H), 6.53 (m, 1H), 4.65 (m, 1H), 4.39 (s, 2H), 4.28 (s, 4H), 3.63 (d, 2H, J= 5.7 Hz), 1.31 (s, 6H); LCMS· ret. time: 19.19 min.; purity: 89%; MS (m/e): 484 (MH^+).
7.3.540	N2-[3-(N-Cyclohexylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)- 5-fluoro-2,4-pyrimidinediamine (R926765)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and cyclohexylamine gave N2-[3-(N-cyclohexylamino)carbonyl methyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.94 (d, 1H, J= 3.3 Hz), 7.41 (t, 1H, J= 2.4 Hz), 7.28 (d, 1H, J= 2.4 Hz), 7.20 (t, 1H, J= 7.5 Hz), 7.04 (dd, 1H, J= 1.2 and 8.1 Hz), 6.95 (m, 2H), 6.85 (d, 1H, J= 8.7 Hz), 6.68 (d, 1H, J= 3.0 Hz), 6.53 (dd, 1H, J= 2.4 and 8.4 Hz), 6.45 (bd, 1H, J= 8.1 Hz), 4.43 (s, 2H), 4.24 (s, 4H), 3.85 (m, 1H), 1.90 (m, 2H), 1.75-1.55 (m, 2H), 1.45-1.05 (m, 6H); LCMS: ret. time: 23.70 min.; purity: 97%; MS (m/e): 494 (MH^+).
7.3.541	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[N-methyl-N-(2-hydroxyethyl)amino]carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926766)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and N-methyl-N-2-hydroxyethylamine gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[N-methyl-N-(2-hydroxyethyl)amino] carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.93 (d, 1H, J= 3 Hz), 7.92 (bs, 1H), 7.35 (t, 1H, J= 2.4 Hz), 7.18 (m, 1H), 7.06 (dd, 1H, J= 1.2 and 8.7 Hz), 6.97 (t, 1H, J= 2.4 Hz), 6.94 (m, 1H), 6.85 (d, 1H, J= 8.7 Hz), 6.70 (bd, 1H), 6.59 (dd, 1H, J= 1.8 and 8.1 Hz), 4.66 (s, 2H), 4.28 (s, 4H), 3.79 (t, 2H, J= 5.4 Hz), 3.56 (t, 3H, J= 5.4 Hz), 3.10 (s, 3H); LCMS: ret. time: 16.64 min.; purity: 97%; MS (m/e): 470 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.542	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-homopiperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926767)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and homopiperazine gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-homopiperazinocarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.27 (s, 1H), 9.17 (d, 1H, J= 1.2 Hz), 8.14 (s, 1H), 8.05 (d, 1H, J= 3.6 Hz), 7.54-7.46 (m, 2H), 7.30 (d, 1H, J= 2.4 Hz), 7.24 (s, 1H), 7.17 (dd, 1H, J= 2.4 and 8.7 Hz), 6.80 (d, 1H, J= 8.7 Hz), 4.22 (s, 4H), 3.79 (m, 2H), 3.65 (m, 2H), 3.01 (m, 2H), 2.89 (m, 2H), 1.90 (m, 1H), 1.80 (m, 1H); ^{19}F NMR (DMSO-d6): - 46687; LCMS: ret. time: 14.99 min.; purity: 77%; MS (m/e): 505 (MH^+).
7.3.543	N4-(3,4-Ethylenedioxyphenyl)-N2-[3-(N,N-dimethylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R925755)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and N,N-dimethylamine hydrochloride gave N4-(3,4-ethylenedioxyphenyl)-N2-[3-(N,N-dimethylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.16 (d, 1H, J= 1.2 Hz), 9.15 (s, 1H), 8.04 (d, 1H), J= 5.6 Hz), 7.30-7.21 (m, 4H), 7.06 (t, 1H, J= 9Hz), 6.78 (d, 1H, J= 9Hz), 6.43 (m, 1H), 4.65 (s, 2H), 4.21 (s, 4H), 2.94 (s, 3H), 2.82 (s, 3H); LCMS: ret. time: 18.70 min.; purity: 83%; MS (m/e): 440 (MH^+).
7.3.544	N2-[3-[N,N-Bis-(2-hydroxyethylamino)] carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926781)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and N,N-bis(hydroxyethyl)amine gave N2-[3-[N,N-bis-(2-hydroxyethylamino)]carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.86 (d, 1H, J= 3.6 Hz), 7.25 (m, 2H), 7.17-7.03 (m, 3H), 6.78 (d, 1H, J= 9Hz), 6.58 (bd, 1H), 4.80 (s, 2H), 4.23 (s, 4H), 3.71 (t, 4H, J= 4.8 Hz), 3.53 (t, 2H, J= 6Hz), 3.49 (t, 3H, J= 5.4 Hz); LCMS: ret. time: 16.25 min.; purity: 94%; MS (m/e): 500 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.545	N2-[3-(N-2,3-Dihydroxypropylamino) carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926782)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and 2,3-dihydroxypropylamine gave N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.86 (d, 1H, J= 4.2 Hz), 7.37 (t, 1H, J= 1.8 Hz), 7.24 (d, 1H, J= 2.4 Hz), 7.14 (m, 2H), 7.09 (dd, 1H, J= 2.4 and 9 Hz), 6.78 (d, 1H, J= 8.7 Hz), 6.59 (m, 1H), 4.39 (s, 2H), 4.22 (s, 4H), 3.73 (m, 1H), 3.48 (m, 4H); ^{19}F NMR (CD_3OD): -47575; LCMS: ret. time: 15.97; purity: 98%; MS (m/e): 486 (MH^+).
7.3.546	N2-[2-(N-2,3-Dihydroxypropylamino)carbonylbenzofuran-5-yl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926783)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and 2,3-dihydroxypropylamine gave N2-[2-(N-2,3-dihydroxypropylamino)carbonylbenzofuran-5-yl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.86 (d, 1H, J= 4.2 Hz), 7.35 (t, 1H, J= 1.2 Hz), 7.24 (d, 1H, J= 3 Hz), 7.15 (m, 2H), 7.07 (dd, 1H, J= 2.1 and 8.7 Hz), 6.78 (d, 1H, J= 8.7 Hz), 6.59 (m, 1H), 4.40 9s, 1H), 4.23 (s, 4H), 4.03 (t, 1H, J= 5.7 Hz), 3.67 (d, 2H, 3.6 Hz), 3.65 (d, 2H, J= 4.2 Hz); ^{19}F NMR (CD_3OD): -47578; LCMS: ret. time: 15.72 min.; purity: 99%; MS (m/e): 486 (MH^+).
7.3.547	N2-[3-(N-1,3-Dihydroxy-2-propylamino) carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926784)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethylenedioxyphenyl)-2,4-pyrimidinediamine and 2-amino-1,3-propanediol gave N2-[3-(N-1,3-dihydroxy-2-propylamino)carbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.08 (bd, 1H), 7.86 (bs, 1H), 7.44 (s, 2H), 7.39 (s, 1H), 7.29 (d, 1H, J= 2.4 Hz), 6.97 (dd, 1H, J= 2.4 and 8.7 Hz), 6.78 (d, 1H, J== 8.7 Hz), 4.24 (s, 4H), 3.84 (m, 1H), 3.56 (m, 2H), 3.44 (m, 2H); LCMS: ret. time: 16.63 min.; purity: 97%; MS (m/e): 496 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.548	N2-[2-(N-1,3-Dihydroxy-2-propylamino)carbonylbenzofuran-5-yl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926785)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and 2-amino-1,3-propanediol gave N2-[2-(N-1,3-dihydroxy-2-propylamino)carbonylbenzofuran-5-yl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.08 (t, 1H, J= 1.8 Hz), 7.86 (d, 1H, J= 3.9 Hz), 7.45 (s, 2H), 7.41 (s, 1H), 7.29 (d, 1H, J= 2.4 Hz), 6.97 (dd, 1H, J= 3 and 8.7 Hz), 6.77 (d, 1H, J= 8.7 Hz), 4.24 (s, 4H), 4.19 (t, 1H, J= 5.7 Hz), 3.75 (d, 4H, J= 5.4 Hz); ^{19}F NMR (CD_3OD): - 47745; LCMS: ret. time: 15.09 min., purity: 97%; MS (m/e): 496 (MH^+).
7.3.549	N4-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R940265)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3-chloro-4-hydroxy-5-methylphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with morpholine gave N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 18.66 min.; purity: 92 %; MS (m/e): 487 (M^+), 489 (MH^+); ^{1}H NMR (DMSO-d6): 9.28 (2H, s), 9.01 (1H, s), 8.17 (1H, d, J= 3.6 Hz), 7.65 (1H, d, J= 2.4 Hz), 7.5 (1H, d, J= 2.7 Hz), 7.42 (1H, d, J= 6.6 Hz), 7.29 (1H, s), 7.18 (1H, t, J= 8.1 Hz), 6.57 (1H, dd, J= 6.6 and 2.2 Hz), 4.79 (2H, s), 3.67 (4H, m), 3.52 (4H, m), 2.29 (3H, s).
7.3.550	N4-(3,5-Dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950187)	N4-(3,5-Dichlorophenyl-4-hydroxy)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (0.5 g, 1.1 mmol) was dissolved in EtOH:morpholine (4 ml : 4ml) and the mixture was refluxed for 1 day (100 °C oil-bath temperature). The mixture was cooled to 22 °C, diluted with water and brine, filtered, and dried under reduced pressure to give N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.35 (s, 1H), 9.22 (s, 1H), 8.09 (d, 1H, J= 3.6 Hz), 7.94 (m, 1H), 7.75 (m, 1H), 7.27 (m, 1H), 7.18 (m, 1H), 7.12 (t, 1H, J= 8.4 Hz), 6.44 (m, 1H), 4.64 (s, 2H), 3.39 (m, 4H), 2.68 (m, 4H); LCMS purity: 92.6%; MS (m/e): 507.89 (M^+, 100).
7.3.551	N4-(3,5-Dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950188)	In like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,5-dichloro-4-hydroxyphenyl)-N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine and piperazine were reacted to prepare N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.26 min.; purity: 88.5%; MS (m/e): 506.89 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.552	N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[3-(N-methylamino)carbonylmethyeleneoxyphenyl]-2,4-pyrimidinediamine (R926776)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3-ethoxycarbonylmethyleneoxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine with methylamine hydrochloride gave N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[3-(N-methylamino)carbonylmethyeleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 16.94 min.; purity: 73%; MS (m/e): 426 (MH^+).
7.3.553	N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-(4-methylaminocarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945173)	In a manner analogous to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(4-methylaminocarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine, N4-(4-cyanomethyleneoxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride salt gave N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(4-methylaminocarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (acetone-d_6): δ 2.80 (d, 3H), 4.21-4.28 (m, 4H), 4.47 (s, 2H), 6.71 (d, J= 8.7 Hz, 1H), 6.96 (d, J= 9.0 Hz, 2H), 7.06 (dd, J= 2.7 and 9.0 Hz, 1H), 7.41 (d, J= 2.4 Hz, 1H), 7.74 (d, J= 9.0 Hz, 2H), 7.93 (d, J= 3.6 Hz, 1H), 8.20 (br, 1H, NH), 8.41 (br, 1H, NH); ^{19}F NMR (282 MHz, acetone-d_6): δ -169.05; LCMS: ret. time: 17.47 min.; purity: 98.99%; MS (m/e): 425.89 (MH^+).
7.3.554	N2-[4-(2-N,N-Dimethylaminoethyl)oxyphenyl]-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R909253)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-chloro-5-fluoro-N4-[3-(N-methylamino)carbonylmethylene oxyphenyl]-4-pyrimidineamine and 4-(2-N,N-dimethylaminoethyl)oxyaniline were reacted to yield N2-[4-(2-N,N-dimethylaminoethyl)oxyphenyl]-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 8.0 (d, 1H J= 4 Hz), 7.42 (m, 2H), 7.24 (m, 2H), 7.05 (m, 2H), 6.85 (m, 1H), 4.39 (s, 2H), 4.30 (m, 2H), 3.66 (m, 2H), 3.04 (s, 6H), 2.83 (s, 3H); LCMS: ret. time: 14.0 min.; purity: 96 %; MS (m/e): 455 (MH^+).
7.3.555	N2-(1,4-Benzoxazin-6-yl)-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R909247)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-chloro-5-fluoro-N4-[3-(N-methylamino)carbonylmethylene oxyphenyl]-4-pyrimidineamine and 6-amino-1,4-benzoxazine were reacted to yield N2-(1,4-benzoxazin-6-yl)-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^1H (DMSO-d6): δ 8.0 (d, 1H), 7.6 (m, 1H), 7.42 (m, 1H), 7.20 (m, 1H), 6.95 (m, 1H), 6.76 (m, 1H), 6.56 (m, 1H), 4.43 (s, 2H), 4.05 (m, 2H), 3.25 (s, 3H), 3.13 (m, 2H); LCMS: ret time: 17.67 min.; MS (m/e): 425 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.556	N2-(4-Dihydrobenzofuranyl)-5-fluoro-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R909249)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-chloro-5-fluoro-N4-[3-(N-methylamino)carbonylmethylene oxyphenyl]-4-pyrimidineamine and 5-amino-2,3-dihydrobenzofuran were reacted to yield N2-(4-dihydrobenzofuranyl)-5-fluoro-N4-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.09 (d, 1H), 8.00 (m, 1H), 7.42 (m, 2H), 7.05 (m, 1H), 6.96 (m, 1H), 6.76 (m, 1H), 6.58 (m, 1H), 4.53 (m, 2H), 4.25 (s, 2H), 3.15 (m, 2H), 2.70 (m, 3H); LCMS: ret time: 19.24 min; MS (m/e): 410 (MH^+).
7.3.557	N2-(3-*tert*-Butylphenyl)-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R940267)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-(3-*tert*-butylphenyl)-N4-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with methylamine hydrochloride gave N2-(3-*tert*-butylphenyl)-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 22.22 min.; purity: 97 %; MS (m/e): 424 (MH^+); ^{1}H NMR ($CDCl_3$): δ 7.98 (2H, m), 7.76 (2H, m), 7.56 (1H, t, J= 1.3 Hz), 7.28-7.22 (1H, m), 7.04 (1H, d, J= 7.8 Hz), 6.90 (1H, dd, J= 9 Hz, J= 1.3 Hz), 6.80 (1H, 2.6 Hz), 6.66 (1H, dd, J= 9 and 2.6 Hz), 6.46 (1H, s), 4.53 (2H, s), 2.88 (3H, d, J= 5.1 Hz), 1.31 (9H, s).
7.3.558	N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R926491)	In like manner to the preparation of N4-(ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-(3,4-ethylenedioxyphenyl)-N4-(2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine with methylamine hydrochloride gave N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.10 (s, 1H), 7.94 (d, 1H, J= 5.1 Hz), 7.59 (s, 2H), 7.44 (s, 1H), 6.96 (d, 1H, J= 2.4 Hz), 6.82 (d, 1H, J= 8.4 Hz), 6.76 (dd, 1H, J= 3.6 and 8.1 Hz), 4.22 (s, 2H), 4.21 (s, 2H), 2.95 (s, 3H); LCMS: ret. time: 17.76 min.; purity: 97%; MS (m/e): 436 (MH^+).
7.3.559	N2-(3,5-Dimethoxyphenyl)-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926810)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine, the reaction of N2-(3,5-dimethoxyphenyl)-N4-(3-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with methylamine hydrochloride gave N2-(3,5-dimethoxyphenyl)-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.93 (d, 1H, J= 3.9 Hz), 7.72 (t, 1H, J= 1.8 Hz), 7.27-7.19 9m, 2H), 6.88 (d, 2H, J= 2.4 Hz), 6.72 (m, 1H), 6.01 (t, 1H, J= 2.4 Hz), 4.44 (s, 2H), 3.67 (s, 6H), 2.80 (s, 3H).

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Section Number	Name of compound and reference number	Experimental
7.3.560	5-Bromo-N2-(3,4-ethylenedioxyphenyl)-N4-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R925851)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-bromo-N2-(3,4-ethylenedioxyphenyl)-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield 5-bromo-N2-(3,4-ethylenedioxyphenyl)-N4-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.01 (s, 1H), 7.48 (d, 2H, J= 8.7 Hz), 7.09 (d, 1H, J= 3.0 Hz), 7.08 (d, 2H, J= 8 7 Hz), 6.81 (dd, 1H, J= 8.7 Hz), 6.64 (d, 1H, J= 8.7 Hz), 4.52 (s, 2H), 4.20 (bs, 4H), 2.83 (s, 3H); LCMS: ret. time: 19.13 min.; purity: 94 %; MS (m/e): 487 (MH^+).
7.3.561	N2-(3-Hydroxyphenyl)-5-trifluoromethyl-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926741)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-(3-hydroxyphenyl)-5-trifluoromethyl-N4-(3-N-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield N2-(3-hydroxyphenyl)-5-trifluoromethyl-N4-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 18.52 min.; purity: 96%; MS (m/e): 434 (MH^+).
7.3.562	N2,N4-Bis[4-(N-n-butylamino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine (R925860)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and n-butylamine were reacted to yield N2,N4-bis[4-(N-n-butylamino)carbonylmethylene oxyphenyl)-5-cyano-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.77 (bs, 1H), 9.38 (bs, 1H), 8.42 (s, 1H), 8.09 (t, 1H, J= 5.4 Hz), 8.02 (t, 1H, J= 5.7 Hz), 7.48-7.34 (m, 4H), 6.93 (d, 2H, J= 9.3 Hz), 6.82-6.72 (m, 2H), 4.47 (s, 2H), 4.38 (s, 2H), 3.14-3.06 (m, 4H), 1.42-1.33 (m, 4H), 1.28-1.18 (m, 4H), 0.83 (t, 6H, J= 6.9 Hz); LCMS: ret. time: 26.40 min.; purity: 97 %; MS (m/e): 546 (MH^+).
7.3.563	N2,N4-Bis[4-(N-isopropylamino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine (R925861)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and isopropylamine were reacted to yield N2,N4-bis[4-(N-isopropylamino)carbonylmethylene oxyphenyl]-5-cyano-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.41 (s, 1H), 7.90 (d, 1H, J= 7.5 Hz), 7.81 (d, 1H, J= 7.5 Hz), 7.50-7.36 (m, 4H), 6.93 (d, 2H, J= 8.7 Hz), 6.84-6.75 (m, 2H), 4.45 (s, 2H), 4.36 (s, 2H), 3.99-3.87 (m, 2H), 1.08 (d, 6H, J= 3.0 Hz), 1.06 (d, 6H, J= 2.4 Hz); LCMS: ret. time: 23.45 min.; purity: 89 %; MS (m/e): 518 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.564	N2,N4-Bis[4-(N-n-propylamino)carbonylmethylene oxyphenyl]-5-cyano-2,4-pyrimidinediamine (R925853)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and n-propyl amine were reacted to yield N2,N4-bis[4-(N-n-propylamino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.78 (bs, 1H), 9.38 (bs, 1H), 8.41 (s, 1H), 8.07 (dt, 2H, J= 6.0 and 22.5 Hz), 7.48-7.36 (m, 4H), 6.93 (d, 2H, J= 8.7 Hz), 6.78 (d, 2H, J= 8.1 Hz), 4.48 (s, 2H), 4.39 (s, 2H), 3.07 (2q, 4H, J= 7.2 Hz), 1.47-1.38 (m, 4H), 0.90-0.77 (m, 6H); LCMS: ret. time: 23.67 min.; purity: 94 %; MS (m/e): 519 (MH^+).
7.3.565	N2,N4-Bis[4-(N-morphonlino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine (R925854)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and morpholine were reacted to yield N2,N4-bis[4-(N-morphonlino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.78 (bs, 1H), 9.31 (bs, 1H), 8.41 (s, 1H), 7.43 (d, 4H, J= 8.1 Hz), 6.89 (d, 2H, J= 9.3 Hz), 6.75 (d, 2H, J= 8.4 Hz), 4.84 (s, 2H), 4.74 (s, 2H), 3.76 (t, 4H, J= 5.1 Hz), 3.62-3.50 (m, 4H), 3.49-3.38 (m, 4H), 3.08-3.01 (m, 4H); LCMS: ret. time: 19.25 min.; purity: 89 %; MS (m/e): 574 MH^+).
7.3.566	N2,N4-Bis[4-(N-piperidino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine (R925855)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and piperidine were cted to yield N2,N4-bis[4-(N-piperidino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine. ^{1}H NMR (acetone-d_6): δ 8.86 (bs, 1H), 8.48 (bs, 1H), 8.34 (s, 1H), 7.61-7.50 (m, 4H), 6.98 (d, 2H, J= 8.7 Hz), 6.90 (d, 2H, J= 9.3 Hz), 4.84 (s, 2H), 4.75 (s, 2H), 3.59-3.48 (m, 8H), 1.68-1.44 (m, 12H); LCMS: ret. time: 24.76 min.; purity: 98 %; MS (m/e): 571 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.567	N2,N4-Bis[4-(N-cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine (R925859)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and cyclopropylmethylamine were reacted to yield N2,N4-bis[4-(N-cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-5-cyano-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.78 (bs, 1H), 9.36 (bs, 1H), 8.41 (s, 1H), 8.18 (t, 1H, J= 5.1 Hz), 8.10 (t, 1H, J= 5.1 Hz), 7.52-7.38 (m, 4H), 6.94 (d, 2H, J= 8.7 Hz), 6.84-6.76 (m, 2H), 4 48 (s, 2H), 4.40 (s, 2H), 3.00 (q, 4H, J= 6.3 Hz), 0.97-0.88 (m, 2H), 0.40-0.33 (m, 4H), 0.18-0.03 (m, 4H); ^{19}F NMR ($CDCl_3$): LCMS: ret. time: 24.58 min.; purity: 100 %; MS (m/e): 543 (MH^+).
7.3.568	N4-(3-Aminophenyl)-N2-(1,4-benzoxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950254)	N4-(3-Nitrophenyl)-N2-[(2H)1,4-benzoxazin-3(4H)-one-6-yl]-5-fluoro-2,4-pyrimidinediamine (940 mg, 2.5 mmol) and Pd/C 10% (300 mg, 50% water content) were suspended in EtOH (7 mL) and 10% aqueous HCl (5 mL) and hydrogenated in a Parr apparatus for 3 hours (22 °C, 60 psi). The suspension was filtered over celite and neutralized by addition of K_2CO_3. The solvents were removed and the resulting black slurry was suspended in MeOH. Silica gel (4 g) was added and the volatiles were removed under reduced pressure. The residue was subjected to column chromatography on silica gel ($CHCl_3$–Acetone, 2:1) to give 186 mg of N4-(3-aminophenyl)-N2-(1,4-benzoxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine as brownish solid. ^{1}H NMR (DMSO-d6): δ 8.92 (s, 1H), 8.64 (s, 1H), 7.95 (d, 1H, J= 3.6 Hz), 7.11 (s, 1H), 6.84-6.95 (m, 3H), 6.66 (dd, 1H, J= 2.4, 9.0 Hz), 6.46 (d, 1H, J= 8.1 Hz), 6.28 (d, 1H, J= 8.1 Hz), 5.62 (s, 1H), 4.98 (s, 2H), 4.03 (m, 2H), 3.31 (m, 2H); LCMS purity: 98.4%; MS (m/e): 352.7 (M^+, 100).
7.3.569	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950200)	N2-(3-Ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (50 mg, 0.11 mmol) was dissolved in EtOH:4-(2-aminoethyl)morpholine (0.5 ml : 0.5 ml) and the mixture was refluxed for 3 hours (100 °C oil-bath temperature). The mixture was cooled to 22 °C, diluted with water and washed with EtOAc. The organic phase was dried over $MgSO_4$, concentrated under educed pressure, and the residue was subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 2:1) to give N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-morpholinoethyleneamino) carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6 + CD_3OD): δ 7.92 (d, 1H, J= 4.1 Hz), 7.31 (d, 1H, J= 2.3 Hz), 7.20 (dd, 1H, J= 2.7, 8.8 Hz), 6.87-6.99 (m, 2H), 6.74 (d, 1H, J= 8.8Hz), 6.09 (m, 1H), 4.19 (m, 4H), 3.38 (m, 4H), 3.16 (t, 2H, J= 6.3 Hz), 2.28 (t, 2H, J= 6.3 Hz); LCMS purity: 99.2%; MS (m/e): 524.01 (M^+, 100).

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Section Number	Name of compound and reference number	Experimental
7.3.570	N4-(3,4-Ethylenedioxyphenyl)-N2-[3-N-methylamino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950191)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and methylamine were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 17.32 min.; purity: 99.3%; MS (m/e): 425.04 (MH^+).
7.3.571	N2-[3-(N-Amino)carbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950192)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and aqueous ammonia were reacted to prepare N2-[3-(N-amino)carbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 16.59 min.; purity: 98.8%; MS (m/e): 411.02 (MH^+).
7.3.572	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950193)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and morpholine were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 18.70 min.; purity: 85.8%; MS (m/e): 481.05 (MH^+).
7.3.573	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-(N-methyl)-piperazino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950194)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and N-methylpiperazine were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-(N-methyl)piperazino)carbonyl methyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.75 min.; purity: 99.1%; MS (m/e): 494.06 (MH^+).
7.3.574	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxyethyleneamino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950195)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and 2-aminoethanol were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxyethyleneamino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 16.23 min.; purity: 97.3%; MS (m/e): 455.02 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.575	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)ethyleneaminocarbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950196)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and N-methyl-ethylen-1,2-diamine were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)ethyleneaminocarbonyl methyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.34 min.; purity: 98.2%; MS (m/e): 468.06 (MH^+).
7.3.576	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950197)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and piperazine were reacted to prepare N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 15.38 min.; purity: 93.2%; MS (m/e): 479.99 (MH^+).
7.3.577	N2-[3-(N-Benzylamino)ethyleneaminocarbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950198)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and N-benzyl-ethylen-1,2-diamine were reacted to prepare N2-[3-(N-benzylamino)ethyleneaminocarbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 17.70 min.; purity: 92.5%; MS (m/e): 544.04 (MH^+).
7.3.578	N2-[3-(N,N'-Bis(2-N-hydroxyethyl)amino)carbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-imidinediamine (R950199)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and N,N'-bis(2-hydroxyethylene)amine were reacted to N2-[3-(N,N'-bis(2-N-hydroxyethyl)amino)carbonylmethyleneaminophenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 15.81 min.; purity: 99.4%; MS (m/e): 499.01 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.579	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950217)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and methylamine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 14.41 min.; purity: 93.0%; MS (m/e): 383.02 (MH^+).
7.3.580	N2-(3-Aminocarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R950219)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and aqueous ammonia were reacted to prepare N2-(3-aminocarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 14.23 min.; purity: 95.0%; MS (m/e): 369.03 (MH^+).
7.3.581	N2-[3-(N,N-Dimethylamino)carbonylmethyleneaminophenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R950220)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and dimethylamine were reacted to prepare N2-[3-(N,N-dimethylamino)carbonylmethyleneaminophenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 16.59 min.; purity: 96.5%; MS (m/e): 397.06 (MH^+).
7.3.582	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950221)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and morpholine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 16.29 min.; purity: 91.5%; MS (m/e): 439.03 (MH^+).
7.3.583	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950222)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and piperazine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 13.04 min.; purity: 89.9%; MS (m/e): 438.06 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.584	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[N-(N-methyl)piperazino]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950223)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and N-methylpiperazine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-[N-(N-methyl)piperazino]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.06 min.; purity: 98.7%; MS (m/e): 452.06 (MH^+).
7.3.585	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950224)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and 2-aminoethanol were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 13.28 min.; purity: 97.3%; MS (m/e): 413.04 (MH^+).
7.3.586	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)ethylamino]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950225)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and N-methyl-ethylen-1,2-diamine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)ethylamino]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.31 min.; purity: 94.7%; MS (m/e): 426.01 (MH^+).
7.3.587	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-2-morpholinoethylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950226)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and N-morpholinylethylamine were reacted to prepare 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-2-morpholinoethylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.66 min.; MS (m/e): 482.39 (MH^+).
7.3.588	R935184: 5-Fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine was reacted with $Me_2NH.HCl$ and *i*-Pr_2NEt in methanol to produce 5-fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 6.91 min.; purity: 98%; MS (*m/e*): 440 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.589	R935196: N2-[3-(1-Bis(N-methylaminocarbonyl)ethoxy)phenyl]-5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidineamine:	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[3-(1-bis(ethyloxycarbonyl)ethoxy)phenyl]-5-fluoro-N2-[4-isopropoxyphenyl)-2,4-pyrimidinediamine was reacted with $Me_2NH.HCl$ and *i*-Pr_2NEt in presence of methanol to produce N2-[3-(1-bis(N-methylaminocarbonyl)ethoxy)phenyl]-5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidineamine. ^1H NMR (DMSO-d6): δ 9.18 (s, 1H), 9.15 (s, 1H), 8.07 (app qt, 2H, J= 4.7 Hz), 8.01 (d, 1H, J= 3.5 Hz), 7.65-7.62 (m 2H), 7.36 (br s, 1H), 7.28 (dd, 1H, J= 1.1 and 8.2 Hz), 7.03 (t, 1H, J= 8.2 Hz), 6.87 (d, 2H, J= 8.8 Hz), 6.35 (dd, 1H, J= 1.1 and 8.8 Hz), 4.54 (q, 1H, J= 6.4 Hz), 2.62 (d, 6H, J= 4.7 Hz), 1.49 (s, 3H), 1.23 (d, 6H, J= 5.8 Hz). LCMS: ret. time: 19.40 min.; purity: 94%; MS (*m/e*): 497 (MH^+).
7.3.590	R935202: 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine:	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine was reacted with $Me_2NH.HCl$ to give 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 9.21 (s, 1H), 9.19 (s, 1H), 8.06 (d, 1H, J= 4.1 Hz), 7.94 (q, 1H, J= 3.5 Hz), 7.42-7.38 (m, 2H), 7.30 (d, 2H, J= 7.6 Hz), 7.12 (t, 1H, J= 7.6 Hz), 6.89 (d, 1H, J= 8.2 Hz), 6.47 (dd, 1H, J= 2.3 and 8.8 Hz), 4.33 (s, 2H), 4.11-4.03 (m, 4H), 2.63 (d, 3H, J= 4.7 Hz)), 2.08-2.03 (m, 2H). LCMS: ret. time: 17.33 min.; purity: 98%; MS (*m/e*): 440 (MH^+).
7.3.591	R935206: N2, N4-Bis[1-(N-methylaminocarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2, N4-Bis[1-(methoxycarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine and was reacted with $Me_2NH.HCl$ and *i*-PrN_2Et in presence of methanol to produce N2, N4-bis[1-(N-methylaminocarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 9.56 (s, 1H), 9.40 (s, 1H), 8.17 (d, 1H, J= 3.5 Hz), 8.12 (s, 1H), 7.99 (s, 1H), 7.96 (s, 2H), 7.90 (s, 2H), 7.66 (d, 1H, J= 8.8 Hz), 7.56 (d, 1H, J= 8.8 Hz), 7.49 (dd, 1H, J= 1.7 and 8.8 Hz), 7.34 (dd, 1H, J= 1.7 and 8.8 Hz), 4.90 (s, 2H), 4.66 (s, 2H), 2.56 (d, 6H, J= 4.11 Hz). LCMS: ret. time: 13.85 min.; purity: 98%; MS (*m/e*): 503 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.592	R935212: N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(N-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine and $Me_2NH.HCl$ was reacted to produce N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(N-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 9.35 (s, 1H), 9.17 (s, 1H), 8.07 (d, 1H, J= 4.8 Hz), 7.92 (s, 1H), 7.89 (s, 1H), 7.66 (q, 1H, J= 4.7 Hz), 7.54 (d, 1H, J= 8.8 Hz), 7.35-7.24 (m, 3H), 6.76 (d, 1H, J= 8.8 Hz), 4.77 (s, 2H), 4.20 (s, 4H), 2.57 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 15.82 min.; purity: 94%; MS (*m/e*): 450 (MH^+).
7.3.593	R935213: N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-(N-methylamino)carbonyl-fur-4-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-methoxycarbonyl-fur-4-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine was reacted with $Me_2NH.HCl$ and *i*-Pr_2NEt. to give N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-(N-methylamino)carbonyl-fur-4-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 9 17 (s, 2H), 8.30 (q, 1H, J= 4.7 Hz), 8.05 (d, 1H, J= 3.5 Hz), 7.42 (s, 1H), 7.29-7.19 (m, 2H), 7.09 (t, 1H, J= 8.2 Hz), 7.02 (d, 1H, J= 2.9 Hz), 6.76 (d, 1H, J= 8.8 Hz), 6.67 (d, 1H, J= 2.9 Hz), 6.54 (dd, 1H, J= 1.7 and 8.2 Hz), 4.94 (s, 2H), 4.21-4.18 (m, 4H), 2.70 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 18.85 min.; purity: 91%; MS (*m/e*): 492 (MH^+).
7.3.594	R935216: 5-Fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N2-[4-(N-methylamino)carbonylmethyleneoxy)phenyl]-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine ^1H NMR (DMSO-d6): δ 9.31 (s, 1H), 9.00 (s, 1H), 8.17 (s, 1H), 8.02 (d, 1H, J= 3.5 Hz), 7.99 (m, 1H), 7.93 (s, 1H), 7.59 (m, 2H), 7.52 (d, 2H, J= 8.8 Hz), 6.78 (d, 2H, J= 8.8 Hz), 4.36 (s, 2H), 4.03 (s, 3H), 2.63 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 14.81 min.; purity: 99%; MS (*m/e*): 422 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.595	R935217: N2, N4-Bis[1-(N-methylaminocarbonyl)methyl-indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2, N4-bis[1-(methoxycarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to produce N2, N4-bis[1-(N-methylaminocarbonyl)methyl-indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 9.35 (s, 1H), 9.15 (s, 1H), 8.09-8.06 (m, 2H), 7.97-7.96 (m, 2H), 7.91 (s, 1H), 7.70 (s, 1H), 7.69 (s, 1H), 7.64-7.55 (m, 2H), 7.48-7.40 (m, 2H), 5.06 (s, 2H), 4.97 (s, 2H), 2.62 (d, 3H, J= 4.7 Hz), 2.61 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 12.54 min.; purity: 95%; MS (*m/e*): 503 (MH^+).
7.3.596	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926486)	A dry reaction vial equipped with a rubber septum was charged with N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (0.019 g, 0.04 mmol) and THF (1 mL). To this was added boranemethyl sulfide complex (0.044 mL, 0.088 mmol) and stirred at room temperature for 2h. The amount of boranemethyl sulfide complex was evaporated and the reaction was quenched with MeOH (CAUTION: vigorous evolution of hydrogen gas occurs during the addition of MeOH), heated for 30 min. The solvent was removed and again the residue was suspended in MeOH, extracted with EtOAc, EtOAc was evaporated and the residue was purified by preparative TLC to obtain N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 8.20 (s, 1H), 8.01 (d, 1H, J= 6 Hz), 7.26-7.05 (m, 3H), 7.05-6.97 (m, 3H), 6.82 (d, 1H, J= 9.3 Hz), 6.67 (dd, 1H, J= 1.8 and 8.1 Hz), 4.44 (t, 2H), 4.27 (s, 4H), 4.14 (m, 2H), 3.76 (m, 2H), 3.22 (t, 2H, J= 5.4 Hz), 3.05 (m, 2H), 2.88 (m, 2H).
7.3.597	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-morpholinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine (R926490)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-morpholino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine with boranemethyl sulfide complex gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-morpholinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 8.65 (d, 2H, J= 2.1 Hz), 8.30 (dd, 2H, J= 2.1 and 9.6 Hz), 7.73 (d, 2H, J= 9.3 Hz), 7.49 (bs, 2H), 7.32 (m, 1H), 6.74 (m, 1H), 4.24 (s, 4H), 3.97 (s, 2H), 3.78 (m, 4H), 3.56 (m, 4H).

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Section Number	Name of compound and reference number	Experimental
7.3.598	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-methylamino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926510)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and boranemethyl sulfide complex gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-methylamino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.00 (d, 1H, J= 5.2 Hz), 7.50-7.30 (m, 2H), 7.16- 6.80 (m, 5H), 4,28 (m, 1H), 4.27 (bs, 4H), 4.22 (m, 1H), 3.44 (m, 2H), 2.79 (d, 3H, J= 3Hz); LCMS: ret. time: 15.64 min.; purity: 96%; MS (m/e): 412 (MH^+).
7.3.599	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine (R926770)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine with boranemethyl sulfide complex gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.06 min.; purity: 75%; MS (m/e): 435 (MH^+).
7.3.600	N4-(3,5-Dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine (R940255)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with boranemethyl sulfide complex gave N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.94 min.; purity: 99 %; MS (m/e): 454 (MH^+); ^{1}H NMR (DMSO-d6): δ 9.16 (1H, s), 9.07 (1H, s), 8.15 (1H, s), 8.11 (1H, d, J= 3.9 Hz), 7.40-7.30 (4H, m), 7.13 (1H, t, 8.1 Hz), 6.55 (1H, dd, J= 8.1 Hz, 3.2 Hz), 4.01 (2H, t, J= 5.7 Hz), 3.65 (4H, t, J= 4.2 Hz), 2.72 (2H, t, J= 5.7 Hz), 2.515 (4H, t, J= 4.5 Hz), 2.24 (6H, s).

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Section Number	Name of compound and reference number	Experimental
7.3.601	N4-(3,5-Dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine bis Hydrogen Chloride Salt (R945142)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine was treated with boranemethyl sulfide complex to give N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethyloxy]phenyl]-2,4-pyrimidinediamine, which was then treated with 4N HCl in dioxane (3 mL) followed crystallization from MeOH/EtOAc to give N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine bis Hydrogen Chloride Salt. ^{1}H NMR (CD_3OD): δ 2.17 (s, 6H), 3.66 (m, 10H), 4.26 (t, J= 4.5 Hz, 2H), 6.93 (dd, J= 1.5, 7.2 Hz, 1H), 7.10-7.13 (m, 2H), 7.17 (s, 2H), 7.31 (t, J= 8.4 Hz, 1H), 7.98 (d, J= 6.0 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD). δ - 162.93, LCMS: ret. time: 13.25 min.; purity: 96.08%; MS (m/e): 453.09 (MH^+).
7.3.602	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[4-(2-hydroxyethyloxy)phenyl]-2,4-pyrimidinediamine (R945144)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, the reaction of N2-(4-carboxymethyleneoxyphenyl)-N4-(3,4-ethylendioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and boranemethyl sulfide complex gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (acetone-d_6): δ 3.86 (t, J= 4.8 Hz, 2H), 4.04 (t, J= 4.8 Hz, 2H), 4.28 (m, 4H), 6.78 (d, J= 9.0 Hz, 1H), 6.86 (d, J= 9.0 Hz, 2H), 7.18 (dd, J= 2.7, 8.7 Hz, 1H), 7.47 (d, J= 2.7 Hz, 1H), 7.63 (d, J= 9.0 Hz, 2H), 7.91 (d, J= 3.6 Hz, 1H), 8.29 (br, 1H, NH), 8.31 (br, 1H, NH); ^{19}F NMR (282 MHz, acetone-d_6): δ - 169.18; LCMS: ret. time: 17.41 min.; purity: 98.36%; MS (m/e): 399.01 (MH^+).

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7.3.603	N4-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine Dihydrochloride Salt (R945150)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine was treated with boranemethyl sulfide complex to give N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethyloxy]phenyl]-2,4-pyrimidinediamine, which was then treated with 4N HCl in dioxane (3 mL) followed crystallization from MeOH/EtOAc to give N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine bis Hydrogen Chloride Salt. ^{1}H NMR (CD_3OD): δ 2.21 (s, 3H), 3.72 (m, 10H), 4.35 (t, J= 4.5 Hz, 2H), 6.95 (dt, J= 1.5 and 9.0 Hz, 1H), 7.11-7.14 (m, 2H), 7.26 (dd, J= 0.9 and 2.7 Hz, 1H), 7.34 (t, J= 8.4 Hz, 1H), 7.50 (d, J= 2.4 Hz, 1H), 8.03 (d, J= 5.4 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD): δ - 162.74; LCMS: ret. time: 14.50 min.; purity: 94.75%; MS (m/e): 472.98 (MH^+).
7.3.604	N4-(3,5-Dimethyl-4-methoxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine Dihydrochloride Salt (R945157)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3,5-dimethyl-4-methoxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine was treated with boranemethyl sulfide complex to give N4-(3,5-dimethyl-4-methoxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethyloxy]phenyl]-2,4-pyrimidinediamine, which was then treated with 4N HCl in dioxane (3 mL) followed crystallization from MeOH/EtOAc to give N4-5-dimethyl-4-methoxyphenyl)-5-fluoro-N2-[3-[2-(N-piperazino)ethoxy]phenyl]-2,4-pyrimidinediamine bis Hydrogen Chloride Salt. ^{1}H NMR (CD_3OD): δ 2.23 (s, 6H), 3.66 (m, 10H), 3.72 (s, 3H), 4.31 (t, J= 4.5 Hz, 2H), 6.95 (dd, J= 1.8 and 8.4 Hz, 1H), 7.09-7.15 (m, 2H), 7.27 (s, 2H), 7.32 (t, J= 8.1 Hz, 1H), 8.01 (d, J= 5.4 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD): δ - 162.71; LCMS: ret. time: 16.41 min.; purity: 97.50%; MS (m/e): 467.12 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.605	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926501)	The reaction of equivalent amount of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) in methanol at 0 °C followed by dilution with dry ethyl ether or ethyl acetate gave the precipitate. The resulting precipitate was isolated by filtration (and/or using centrifuse technique) to give N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. ^{1}H NMR (CD_3OD): δ 7.97 (d, 1H, J= 5.4 Hz), 7.92 (d, 1H, J= 1.8 Hz), 7.62 (d, 1H, J= 8.2 Hz), 7.48 (s, 1H), 7.43 (dd, 1H, J= J= 2.4 and 8.7 Hz), 7.17 (d, 1H, J=2.4 Hz), 6.98 (dd, 1H, J= 2.4 and 8.7 Hz), 6.77 (d, 1H, J= 8.7 Hz), 4.13 (m, 4H), 4.22 (s, 4H), 3.38 (t, 4H, J= 5.7 Hz); LCMS: ret. time: 15.12 min; purity: 89%; MS (m/e): 491 (MH^+).
7.3.606	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926504)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydrogen chloride gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-piperazino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. ^{1}H NMR (DMSO-d6): δ 9.6 (bs, 1H), 9.04 (bs, 1H), 8.12 (d, 1H, J= 3.6 Hz), 7.25-7.00 (m, 5H), 7.81 (d, 1H, J= 8.7 Hz), 6.54 (d, 1H, J= 8.4 Hz), 4.74 (s, 2H), 4.22 (s, 4H), 3.64 (m, 4H), 3.11 (m, 4H); LCMS: ret. time: 15.34 min.; purity: 100%; MS (m/e): 481 (MH^+).
7.3.607	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-N-methylaminoethyl)phenyl] -2,4-pyrimidinediamine Hydrogen Chloride Salt (R926509)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-methylamino)ethyloxy]phenyl]-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-methylamino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. LCMS: ret. time: 15.88 min.; purity: 92%; MS (m/e): 412 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.608	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926511)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine and hydrogen chloride gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. ^{1}H NMR (CD_3OD): δ 7.98 (d, 1H, J= 5.4 Hz), 7.34 (t, 1H, 8.4 Hz), 7.16-6.81 (m, 6H), 4.42 (m, 1H), 4.40 (m, 2H), 4.25 (m, 5H), 4.10 (m, 2H), 3.90 (bs, 2H), 3.60 (m, 4H); LCMS: ret. time: 16.39 min.; purity: 100%; MS (m/e): 468 (MH^+).
7.3.609	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-homopiperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926768)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-homopiperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine with hydrogen chloride treatment gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-homopiperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. ^{1}H NMR (DMSO-d6): δ 9.98 (bs, 1H), 9.05 (bs, 1H), 8.18 (d, 1H, J= 4.8 Hz), 8.01 (s, 1H), 7.58 (d, 1H, J= 8.7 Hz), 7.50 (bd, 1H), 7.35 (s, 1H), 7.24 (d, 1H, J= 2.4 Hz), 7.11 (dd, 1H, J= 3 and 9 Hz), 6.80 (d, 1H, J= 8.7 Hz), 4.22 (s, 4H), 4.20-3.60 (m, 8H), 3.20 (m, 2H); LCMS: ret. time: 14.91 min.; purity: 86%; MS (m/e): 505 (MH^+).
7.3.610	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt R926502)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine upon treatment with hydrogen chloride (4M, dioxane) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. ^{1}H NMR (CDC_3OD): δ 8.00 (s, 1H), 7.89 (s, 1H), 7.98 (s, 1H), 7.60 (d, 1H, J= 8.7 Hz), 7.45 (m, 3H), 7.16 (t, 1H, J= 8.1 Hz), 7.10 (m, 1H), 7.02 (dd, 1H, J= 1.2 and 7.2 Hz), 6.70 (dd, 1H, J= 2.4 and 8.4 Hz), 4.13 (m, 4H), 3.37 (t, 4H, J= 5.4 Hz), 3.38 (t, 4H, J= 5.7 Hz); LCMS: ret. time: 13.40 min; purity: 79%; MS (m/e): 450 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.611	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-, pyrimidinediamine Dihydrochloride Salt (R926769)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(N-piperazinomethylene)benzofuran-5-yl]-2,4-pyrimidinediamine Dihydrochloride Salt. ^{1}H NMR (CD_3OD): δ 8.00 (d, 1H), 7.85 (bd, 1H), 7.75 (m, 3H), 7.60 (m, 2H), 7.40-7.15 (m, 4H), 7.05 (s, 1H), 7.00-6.800 (m, 3H), 4.65 (dd, 2H), 3.60 (m, 8H).
7.3.612	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926773)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydrogen chloride (4M, dioxane) gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-piperazino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. ^{1}H NMR (CD_3OD): δ 7.99 (d, 1H, J= 5.1 Hz), 7.29 (t, 1H, J= 8.1 Hz), 7.21-7.05 (m, 5H), 6.83 (dd, 1H, J= 2.4 and 8.7 Hz), 6.77 (bd, 1H), 4.79 (s, 2H), 3.83 (m, 2H), 3.78 (m, 2H), 3 25 (m, 2H); LCMS: ret. time: 12.27 min.; purity: 91%; MS (m/e): 439 (MH^+).
7.3.613	N2-[3-[2-(N, N-Dimethylamino)ethyloxy]phenyl]-N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926771)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the treatment of N4-(3,4-ethylenedioxyphenyl)-N2-[3-[2-(N, N-dimethylamino)ethyloxy]phenyl]-5-fluoro-2,4-pyrimidinediamine with equivalent amount of hydrogen chloride (4M, dioxane) gave N4-(3,4-ethylenedioxyphenyl)-N2-[3-[2-(N, N-dimethylamino)ethyloxy]phenyl]-5-fluoro-2,4-pyrimidinediamine Hydrogen Chloride Salt. LCMS: ret. time: 15.37 min.; purity: 93%; MS (m/e): 426 (MH^+).
7.3.614	N4-(3,5-Dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R940256)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) gave N4-(3,5-dimethyl-4-hydroxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. LCMS: ret. time: 15.78 min.; purity: 98 %; MS (M/e): 454 (MH^+); 1H NMR (DMSO-d6): δ 10.60 (1H, s), 9.58 (1H, s), 8.29 (1H, s), 8.20 (1H, s), 7.43 (1H, d, J= 9Hz), 7.38-7.30 (3H, m), 7.24 (1H, t, J= 9 Hz), 6.70 (1H, d, J= 9 Hz), 4.35 (2H, m), 4.05 (2H, m), 3.84 (4H, m), 3.65-3.50 (2H, m), 3.26 (2H, m), 2.25 (6H, s).

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Section Number	Name of compound and reference number	Experimental
7.3.615	N4-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R940269)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the reaction of N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) gave N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyloxy]phenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. LCMS: ret. time: 14.74 min.; purity: 96 %; MS (m/e). 474 (M^+), 475 (MH^+), ^{1}H NMR (DMSO-d6): δ 10.03 (1H, s), 9.35 (2H, s), 9.06 (1H, s), 8.17 (1H, d, J= 3.9 Hz), 7.67 (1H, m), 7.52 (1H, m), 7.46 (1H, d, J= 8.7 Hz), 7.39 (1H, s), 7.24 (1H, t, J= 8.1 Hz), 6.66 (1H, d, J= 8.1 Hz), 4.33 (1H, m), 4.07 (1H, d, J= 13 Hz), 3.79 (1H, t, J= 12.5 Hz), 3.56 (4H, m), 3.49 (4H, m), 3.29 (1H, t, J= 12.5 Hz), 2.29 (3H, s).
7.3.616	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R926816)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(N-piperazino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine Hydrogen Chloride Salt, the treatment of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine with equivalent amount of hydrohen chloride (4M, dioxane) gave the N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride salt. LCMS: ret. time: 17.04 min., purity: 96%, MS (m/e): 426 (MH+).
7.3.617	N4-(3,4-Ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine (R926696)	A dry reaction flask charged with N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine was recated with diisobutylaluminum hydride (DIBALH) (5 equivalents) in CH_2Cl_2 at –78 °C (reaction was monitored by TLC) followed by treatment with Rochell's salt to yield N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.11 (s, 1H), 8.02 (d, 1H, J= 3.3 Hz), 7.96 (t, 1H, J= 1.8 Hz), 7.40-7.30 (m, 3H), 7.19 (dt, 1H, J= 3.6 and 8.1 Hz), 6.78 (d, 1H, J= 8.7 Hz), 6.59 (s, 1H), 4.52 (d, 2H, J= 5.1 Hz), 4.22 (s, 4H); ^{19}F NMR (DMSO-d6): - 46802; LCMS: ret. time: 19.14 min.; purity: 95 %; MS (m/e): 409 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.618	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(hydroxymethyl)-(1H)-indol-5-yl]-2,4-pyrimidinediamine (R926700)	In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(methoxycarbonyl)-(1H)-indol-5-yl]-2,4-pyrimidinediamine was reduced with DIBALH to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(hydroxymethyl)-(1H)-indol-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.81 (d, 1H, J= 4.2 Hz), 7.23 (d, 1H, J= 1.8 Hz), 7.28-7.23 (m, 2H), 7.19 (t, 1H, J= 2.4 Hz), 7.12 (dd, 1H, J= 1.8 and 9.0 Hz), 7.07 (t, 1H, J= 8.4 Hz), 6.52 (ddd, 1H, J= 1 2 and 8.1 Hz), 6.30 (s, 1H), 4.71 (s, 2H); ^{19}F NMR (CD_3OD): - 47971, LCMS: ret. time: 15.36 min.; purity: 100 %; MS (m/e): 366 (MH^+).
7.3.619	5-Fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-N4-[4-(isopropoxy)phenyl]-2,4-pyrimidinediamine (R926705)	In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to yield 5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.83 (d, 1H, J= 3.3 Hz), 7.81 (s, 1H), 7.50 (d, 2H, J= 9.0 Hz), 7.29 (d, 1H, J= 9.0 Hz), 7.22 (dd, 1H, J= 2.4 and 8.7 Hz), 6.84 (d, 2H, J= 8.7 Hz), 6.56 (d, 1H, J= 1.2 Hz), 4.64 (s, 2H), 4.56 (2q, 1H, J= 5.7 Hz), 1.31 (d, 6H, J= 6.0 Hz); ^{19}F NMR (CD_3OD): - 47926; LCMS: ret. time: 21.03 min.; purity: 99 %; MS (m/e): 409 (MH^+).
7.3.620	5-Fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926707)	In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine was reduced with DIBALH to yield 5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.37 (s, 1H), 9.17 (s, 1H), 9.12 (s, 1H), 8.06 (d, 1H, J= 3.9 Hz), 8.01 (d, 1H, J= 1.8 Hz), 7.41-7.35 (m, 2H), 7.26 (d, 1H, J= 8.1 Hz), 7.11-7.05 (m, 2H), 6.60 (s, 1H), 6.51 (dd, 1H, J= 2.4 and 8.4 Hz), 5.41 (t, 1H, J= 6.0 Hz), 4.51 (d, 2H, J= 5.7 Hz); LCMS: ret. time. 16.21 min.; purity: 95 %; MS (m/e): 367 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.621	N4-(4-*tert* -Butyl)phenyl)-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine (R926728)	In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBAL to yield N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[3-(2-hydroxyethyleneoxy) phenyl]- 2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.94 (d, 1H, J= 3.0 Hz), 7.54 (d, 2H, J= 9.0 Hz), 7.37 (d, 2H, J= 8.4 Hz), 7.29-7.35 (m, 1H), 7.19-7.14 (m, 2H), 7.06 (d, 1H, J= 8.1 Hz), 6.82 (d, 1H, J= 2.7 Hz), 6.57 (dd, 1H, J= 2.4 and 8.1 Hz), 4.04-4.00 (m, 2H), 3.93-3.89 (m, 2H), 1.33 (s, 9H); ^{19}F NMR ($CDCl_3$): -47214; LCMS: ret. time: 22.39 min.; purity: 94 %; MS (m/e): 397 (MH^+).
7.3.622	5-(Hydroxymethyl)-N2-[3-(2-hydroxyethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926735)	In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, N4-(3-hydroxyphenyl)-5-methoxycarbonyl-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine was reduced with DIBALH to yield 5-(hydroxymethyl)-N2-[3-(2-hydroxyethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.87 (s, 1H), 7.35 (t, 1H, J= 1.5 Hz), 7.15-7.08 (m, 5H), 6.57-6.50 (m, 2H), 4.56 (s, 2H), 3.92-3.86 (m, 2H), 3.84-3.79 (m, 2H); LCMS: ret. time: 14.11 min.; purity: 89 %; MS (m/e): 369 (MH^+).
7.3.623	5-Fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-N4-(3-isopropylphenyl)-2,4-pyrimidinediamine R940289	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-isopropylphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine reacted with DIBALH to give 5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-N4-(3-isopropylphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 23.03 min.; purity: 93 %; MS (m/e): 382 (M^+), 384 (MH^+); ^{1}H NMR (DMSO-d6): δ 9.36 (1H, s), 9.24 (1H, s), 8.20 (1H, d, J= 4.2 Hz), 7.85 (1H, d, J= 8.5 Hz), 7.57 (1H, s), 7.41 (1H, s), 7.33 (1H, t, J= 8.5 Hz), 7.17 (1H, t, J= 8.5 Hz), 7.05 (1H, d, J= 8.5 Hz), 6.56 (1H, dd, J= 8.5 Hz, J= 2 Hz) 4.94 (1H, t, J= 12 Hz), 3.94 (2H, t, J= 4.7 Hz), 3.76 (2H, m), 2.95 (1H, sept, J= 6.9 Hz), 1.28 (6H, dd, J= 6.9 Hz, J= 0.6Hz).

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Section Number	Name of compound and reference number	Experimental
7.3.624	N4-(3-*tert*-Butylphenyl)-5-fluoro-N2-[(2-hydroxymethylene)benzofur-5-yl]-2,4-pyrimidinediamine R940287	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine reacted with DIBALH to give N4-(3-*tert*-butylphenyl)-5-fluoro-N2-[2-(hydroxymethylene)benzofur-5-yl]-2,4-pyrimidinediamine. LCMS: retn, time: 23.15 min.; purity: 99 %; MS (m/e): 407 (MH^+); 1H NMR (DMSO-d6): δ 9.34 (1H, s), 9.22 (1H, s), 8.18 (1H, d, J= 3.9 Hz), 8.04 (1H, s), 8.00 (1H, d, J= 8.7 Hz), 7.60 (1H, t, J= 2.1 Hz), 7.47 (2H, m), 7.34 (1H, t, J= 7.8 Hz), 7.21 (1H, d, J= 8.7 Hz), 6.69 (1H, s), 5.54 (1H, t, J= 5.8 Hz), 4.63 (2H, d, J= 5.8 Hz), 1.35 (9H, s).
7.3.625	5-Fluoro-N4-(3-isopropylphenyl)-N2-[(2-hydroxymethylene]benzofur-5-yl]-2,4-pyrimidinediamine R940286	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-isopropylphenyl)-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine reacted with DIBALH to give 5-fluoro-N4-(3-isopropylphenyl)-N2-[(2-hydroxymethylene)benzofur-5-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 21.93 min.; purity: 99 %; MS (m/e): 393 (MH^+); ^1H NMR (DMSO-d6): δ 9.33 (1H, s), 9.23 (1H, s), 8.18 (1H, d, J= 3.9 Hz), 8.03 (1H, s), 7.86 (1H, d, J= 7.1 Hz), 7.57 (1H, s), 7.49 (2H, m), 7.33 (1H, t, J= 7.1 Hz), 7.05 (1H, d, J= 7.1 Hz), 6.69 (1H, s), 5.54 (1H, t, J= 5.7 Hz), 4.63 (2H, d, J= 5.7 Hz), 2.90 (1H, sept, J= 6.9 Hz), 1.26 (6H, d, J= 6.9 Hz).
7.3.626	N4-(3-*tert*-Butylphenyl)-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine R940282	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine reacted with DIBALH to give N4-(3-*tert*-butylphenyl)-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 21.63 min.; Purity: 98 %; MS (m/e): 396 (M^+).
7.3.627	N4-[3,4-Bis(hydroxymethyl)phenyl]-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940292)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, N2-(3-ethoxycarbonylmethyleneoxyphenyl)-N4-[6-(3,3-dihydroisobenzofuranyl-1-one)]-5-fluoro-2,4-pyrimidinediamine reacted with DIBALH to give N4-[3,4-bis(hydroxymethyl)phenyl]-5-fluoro-N2-[3-(2-hydroxyethyleneoxy)phenyl]-2,4-pyrimidinediamine. LCMS: retn, time: 13.06 min.; purity: 100 %; MS (m/e): 400 (M^+).

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Section Number	Name of compound and reference number	Experimental
7.3.628	(R935149): N2-(3,4-Ethylenedioxyphenyl)-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-5-fluoro-2,4-pyrimidinediamine	2-Chloro-5-fluoro-N4-[4-[ethoxycarbonyl(dimethyl)methyl]phenyl]-N2-(3,4-ethylenedioxyphenyl)-2,4-pyrimidinediamine was reduced with 10 eq. DIBALH (1.0 M in toluene) at 0 ^{0}C in dichloromethane. Reaction was quenched with methanol, diluted with ethylacetate followed by the addition of aqueous Rochelle's salt solution, stirred at room temperature for 30 minutes followed by the addition of anhydrous sodium sulfate. The solution was filtered through Celite, concentrated and purified the concentrated by silica gel column chromatography to furnish the N2-(3,4-ethylenedioxyphenyl)-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.01 (br s, 1H), 9.6 (br s, 1H), 8 13 (d, 1H, J= 4.7 Hz), 7.58 (d, 2H, J= 8 2 Hz), 7.31 (d, 2H, J= 8.8 Hz), 7.18 (d, 1H, J= 2.3 Hz), 6.88 (dd, 1H, J= 2.3 and 8.8 Hz), 6.73 (d, 1H, J= 8.8 Hz), 4.21-4 19 (m, 4H), 3.56 (br s, 2H), 1.20 (s, 6H); LCMS: ret. time: 20.34 min.; purity: 98%; MS (*m/e*): 411 (MH^+).
7.3.629	(R935151): 5-Fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.89 (d, 1H, J= 2.9 Hz), 7.46 (d, 3H, J= 8.8 Hz), 7.27 (d, 2H, J= 8.2 Hz), 6.89 (d, 2H, J= 9.3 Hz), 6.68-6.65 (m, 1H), 4.53 (septet, 1H, J= 5.8 Hz), 3.57 (s, 2H), 1.36 (d, 6H, J= 5.8 Hz), 1.31 (s, 6H); LCMS: ret. time: 23.43 min.; purity: 99%; MS (*m/e*): 411 (MH^+).
7.3.630	(R935153): 5-Fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine:	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[4-[ethoxycarbonyl(dimethyl)methyl]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.89 (d, 1H, J= 2.9 Hz), 7.57 (s, 1H), 7.41 (d, 2H, J= 8.8 Hz), 7.29 (d, 2H, J= 8.2 Hz), 7.16 (d, 1H, J= 8.2 Hz), 7.10 (d, 1H, J= 8.8 Hz), 6.80-6.55 (m, 2H), 5.58 (s, 2H), 1.30 (s, 6H); LCMS: ret. time: 18.01 min.; purity: 98%; MS (*m/e*): 369 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.631	(R935154): N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1H, J= 3.8 Hz), 7.34 (t, 1H, J= 2.3 Hz), 7.19 (dd, 1H, J= 2.3 and 8.2 Hz), 7.14 (d, 1H, J= 7.6 Hz), 7.01-6.97 (m, 2H), 6.84 (d, 1H, J= 8.8 Hz), 6.53 (dd, 1H, J= 1.7 and 7.6 Hz), 4.26 (s, 4H), 3.98 (t, 2H, J= 4.1 Hz), 3.89 (t, 2H, J= 4.1 Hz); LCMS: ret. time: 18.36 min.; purity: 99%; MS (*m/e*): 399 (MH^+).
7.3.632	(R935155): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine:	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine was reduced to 5-fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine with DIBALH. ^{1}H NMR ($CDCl_3$): δ 7.73 (d, 1H, J= 3.5 Hz), 7.33 (d, 2H, J= 8.8 Hz), 7.15 (br s, 1H), 7.04 (app t, 2H, J= 8.2 and 7.6 Hz), 6.78 (d, 2H, J= 8.8 Hz), 6.49 (d, 1H, J= 7.6 Hz), 3.95 (t, 2H, J= 4.7 Hz), 3.80 (t, 2H, J= 4.7 Hz); LCMS: ret. time: 14.49 min.; purity: 98%; MS (*m/e*): 357 (MH^+).
7.3.633	(R935156): 5-Fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(4-isopropoxyphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.90 (d, 1H, J= 3.5 Hz), 7.45 (d, 2H, J= 8.8 Hz), 7.34 (t, 1H, J= 2.3 Hz), 7.13 (t, 1H, J= 8.2 Hz), 6.93 (m, 3H), 7.76 (d, 1H, J= 2.3 Hz), 6.52 (dd, 1H, J= 2.3 and 8.2 Hz), 4.52 (septet, 1H, J= 5.7 Hz), 3.95-3.85 (m, 4H), 1.34 (d, 6H, J= 5.7 Hz); LCMS: ret. time: 21.17 min.; purity: 98%; MS (*m/e*): 399 (MH^+).
7.3.634	(R935158): 5-Fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-[4-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine:	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[4-[1-ethoxycarbonyl 1-methyl)ethyl]phenyl]-5-fluoro-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to give 5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-[4-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.83 (d, 1H, J= 3.5 Hz), 7.49 (d, 2H, J= 8.8 Hz), 7.35 (d, 2H, J= 8.8 Hz), 7.31 (d, 2H, J= 8.8 Hz), 6.82 (d, 2H, J= 8.8 Hz), 4.03 (t, 2H, J= 4.7 Hz), 3.89 (t, 2H, J= 4.7 Hz), 3.56 (s, 2H), 1.30 (s, 6H); LCMS: ret. time: 16.86 min.; purity: 96%; MS (*m/e*): 413 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.635	(R935160): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine:	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(4-isopropoxyphenyl)-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to give 5-fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.12 (s, 1H), 8.92 (s, 1H), 7.98 (d, 1H, J= 3.5 Hz), 7.59 (d, 2H, J= 8.8 Hz), 7.49 (d, 2H, J= 9.3 Hz), 6.86 (d, 2H, J= 8.8 Hz), 6.76 (d, 2H, J= 9.3 Hz), 4.82 (t, 1H, J= 4.9 Hz), 4.55 (septet, 1H, J= 6.4 Hz), 3.89 (t, 2H, J= 5.3 Hz), 3.67 (app q, 2H, J= 5.3 and 4.9 Hz), 1.24 (d, 6H, J= 6.4 Hz); LCMS: ret. time: 19.56 min.; purity: 100%; MS (*m/e*): 399 (MH^+).
7.3.636	(R935161): 5-Fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[4-(1-ethoxycarbonyl-1-methyl)ethylphenyl]-5-fluoro-N2-(3-methoxycarbonylmethylphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to give 5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.27 (s, 1H), 9.11 (s, 1H), 8.07 (d, 1H, J= 3.5 Hz), 7.67 (d, 2H, J= 8.8 Hz), 7.38-7.24 (m, 4H), 7.06 (t, 1H, J= 8.2 Hz), 6.46 (dd, 1H, J= 8.2 Hz), 4.83 (t, 1H, J= 5.3 Hz), 4.66 (t, 1H, J= 5.3 Hz), 3.88 (t, 2H, J= 5.3 Hz), 3.67 (t, 1H, J= 5.3 Hz), 3.66 (t, 1H, J= 5.3 Hz), 3.38 (d, 2H, J= 5.3 Hz), 1.20 (s, 6H); LCMS: ret. time: 17.17 min.; purity: 96%; MS (*m/e*): 413 (MH^+).
7.3.637	(R935168): 5-Fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[4-(1-ethoxycarbonyl-1-methyl)ethylphenyl]-5-fluoro-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to produce 5-fluoro- N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.21 (s, 1H), 8.93 (s, 1H), 8.00 (d, 1H, J= 4.1 Hz), 7.62 (d, 2H, J= 8.8 Hz), 7.48 (d, 2H, J= 8.8 Hz), 7.27 (d, 2H, J= 8.8 Hz), 6.75 (d, 2H, J= 8.8 Hz), 4.65 (t, 1H, J= 5.3 Hz), 4.47 (septet, 1H, J= 5.8 Hz), 3.38 (d, 2H, J= 5.3 Hz), 1.22 (d, 6H, J= 5.8 Hz), 1.20 (s, 6H); LCMS: ret. time: 22.97 min.; purity: 99%; MS (*m/e*): 411 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.638	(R935170): 5-Fluoro-N4-[3-(2-hydroxyethoxy)phenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine:	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-(3-hydroxyphenyl)-N4-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to produce 5-fluoro- N4-[3-(2-hydroxyethoxy)phenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.23 (s, 1H), 9.14 (s, 1H), 9.06 (s, 1H), 8.07 (d, 1H, J= 4.1 Hz), 7.51 (dd, 1H, J= 1.7 and 7.6 Hz), 7.30 (app t, 1H, J= 2.3 and 1.7 Hz), 7.19 (t, 1H, J= 8.2 Hz), 7.13 (br s, 1H), 7.11 (m, 1H), 6.96 (t, 1H, J= 7.6 Hz), 6.61 (dd, 1H, J= 2.3 and 8.2 Hz), 6.28 (dd, 1H, J= 2.3 Hz and 8.2 Hz), 4,84 (t, 1H, J= 5.8 Hz), 3.92 (t, 2H, J= 5.2 Hz), 3.68 (app qt, 2H, J= 5.2 Hz); LCMS: ret. time: 14.71 min.; purity: 96%; MS (*m/e*): 357 (MH^+).
7.3.639	(R935171): 5-Fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(3-hydroxyphenyl)- -2,4-pyrimidinediamine	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-pyrimidine-2,4-diamine, N4-[4-(1-ethoxycarbonyl-1-methyl)ethyl)phenyl]-5-fluoro-N2-(3-hydoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to give 5-fluoro-N2-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.24 (s, 1H), 9.13 (s, 1H), 9.01 (s, 1H), 8.04 (d, 1H, J= 3.5 Hz), 7.68 (d, 2H, J= 8.8 Hz), 7.29 (d, 2H, J= 8.8 Hz), 7.16 (br s, 1H), 7.07 (m, 1H), 6.94 (t, 1H, 8.8 Hz), 6.30 (m, 1H), 4.64 (t, 1H, J= 5.8 Hz), 3.38 (d, 2H, J= 5.3 Hz), 1.20 (s, 6H); LCMS: ret. time: 17.36 min.; purity: 100%; MS (*m/e*): 369 (MH^+).
7.3.640	(R935174): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-(2-carbomethoxybenzofur-5-yl)-5-fluoro-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2[4-(2-hydroxyethoxy)phenyl]-N2-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.26 (s, 1H), 8.94 (s, 1H), 8.01 (d, 1H, J= 4.1 H), 7.99 (s, 1H), 7.52-7.45 (m, 4H), 6.72 (d, 2H, J= 9.3 Hz), 6.66 (s, 1H), 5.46 (t, 1H, J= 5.3 Hz), 4.82 (t, 1H, J= 5.8 Hz), 4.55 (d, 2H, J= 5.8 Hz), 3.89 (t, 2H, J= 5.3 Hz), 3.67 (app qt, 2H, J= 5.3 Hz); LCMS: ret. time: 14.97 min.; purity: 91%; MS (*m/e*): 411 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.641	(R935176): N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine:	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(3-methoxycarbonylmethyleneoxypheny)-2,4-pyrimidinediamine was reduced with DIBALH to provide N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.22 (s, 1H), 8.98 (s, 1H), 8.05 (d, 1H, J= 3.5 Hz), 7.47 (dd, 1H, J= 1.1 and 8.2 Hz), 7.27 (t, 1H, J= 1.7 Hz), 7.23 (d, 1H, J= 2.3 Hz), 7.18 (t, 1H, J= 8.2 Hz), 7.05 (dd, 1H, J= 2.3 and 8.8 Hz), 6.68 (d, 1H, J= 8.2 Hz), 6.61 (dd, 1H, J= 1.7 and 8.8 Hz), 4.85 (t, 1H, J= 5.3 Hz), 4.18-4.14 (m, 4H), 3.91 (t, 2H, J= 5.3 Hz), 3.68 (qt, 2H, J= 5.3 Hz); LCMS: ret. time: 17.35 min.; purity: 92%; MS (*m/e*): 399 (MH^+).
7.3.642	(R935177): 5-Fluoro-N2-[4-(2-hydroxy-1,1,dimethylethyl)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(2-carbomethoxybenzofur-5-yl)-N2-[4-(1-ethoxycarbonyl-1-methyl)ethylphenyl]-5-fluoro-2,4-pyrimidinediamine was reduced with DIBALH to produce 5-fluoro- N2-[4-(2-hydroxy-1,1,dimethylethyl)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine. LCMS: ret. time: 18.17 min.; purity: 94%; MS (*m/e*): 423 (MH^+).
7.3.643	(R935178): 5-Fluoro-N2-[3-(2-hydroxyethyloxy)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(2-carbomethoxybenzofur-5-yl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[3-(2-hydroxyethyloxy)phenyl]-N4-(2-hydroxymethylbenzofur-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.93 (s, 1H), 9.12 (s, 1H), 8.07 (d, 1H, J= 3.6 Hz), 8.01 (d, 1H, J= 2.3 Hz), 7.55-7.46 (m, 2H), 7.29 (br s, 1H), 7.23 (d, 1H, J= 8.2 Hz), 7.03 (t, 1H, J= 8.2 Hz), 6.68 (s, 1H), 6.44 (dd, 1H, J= 2.3 and 8.2 Hz), 5.47 (t, 1H, J= 5.8 Hz), 4.80 (t, 1H, J= 5.3 Hz), 4.55 (d, 2H, J= 5.3 Hz), 3.81 (qt, 2H, J= 5.3 Hz), 3.63 (qt, 2H, J= 5.3 Hz); LCMS: ret. time: 15.41 min.; purity: 88%; MS (*m/e*): 411 (MH^+).
7.3.644	(R935181): N4-(3,5-Dimethoxyphenyl)-5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-imidinediamine	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3,5-dimethoxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidineamine was reduced with DIBALH to give N4-(3,5-dimethoxyphenyl)-5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-2,4-pyrimidinediamine: ^{1}H NMR (DMSO-d6):δ 9.24 (s, 1H), 9.18 (s, 1H), 8.11 (d, 1H, J= 3.5 Hz), 7.31-7.26 (m, 2H), 7.05 (d, 1H, J= 8.2 Hz), 6.99 (d, 1H, J= 2.3 Hz), 6.43 (dd, 1H, J= 2.3 Hz, 8.2 Hz), 6.20 (t, 1H, J= 2.3 Hz), 4.80 (t, 1H, J= 5.8 Hz), 3.83 (t, 2H, J= 5.3 Hz), 3.67 (s, 6H), 3.66-3.60 (m, 2H); LCMS: ret. time: 18.78 min.; purity: 95%; MS (*m/e*): 400 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.645	(R935183): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[4-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine was reduced with DIBAL-H to provide 5-fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine. H NMR (DMSO-d6): δ 9.15 (s, 1H), 8.97 (s, 1H), 8.00 (d, 1H, J= 3.5 Hz), 7.49 (d, 2H; J= 8.8 Hz), 7.40-7.31 (m 2H), 6.88 (d, 1H, J= 8.8 Hz), 6.80 (d, 2H, J= 8.8 Hz), 4.82 (t, 1H, J= 5.3 Hz), 4.12-4.04 (m 4H), 3.90 (t, 2H, J= 5.2 Hz), 3.70-3.65 (app qt, 2H, J= 5.3 Hz), 2.07 (q, 2H, J= 5.3 Hz); LCMS: ret. time: 17.05 min.; purity: 96%; MS (*m/e*): 413 (MH^+).
7.3.646	(R935186): 5-Fluoro-N2-[4-(2-hydroxyethoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine was reduced with DIBALH to provide 5-fluoro-N2-[3-(2-hydroxyethoxy)phenyl]-N4-(3,4-propylenedioxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.21 (s, 1H), 9.14 (s, 1H), 8.07 (d, 1H, J= 3.5 Hz), 7.42-7.36 (m, 2H), 7.29-7.24 (m, 2H), 7.07 (t, 1H, J= 8.2 Hz), 6.90 (d, 1H, J= 8.8 Hz), 6.45 (dd, 1H, J= 1.7 and 8.3 Hz), 4.82 (t, 1H, J= 5.3 Hz), 4.12-4.04 (app q, 2H, J= 5.3 Hz), 3.86 (t, 2H, J= 5.3 Hz), 3.67 (app qt, 2H, J= 5.3 Hz), 2.07 (q, 2H, J= 5.3 Hz); LCMS: ret. time:17.95 min.; purity: 96%; MS (*m/e*): 413 (MH^+).
7.3.647	N4-(4-*tert* –Butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]- 2,4-pyrimidinediamine (R926720)	The reaction of N2-(4-*tert* –butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine and lithium hydroxide(LiOH) in THF:H_2O at room temperature gave N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]- 2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.01 (bs, 1H), 9.69 (bs, 1H), 8.13 (d, 1H, J= 4.8 Hz), 7.57 (d, 2H, J= 8.7 Hz), 7.50 (s, 1H), 7.35 (d, 2H, J= 8.1 Hz), 7.13 (d, 1H, J= 8.7 Hz), 6.75 (d, 1H, J= 9.0 Hz), 5.21 (dd, 1H, J= 6.3 and 10.5 Hz), 3.49 (dd, 1H, J= 10.5 and 16.5 Hz), 3.17 (dd, 1H, J= 6.6 and 16.5 Hz), 1.27 (s, 9H); LCMS: ret time: 22.53 min.; purity: 93 %; MS (m/e): 423 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.648	N4-(4-*tert*-Butylphenyl)-N2-(3-carboxymethyleneoxyphenyl)-5-fluor-2,4-pyrimidinediamine (R926726)	In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and lithium hydroxide were reacted to yield N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(3-carboxymethyleneoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 12.88 (bs, 1H), 9.29 (s, 1H), 9.16 (s, 1H), 8.07 (d, 1H, J= 3.3 Hz), 7.68 (d, 2H, J= 8.7 Hz), 7.35-7.31 (m, 3H), 7.26 (d, 1H, J= 8.4 Hz), 7.06 (t, 1H, J= 8.4 Hz), 6.41 (dd, 1H, J= 2.4 and 8.4 Hz), 4.54 (s, 2H), 1.27 (s, 9H); ^{19}F NMR (DMSO-d6): -46463; LCMS: ret. time: 22.94 min.; purity: 97 %; MS (m/e): 411 (MH^+).
7.3.649	5-Fluoro-N2-[3-(carboxymethyleneoxy)phenyl]-N4-[4-(isopropoxy)phenyl]-2,4-pyrimidinediamine (R926731)	In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine and lithium hydroxide were reacted to yield 5-fluoro-N2-(3-carboxymethyleneoxyphenyl)-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 6.19 (bs, 1H), 9.01 (s, 1H), 8.02 (d, 1H, J= 3.9 Hz), 7.63 (d, 2H, J= 9.3 Hz), 7.19-7.14 (m, 2H), 6.96 (t, 1H, J= 8.7 Hz), 6.87 (d, 2H, J= 9.6 Hz), 6.28 (dd, 1H, J= 2.45 and 9.0 Hz), 4.56 (2q, 1H, J= 6.6 Hz), 3.94 (s, 2H), 1.24 (d, 6H, J= 6.6 Hz); LCMS: ret. time: 20.13 min.; purity: 100 %; MS (m/e): 413 (MH^+).
7.3.650	N2,N4-Bis(4-carboxymethyleneoxy)phenyl-5-fluoro-2,4-pyrimidinediamine (R926560)	In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine,the hydrolysis of N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine with LiOH gave N2,N4-bis(4-carboxymethyleneoxy)phenyl-5-fluoro-2,4-pyrimidinediamine ^{1}H NMR (CD_3OD): δ 7.86 (bs, 1H), 7.55 (d, 2H, J= 9.0 Hz), 7.32 (bd, 2H, J= 9.3 Hz), 6.95 (m, 4H), 4.66 (s, 2H), ^{19}F NMR ($CDCl_3$): - 21852; LCMS: ret. time: 15.16 min.; purity: 77%; MS (m/e): 429 (MH^+).
7.3.651	N2-(3-Carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926483)	In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine,the reaction of N2-(3-ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine with LiOH gave N2-(3-carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 12.90 (s, 1H), 9.20 (s, 2H), 8.05 (d, 1H, J= 1.2 Hz), 7.32-7.21 (m, 3H), 7.08 (t, 1H, J= 8.1 Hz), 6.80 (d, 1H, J= 8.4 Hz), 6.40 (dd, 1H, J= 1.8 and 8.2 Hz), 4.53 (s, 2H), 4.20 (s, 4H); LCMS: ret. time: 18.26 min.; purity: 100%; MS (m/e): 413 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.652	N2-(3-Carboxymethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945126)	In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-(methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with LiOH gave N2-(3-carboxymethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 4.55 (s, 2H), 6.43 (dd, J= 2.1, 8.1 Hz, 1H), 6.48 (dd, J= 2 1 and 7.2 Hz, 1H), 7.06-7.13 (m, 3H), 7 28-7.34 (m, 3H), 8.09 (d, J= 3.6 Hz, 1H), 9.22 (br, 1H), 9.28 (br, 1H), 9.34 (br, 1H); ^{19}F NMR (282 MHz, DMSO-d6): δ - 163.85; LCMS: ret. time: 15.88 min.; purity. 100%; MS (m/e): 370.63 (MH^+).
7.3.653	N2-(4-Carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926238)	In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine with LiOH gave N2-(carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.16 (d, 1H, J= 4.8 Hz), 7.37 (bd, 2H, J= 9 Hz), 7.25 9d, 1H, J= 3Hz), 7.08 (m, 1H), 6 83 (m, 3H), 4.64 (s, 2H), 4.23 (s, 4H); LCMS: ret. time: 19.15 min.; purity: 100%; MS (m/e): 413 (MH^+).
7.3.654	N2-(4-Carboxymethyleneoxyphenyl)-5-Fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926564)	In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine upon treatment with LiOH gave 5-fluoro-N2-(4-carboxymethyleneoxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.89 (d, 1H, J= 5.1 Hz), 7.34 (dd, 2H, J= 2.1 and 9.3 Hz), 7.19-7.08 (m, 2H), 6.98 (dd, 2H, J= 2.4 and 8.4 Hz), 6.69 (m, 1H), 4.68 (s, 2H); ^{19}F NMR (CD_3OD): - 21860; LCMS: ret. time: 15.69 min.; purity: 99%; MS (m/e): 371 (MH^+).
7.3.655	N2-(2-Carboxybenzofuran-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926478)	In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methoxycarbonylbenzofuran-5-yl)-4-pyrimidinediamine upon LiOH treatment gave N2-(2-carboxybenzofuran-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.97 (bd, 2H), 7.60-7.44 (m, 4H), 7.20-7.05 (m, 3H), 6.69 (bd, 1H); ^{19}F NMR (CD_3OD): - 21844; LCMS: ret. time: 16.77 min.; purity: 100%; MS (m/e): 381 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.656	N2-(2-Carboxyindol-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926479)	In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, N2-(2-ethoxycarbonylindol-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine upon LiOH treatment gave N2-(2-carboxyindol-5-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.83 (m, 1H), 7.73 (s, 1H), 7.50 (bd, 1H, J= 8.7 Hz), 7.30-7.11 (m, 5H), 6.68 (bd, 1H); LCMS: ret. time: 16.50 min.; purity: 97%; MS (m/e): 380 (MH^+).
7.3.657	N4-(4-tert-Butylphenyl)-N2-(2-carboxybenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine (R926481)	In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, LiOH treatment with N4-(4-tert-butylphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine gave N4-(4-tert-butylphenyl)-N2-(2-carboxybenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 9.3 (bd, 2H), 8.25 (s, 1H), 8.10 (s, 1H), 7.65-7.30 (m, 5H), 1.25 (s, 9H); ^{19}F NMR (CD_3OD): - 21844; LCMS: ret. time: 23.32 min.; purity: 100%; MS (m/e): 421 (MH^+).
7.3.658	N4-(3-*tert*-Butylphenyl)-N2-[3-carboxymethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine R940280	In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-[2,3-dihydro-2-(carboxy)benzofuran-5-yl]-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was reacted with LiOH to give N4-(3-*tert*-butylphenyl)-N2-(3-carboxymethyleneoxyphenyl)-5-fluoro 2,4-pyrimidinediamine. LCMS: ret. time: 23.61 min.; purity: 99 %; MS (m/e): 410 (M^+), 412 (MH^+); ^{1}H NMR (DMSO-d6): δ 9.45 (1H, s), 9.33 (1H, s), 8.21 (1H, d, J= 3.9 Hz), 7.98 (1H, d, J= 6.6 Hz), 7.60 (1H, t, J= 2 Hz), 7.44-7.34 (3H, m), 7.24-7.15 (2H, m), 6.54 (1H, d, J= 7.8 Hz), 4.68 (2H, s), 1.36 (9H, s)
7.3.659	N2-(3-Carboxymethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950190)	The reaction of N2-(3-ethoxycarbonylmethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (0.1 g) and LiOH (10 equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatement with aqueous HCl gave the solid. The resulting solid was filtered, washed with water and dried to give N2-(3-carboxymethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 18.23 min.; purity: 87.6%; MS (m/e): 412.01 (MH^+).
7.3.660	N2-(Carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethyloxy)phenyl]-2,4-pyrimidinediamine (R950230)	In a manner similar to the preparation of N2-(3-carboxymethyleneaminophenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the hydrolysis of N2-(ethoxycarbonylmethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylenoxy)phenyl]-2,4-pyrimidinediamine with LiOH gave N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethyloxy)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.15 min.; purity: 78.3%; MS (m/e): 413.01 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.661	5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950231)	A mixture of N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine (10 mg), 2-aminoethanol (10 equiv.) and PyBroP (2 equiv.) was stirred in 0.5 ml DMF for 24 hours at room temperature. The mixture was diluted with water, extracted with EtOAc and the organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 2:1) to give 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethylene aminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.98 min.; purity: 92.6%; MS (m/e): 455.97 (MH^+).
7.3.662	N2-[3-(N-2-Aminoethylamino)carbonylmethylene aminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylenoxy)phenyl]-2,4-pyrimidinediamine (R950232)	In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and 1,2-ethylenediamine were reacted to afford N2-[3-(N-2-aminoethylamino)carbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylenoxy)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 11.31 min.; purity: 93.6%; MS (m/e): 454.94 (MH^+).
7.3.663	5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950233)	In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and methylamine were reacted to give 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-methylamino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 14.93 min.; purity: 92.9%; MS (m/e): 426.27 (MH^+).
7.3.664	5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-methylamino)ethylamino]carbonylmethyleneaminophenyl]- 2,4-pyrimidinediamine (R950234)	In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and N-methylethylenediamine were reacted to give 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-methylamino)ethylamino] carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 11.39 min.; purity: 97.7%; MS (m/e): 468.96 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.665	N2-[3-[N-(2-N-Benzylamino)ethylamino]carbonyl methyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine (R950235)	In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and N-benzylethylenediamine were reacted to give N2-[3-[N-(2-N-benzylamino)ethylamino]carbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 14.39 min.; purity: 97.3%; MS (m/e): 545.01 (MH^+).
7.3.666	5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine (R950236)	In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and morpholine were reacted to afford 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-morpholino)carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 15.24 min.; purity: 94.6xx%; MS (m/e): 482.40 (MH^+).
7.3.667	N2-[3-(3-N,N-Dimethylaminopropyl) aminocarbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine (R950237)	In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and N,N-dimethylpropanediamine were reacted to give N2-[3-(3-N,N-Dimethylaminopropyl)aminocarbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 13.33 min.; purity: 91.4%; MS (m/e): 497.47 (MH^+).
7.3.668	N2-[3-[N-(2,3-Dihydroxypropyl)amino]carbonyl methyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine (R950238)	In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and 1-amino-2,3-propanediol were reacted to give N2-[3-[N-(2,3-dihydroxypropyl)amino]carbonylmethyleneaminophenyl]-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 12.86 min.; purity: 90.0%; MS (m/e): 486.40 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.669	5-Fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-morpholinoethyleneamino)carbonylmethyleneamino phenyl]-2,4-pyrimidinediamine (R950239)	In like manner to the preparation of N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-[N-(2-hydroxyethylamino)]carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and 4-(2-aminoethyl)morpholine were reacted to give 5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-N2-[3-(N-morpholinoethyleneamino) carbonylmethyleneaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 13.52 min.; purity: 92.4%; MS (m/e): 525.47 (MH^+).
7.3.670	2,4-Bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine (R926514) and 5-Ethoxycarbonyl-2-methoxy-4-[N-(L)-tyrosine methyl ester]pyrimidine (R926513)	A mixture of tyrosine methyl ester (58 mg, 0.3 mmol), 2,4-dichloro-5-ethoxycarbonylpyrimidine (44 mg, 0.1 mmol) in MeOH (2mL) was heated in a sealed tube at 100 °C for a period of overnight, diluted with H_2O (20 mL), acidified with 2N HCl and extracted with ethyl acetate (3 x 25 mL). The solvent was evaporated and the residue was purified by preparative TLC using 30% EtOAc/Hexanes to obtain a mixture of 2,4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine (**R926514**). ^1H NMR ($CDCl_3$): δ 8.60 (1H, J= 6.6 Hz), 8.36 (s, 1H), 7.05 (d, 2H, J= 8.7 Hz), 6.84 (d, 2H, J= 8.1 Hz), 6.74 (d, 2H, J= 9 Hz), 6.54 (d, 2H, J= 9 Hz), 4.82 (t, 2H, J= 6 Hz), 4.25 (q, 2H, J= 6.3 Hz), 3.73 (s, 3H), 3.72 (s, 3H), 3.06 (m, 4H), 1.31 (t, 3H, J= 7.2 Hz) and 5-ethoxycarbonyl-2-methoxy-4-[N-(L)-tyrosine methyl ester]pyrimidine (**R926513**): ^1H NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.65 (d, 1H, J= 6.9 Hz), 7.02 (dd, 2H, J= 2.1 and 6.3 Hz), 6.77 (dd, 2H, J= 2.4 and 6.6 Hz), 4.93 (q, 1H, J= 1.5 and 6.9 Hz), 4.30 (q, 2H, J= 8.1 Hz), 3.90 (s, 3H), 3.70 (s, 3H), 3.17 (dd, 1H, J= 5.4 Hz), 3.06 (dd, 1H, J= 7.5 and 7.8 Hz), 1.33 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 22.58 min.; purity: 99%; MS (m/e): 376 (M^+).
7.3.671	N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R926252)	In like manner to the preparation of N2,N4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine, the reaction of 2,4-dichloro-5-ethoxycarbonylpyrimidine with 3,4-ethylenedioxyaniline gave N2,N4-bis(3,4-ethylenedioxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 10.01 (s, 1H), 9.65 (bs, 1H), 8.62 (s, 1H), 7.18 (bs, 2H), 7.04 (dd, 1H, J= 1.8 and 8.7 Hz), 6.93 (d, 1H, J= 7.5 Hz), 6.76 (d, 1H, J= 8 7 Hz), 6.65 (d, 1H, J= 8.7 Hz), 4.28 (q, 2H, J= 6.9 Hz), 1.31 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 27.25 min.; purity: 100%; MS (m/e): 451 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.672	N2,N4-Bis(4-hoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R926253)	In like manner to the preparation of N2,N4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine, the reaction of 2,4-dichloro-5-ethoxycarbonylpyrimidine with ethyl 4-aminophenoxyacetate gave N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine **(R926253)**. ^{1}H NMR (CD_3OD): δ 8.60 (bs, 1H), 7.4 (bs, 1H), 7.33 (d, 4H, J= 9Hz), 6.94 (bd, 4H), 4.76 (s, 2H), 4.75 (s, 2H), 4.44 (q, 2H, J= 6.9 Hz), 3.79 (s, 3H), 1.40 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 25.83 min.; purity: 89%; MS (m/e): 511 (MH^+).
7.3.673	2,4-Bis[N-(L)-phenylalaninyl ethyl ester]-5-ethoxycarbonylpyrimidine (R926526)	In like manner to the preparation of N2,N4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine, the reaction of 2,4-dichloro-5-ethoxycarbonylpyrimidine with ethyl (L)-phenylalanine ethyl ester in MeOH or EtOAc gave 2,4-bis[N-(L)-phenylalanine ethyl ester]-5-ethoxycarbonylpyrimidine. ^{1}H NMR ($CDCl_3$): δ 8.55 (d, 1H, J= 7.2 Hz), 8.51 (s, 1H), 7.35-7.10 (m, 10H), 5.88 (d, 1H, J= J= 6 Hz), 4.88 (ddd, 1H, J= 6.3 Hz), 4.80 (ddd, 1H, J= 6.3 Hz), 4.23 (q, 2H, J= 7.2 Hz), 4.12 (q, 4H, J= 7.2 Hz), 3.65 (t, 2H, J= 6 Hz), 3.56 (t, 2H, J= 6.0 Hz), 1.30 (t, 2H,, J= 6 Hz), 1.30 (t, 3H, J= 7.2 Hz), 1.20 (m, 6H); LCMS: ret. time: 32.22 min.; purity: 89%; MS (m/e)· 535 (MH^+).
7.3.674	2,4-Bis[N-(L)-valinyl ethyl ester]-5-ethoxycarbonylpyrimidine (R926527)	In like manner to the preparation of N2,N4-bis[N-(L)-tyrosine methyl ester]-5-ethoxycarbonylpyrimidine, the reaction of 2,4-dichloro-5-ethoxycarbonylpyrimidine with ethyl (L)-valine ethyl ester in MeOH or EtOAc gave 2,4-bis[N-(L)-valinyl ethyl ester]-5-ethoxycarbonylpyrimidine. ^{1}H NMR ($CDCl_3$): δ 8.59 (d, 1H, J= 7.8 Hz), 8.56 (s, 1H), 5.69 (d, 1H, J= 8.7 Hz), 4.62 (m, 1H), 4.51 (m, 1H), 4.25 (q, 2H, J= 7.5 Hz), 4.20 (m, 4H), 2.20 (m, 2H), 1.34 (t, 3H, J= 7.8 Hz), 1.27 (t, 6H, J= 7.5 Hz), 1.00 (m, 12H); LCMS: ret. time: 29.27 min.; purity: 97%; MS (m/e): 439 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.675	5-Ethoxycarbonyl-N2-(3-hydroxyphenyl)-4-[N-(L)-phenylalanine ethyl ester]-2-pyrimidineamine (R926528)	The reaction of 2-chloro-N4-(3-hydroxyphenyl)-5-ethoxycarbonylpyrimidineamine with 3 equivalents of (L)-N-phenylalanine ethyl ester in methanol at 80-100 °C for 24 h followed by dilution with water and acidification with 2N HCl have the acidic solution. The resulting solution was extracted with EtOAc and the residue was purified by silics gel column chromatography to afford 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 9.4 (bs, 1H), 9.13 (d, 1H, J= 6 Hz), 8 45 (bs, 1H), 7.59 (s, 1H), 7.34-7.25 (m, 5H), 7.15 (t, 1H, J= 8.1 Hz), 6.73 (bd, 1H, J= 7.5 Hz), 6.67 (dd, 1H, J= 1.8 and 7.8 Hz), 4.86 (dt, 1H, J= 3 and 5.1 Hz), 4.32 (q, 2H, J= 6.3 Hz), 4.19 (q, 2H, J= 7.2 Hz), 3.30 (dd, 1H, J= 4.8 and 8.7 Hz), 3.18 (dd, 1H, J= 5.1 and 8.7 Hz), 1.36 (t, 3H, J= 6.9 Hz), 1.65 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 27.49 min.; purity: 91%; MS (m/e): 451 (MH^+).
7.3.676	N2-(3,4-Ethylenedioxyphenyl)-5-ethoxycarbonyl-4-[N-(L)-phenyl glycinyl ethyl ester)-2-pyrimidineamine (R926536)	In like manner to the preparation of 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine, the reaction of 2-chloro-5-ethoxycarbonyl-4-[N-(L)-phenyl glycinyl ethyl ester)pyrimidine with 3,4-ethylenedioxyaniline in MeOH or EtOAc gave N2-(3,4-ethylenedioxyphenyl)-5-ethoxycarbonyl-4-[N-(L)-phenyl glycinyl ethyl ester]-2-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 9.15 (s, 1H), 8.9 (s, 1H), 8.61 (s, 1H), 7.48 (m, 2H), 7.38 (m, 3H), 7.16 (bs, 1H), 6.80 (m, 2H0, 5.75 (d, 1H), 4.24 (m, 6H), 3.66 (s, 3H), 1.35 (t, 3H); LCMS: ret. time: 28.16 min.; purity: 85%; MS (m/e): 465 (MH^+).
7.3.677	N4-(4-tert-Butoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R926579)	In like manner to the preparation of 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine, the reaction of N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-2-chloro-5-ethoxycarbonyl-4-pyrimidineamine with methyl 4-aminophenoxyacetate gave N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 10.17 (s, 1H), 8.73 (s, 1H), 8.45 (bs, 1H), 7.49 (d, 2H, J= 8.7 Hz), 7.43 (d, 2H, J= 8.7 Hz), 7.33 (bs, 1H), 6.87 (d, 2H, J= 6 Hz), 6.84 (d, 2H, J= 5.7 Hz), 4.63 (s, 2H), 4.53 (s, 2H), 4.33 (q, 2H, J= 6.9 Hz), 3.81 (s, 3H), 1.49 (s, 9H), 1.39 (t, 3H, J= 7.5 Hz); LCMS: ret. time: 27.93 min.; purity: 96%; MS (m/e): 553 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.678	N4-(4-tert-Butoxycarbonylmethyleneoxyphenyl)-N2-(4-methoxycarbonylmethyleneoxyphenyl)-5-methoxycarbonyl-2,4-pyrimidinediamine (R926580)	In like manner to the preparation of 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine, the reaction of N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-2-chloro-5-ethoxycarbonyl-4-pyrimidineamine with methyl 4-aminophenoxyacetate gave N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-5-methoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. 5-methyl ester was obtained due to the cross esterification reaction in MeOH. ^{1}H NMR ($CDCl_3$): δ 10.13 (s, 1H), 8.73 (s, 1H), 8.45 (bs, 1H), 7.49 (d, 2H, J= 8.7 Hz), 7.43 (d, 2H, J= 8.7 Hz), 7.33 (bs, 1H), 6.87 (m, 4H), 4.63 (s, 2H), 4.53 (s, 2H), 4.33 (q, 2H, J= 6.9 Hz), 3.88 (s, 3H), 3.81 (s, 3H), 1.49 (s, 9H); LCMS: ret. time: 27.43 min.; purity: 100%; MS (m/e): 539 (MH^+).
7.3.679	N4-(4-Carboxymethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R926583)	The treatment of N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with trifluoroacetic acid in THF:H_2O at room temperature afforded N4-(4-carboxymethyleneoxyphenyl)-5-ethoxycarbonyl-N2-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.03 (s, 1H), 8.65 (s, 1H), 7.49 (bd, 4H, J= 8.7 Hz), 6.89 (d, 2H, J= 9.3 Hz), 6.81 (d, 2H, J= 8.1 Hz), 4.70 (s, 2H), 4.65 (s, 2H), 4.33 (q, 2H, J= 6.9 Hz), 3.81 (s, 3H), 1.49 (s, 9H), 1.39 (t, 3H, J= 7.5 Hz); LCMS: ret. time: 22.28 min.; purity: 73%; MS (m/e): 497 (MH^+).
7.3.680	N2-(4-Carboxymethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R926584)	The treatment of N2-(4-tert-butoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with trifluoroacetic acid in THF:H_2O at room temperature afforded N2-(4-carboxymethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine.^{1}H NMR (DMSO-d6): δ 10.01 (s, 1H), 8.64 (s, 1H), 7.45 (bd, 4H, J= 7.2 Hz), 6.90 (d, 2H, J= 8.7 Hz), 6.75 (d, 2H, J= 8.4 Hz), 4.80 (s, 2H), 4.38 (s, 2H), 4.26 (q, 2H, J= 7.2 Hz), 3.70 (s, 3H), 1.30 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 22.37 min.; purity: 100%; MS (m/e): 497 (MH^+).
7.3.681	5-Carboxy-N2-(3-hydroxyphenyl)-N4-[N-(L)-phenylglycine)-2-pyrimidineamine (R926535)	The LiOH hydrolysis of N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-4-[N-(L)-phenyl glycine ethyl ester]-2-pyrimidineamine affored 5-carboxy-N2-(3-hydroxyphenyl)-N4-[N-(L)-phenylglycine)-2-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 8.89 (s, 1H), 8.50 (s, 1H), 7.43 (m, 2H), 7.33 (m, 3H), 7.14 (m, 2H), 6.98 (m, 2H), 6.62 (m, 1H), 5.71 (s, 1H); LCMS: ret. time: 17.75 min ; purity: 73%; MS (m/e): 382 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.682	5-Amino-6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925856)	A suspension of 6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-5-nitro-2,4-pyrimidinediamine and 10% Pd/C (10% by weight) in ethanol was prepared and reacted in a Parr bottle under hydrogen gas (20 PSI) for 1h. The reaction mixture was filtered through Celite. Purification by column chromatography gave 5-amino-6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.30 (bs, 1H), 7.18-7.10 (m, 3H), 7.00 (t, 2H, J= 8.1 Hz), 6.59-6.54 (m, 1H), 6.33 (dd, 1H, J= 2.1 and 11.1 Hz), 4.39 (q, 2H, J= 6.9 Hz), 1.43 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 19.24 min.; purity: 100 %, MS (m/e): 382 (MH^+).
7.3.683	5-Amino-6-ethoxycarbonyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-2,4-pyrimidinediamine (R925857)	In a manner similar to the preparation of 5-amino-6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine, 6-ethoxycarbonyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-5-nitro-2,4-pyrimidinediamine, hydrogen, and 10% Pd/C were reacted to yield 5-amino-6-ethoxycarbonyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.16 (d, 1H, J= 2.4 Hz), 7.07 (d, 1H, J= 2.4 Hz), 7.04 (dd, 1H, J= 2.4 and 9.0 Hz), 6.84-6.79 (m, 2H), 6.70 (d, 1H, J= 9.0), 4.43 (q, 2H, J= 7.8 Hz), 4.25 (s, 4H), 4.21 (bs, 4H), 1.43 (t, 3H, J= 7.8 Hz); LCMS: ret. time: 23.70 min.; purity: 100 %; MS (m/e): 466 (MH^+).
7.3.684	5-Amino-N2,N4-bis(ethoxycarbonylmethyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine (R925865)	In a manner similar to the preparation of 5-amino-6-ethoxycarbonyl-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine, 6-ethoxycarbonyl-N2,N4-bis(ethoxycarbonylmethyl)-5-nitro-2,4-pyrimidinediamine, hydrogen, and 10% Pd/C were reacted to yield 5-amino-N2,N4-bis(ethoxycarbonylmethyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 6.25 (bs, 2H), 4.38 (q, 2H, J= 6.9 Hz), 4.23-4.14 (m, 6H), 4.05 (bs, 2H), 1.39 (t, 3H, J= 6.9 Hz), 1.30-1.22 (m, 6H); LCMS: ret. time: 17.67 min.; purity: 95 %; MS (m/e): 370 (MH^+).
7.3.685	5-Amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine (R926567)	Hydrogenation of N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine using Pd/C in MeOH at 40 PSI gave 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.47 (d, 2H, J= 8.7 Hz), 7.41 (d, 2H, J= 8.7 Hz), 6.88 (d, 2H, J= 8.1 Hz), 6 81 (d, 2H, J= 8.7 Hz), 4.63 (s, 2H), 4.59 (s, 2H), 4.41 (q, 2H, J= 7.5 Hz), 4.29 (m, 4H), 1.44 (t, 3H), 1.31 (m, 6H); LCMS: ret. time: 26.15 min.; purity: 97%; MS (m/e): 554 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.686	N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine (R926571)	A dry reaction flask equipped with a rubber septum and a N_2 inlet was charged with 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine, equimolar amount of pyridine and phenyl isocyanate at room temperature. The reaction was allowed to stirred at room temperature for overnight and the resulting reaction was poured over n-hexane to precipitate the desired product, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.92 (s, 1H), 7.47 (s, 1H), 7.35 (bt, 5H, J= 8.4 Hz), 7.25 (bt, 2H, J= 7.5 Hz), 7.03 (m, 2H), 6.81 (d, 2H, J= 8.7 Hz), 6.76 (d, 2H, J= 8.7 Hz), 4.60 (s, 2H), 4.58 (s, 2H), 4.29 (m, 6H), 1.45 (m, 9H); LCMS: ret. time: 27.75 min.; purity: 91%; MS (m/e): 673 (MH^+).
7.3.687	5-Allylaminocarbonylamino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl)-2,4-pyrimidinediamine (R926585)	In like manner to the preparation of N2,N4-bis(4-ethoxycarbonylmethylene oxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine, the reaction of 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with allyl isocyanate gave 5-allylaminocarbonylamino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl)-2,4-pyrimidinediamine. LCMS: ret. time: 25.60 min.; purity: 91%; MS (m/e): 637 (MH^+).
7.3.688	N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(ethoxycarbonylaminocarbonylamino)-2,4-5-pyrimidinetriamine (R926586)	In like manner to the preparation of N2,N4-bis(4-ethoxycarbonylmethylene oxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine, the reaction of 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with ethoxycarbonyl isocyanate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(ethoxycarbonylaminocarbonylamino)-2,4-pyrimidinediamine. LCMS: ret. time: 26.79 min.; purity: 88%; MS (m/e): 669 (MH^+).
7.3.689	N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(ethoxycarbonylmethylene aminocarbonylamino)-2,4-pyrimidinediamine (R926587)	In like manner to the preparation of N2,N4-bis(4-ethoxycarbonylmethylene oxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine, the reaction of 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with ethylacetyl isocyanate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(ethoxycarbonylmethyleneaminocarbonylamino)-2,4-pyrimidinediamine. LCMS: ret. time: 25.76 min.; purity: 96%; MS (m/e): 683 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.690	N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(cyclopentylaminocarbonylamino)-2,4-pyrimidinediamine (R926588)	In like manner to the preparation of N2,N4-bis(4-ethoxycarbonylmethylene oxyphenyl)-6-ethoxycarbonyl-5-(phenylaminocarbonylamino)-2,4-pyrimidinediamine, the reaction of 5-amino-N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with cyclopentyl isocyanate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(cyclopentylaminoacrbonylamino)-2,4-pyrimidinediamine. LCMS: ret. time: 27.36 min.; purity: 83%; MS (m/e): 665 (MH^+).
7.3.691	N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(chloroacetylaminocarbonylamino)-2,4-pyrimidinediamine (R926589)	In like manner to the preparation of N2,N4-bis(ethoxycarbonylmethylene oxyphenyl)-6-ethoxycarbonyl-5-(N-phenylformyl-amino)-2,4-pyrimidinediamine, the reaction of N5-amino-N2,N4-bis(ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-2,4-pyrimidinediamine with chloroacetylformyl isocyanate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-6-ethoxycarbonyl-5-(chloroacetylamino carbonylamino)-2,4-pyrimidinediamine. LCMS: ret. time: 26.60 min.; purity: 100%; MS (m/e): 580 (MH^+).
7.3.692	(R920669): N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-trifluoro-2,4-pyridinediamine	A mixture of 2,4-dichloro-5-trifluoromethylpyrimidine (416 mg, 1.9 mmol), 3,4-ethylenedioxyaniline (0.5 mL, 4.1 mmol), and concentrated HCl (0.1 mL) in 1:9 acetone/H_2O (10 mL) was heated to reflux. After 1 h, the reaction was complete as determined by TLC. The mixture was cooled to room temperature and EtOAc (30 mL) was added. The organic layer was washed with 2 N HCl (2 x 15 mL), water (15 mL), and dried (Na_2SO_4). The organic layer was filtered through a silica gel pad, washing the filter cake with EtOAc, and concentrated. The material was purified by chromatography (silica gel, 95:5 dichloromethane/ethyl acetate) to afford N2,N4-bis(3,4-ethylenedioxyphenyl)-5-trifluoro-2,4-pyridinediamine (380 mg, 44%): R_f 0.27 (silica gel, 9.5:0.5 dichloromethane/ethyl acetate); mp 141-143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.07 (m, 2H), 6.99 (bs, 1H), 6.93-6.84 (m, 3H), 6.77-6.74 (m, 1H), 6.67 (bs, 1H), 4.29-4.24 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 157.9, 155.8, 143.7, 132.6, 131.1, 117.5, 117.3, 114.4, 113.2, 110.3, 64.7, 64.5; IR (ATR) 3446 cm^{-1}; ESI MS *m/z* 447 $[C_{21}H_{17}F_3N_4O_4 + H]^+$; HPLC (Method C) >99% (AUC), t_R = 8.5 min. Anal. Calcd for $C_{21}H_{17}F_3N_4O_4$: C, 56.50; H, 3.84; N, 12.55. Found: C, 56.46; H, 4.41; N, 12.57.

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Section Number	Name of compound and reference number	Experimental
7.3.693	(R920668): N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3-pyridyl)-2,4-pyrimidinediamine	A mixture of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (280 mg, 1 mmol), 3-aminopyridine (113 mg, 1.2 mmol), sodium *t*-butoxide (134 mg, 1.4 mmol), binap (38 mg, 0.06 mmol), and palladium(II)acetate (14 mg, 0.06 mmol) in 9 mL of toluene was purged with N_2 (3 cycles of alternating N_2 and vacuum). The mixture was heated to 80 °C (oil-bath temperature). After 24 h, the mixture was cooled to room temperature and EtOAc (30 mL) and of water (10 mL) was added. After stirring 15 min, the precipitate was collected by filtration. A ^{1}H NMR spectrum and ESI mass spectrum of the solid (150 mg) indicated the product (TLC analysis of the organic layer of the filtrate detected only starting materials). The crude product was slurried in 2 N HCl and the mixture was filtered. The filtrate was neutralized with 10% aqueous NaOH and concentrated. The material was slurried with MeOH and the solids removed by filtration. The concentrated material was slurried in CH_3CN and TFA was added to afford a solution. *N,N*-diisopropylethylamine was added to the solution and the solid was collected by filtration, washing with CH_3CN followed by Et_2O to afford N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-pyridyl)-2,4-pyrimidinediamine (55 mg, 14%): R_f 0.42 (silica gel, 4:1:0.1:0.1 dichloromethane/ethyl acetate/methanol/concentrated ammonium hydroxide); mp 251-253 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.38 (s, 1H), 9.26 (s, 1H), 8.74 (s, 1H), 8.20-8.17 (m, 1H), 8.09-8.08 (m, 2H), 7.29-7.28 (m, 1H), 7.23-7.17 (m, 2H), 6.83-6.80 (m, 1H), 4.24 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.2, 149.8, 142.9, 141.6, 140.5, 140.0, 139.8, 139.7, 137.5, 132.1, 124.8, 123.0, 116.4, 115.1, 110.9, 64.1, 64.0; IR (ATR) 3264, 3195 cm^{-1}; APCI MS *m/z* 340 $[C_{17}H_{14}FN_5O_2 + H]^+$. Anal. Calcd for $C_{17}H_{14}FN_5O_2 \cdot 0.5H_2O$: C, 58.70; H, 4.20; N, 20.13. Found: C, 58.71; H, 4.20; N, 19.51.

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Section Number	Name of compound and reference number	Experimental
7.3.694	(R920664): N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(4-n-hexyloxyphenyl)-2,4-pyrimidindiamine	To a magnetically stirred solution of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (0.25 g, 0.89 mmol) in ethylene glycol (3.0 mL) under nitrogen at room temperature was added *N,N*-diisopropylethylamine (0.12 g, 0.89 mmol) followed by 4-hexyloxyaniline (0.27 g, 1.4 mmol). The reaction mixture was heated to 170 °C for 5.5 h, cooled to room temperature and partitioned between water (20 mL) and chloroform (20 mL). The aqueous layer was extracted with chloroform (20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The crude brown solid was purified by chromatography (silica gel, 2:1 hexanes/ethyl acetate) to afford N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(4-n-hexyloxyphenyl)-2,4-pyrimidindiamine (0.09 g, 23%) as a white solid: R_f 0.53 (silica gel, 4:1 chloroform/ethyl acetate); mp 115-117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 3.2 Hz, 1H), 7.40 (d, J = 8.9 Hz, 2H), 7.29 (d, J = 2.5 Hz, 2H), 6.98 (d, J = 8.8 Hz, 1H), 6.88-6.82 (m, 3H), 6.61 (s, 1H), 4.29 (d, J = 3.1 Hz, 4H), 3.94 (t, J = 6.6, 6.7 Hz, 2H), 1.77 (m, 2H), 1.47 (m, 2H), 1.35 (m, 4H), 0.92 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 155.1, 150.3, 143.6, 142.7, 140.3, 140,07 139.4, 133.0, 131.7, 121.9, 117.3, 115.0, 114.7, 110.8, 68.6, 64.6, 31.8, 29.5, 25.9, 22.8, 14.2; IR (ATR) 3357 cm^{-1}; ESI MS *m/z* 439 [$C_{24}H_{27}FN_4O_3$ + H]$^+$; HPLC (Method B) 98.5% (AUC), t_R = 7.9 min. Anal. Calcd for $C_{24}H_{27}FN_4O_3$: C, 65.74; H, 6.21; N, 12.78. Found: C, 65.34; H, 6.19; N, 12.96.

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Section Number	Name of compound and reference number	Experimental
7.3.695	(R920666): N2-(4-n-Butyloxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine	To a magnetically stirred solution of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (0.25 g, 0.89 mmol) in ethylene glycol (3.0 mL) under nitrogen at room temperature was added *N,N*-diisopropylethylamine (0.12 g, 0.89 mmol) followed by 4-butoxyaniline (0.18 g, 1.1 mmol). The reaction mixture was heated to 185 °C for 5 h, cooled to room temperature, and partitioned between water (20 mL) and ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The crude brown solid was purified by chromatography (silica gel, 2:1 hexanes/ethyl acetate) to afford N2-(4-n-Butyloxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine (0.18 g, 49%) as a tan solid: R_f 0.66 (silica gel, 4:1 chloroform/ethyl acetate); mp 133-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 3.2 Hz, 1H), 7.39 (d, J = 8.9 Hz, 2H), 7.28 (d, J = 2.5 Hz, 1H), 6 95 (dd, J = 8.7, 2 5 Hz, 1H) 6.90-6.81 (m, 4H), 6.60 (d, J = 2.4 Hz, 1H), 4.27 (s, 4H), 3.94 (t, J = 6.5 Hz, 2H), 1.80-1.71 (m, 2H), 1.55-1.42 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 155.1, 150.4, 143.6, 142.7, 140.3, 140.0, 139.4, 133.0, 131.7, 121.9, 117.3, 115.0, 114.7, 110.8, 68.2, 64.7, 64.5, 31.6, 19.4, 14.0; IR (ATR) 3356 cm^{-1}; ESI MS *m/z* 411 $[C_{22}H_{23}FN_4O_3 + H]^+$; HPLC (Method A) >99% (AUC), t_R = 17.3 min. Anal. Calcd for $C_{22}H_{23}FN_4O_3$: C, 64.38; H, 5.65; N, 13.65. Found: C, 62.64; H, 5.59; N, 13.15.
7.3.696	(R920670): N4-(4-ethyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine	To a solution of 2-chloro-N4-(4-ethyloxyphenyl)-5-fluoro-4-pyrimidineamine (0.25 g, 0.93 mmol) in ethylene glycol (3 mL) under nitrogen at room temperature was added *i*-Pr_2EtN, 0.93 mmol) followed by 3,4-ethylenedioxyaniline (0.17 g, 1.12 mmol). The reaction mixture was heated to 200 °C for 5 h and then cooled to room temperature. The mixture was partitioned between H_2O (20 mL) and EtOAc (20 mL) and the aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude brown solid was purified by chromatography (2:1 $CHCl_3$/EtOAc) to afford N4-(4-ethyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (0.21 g, 60%) as a tan solid: R_f 0.42 (4:1 $CHCl_3$/EtOAc); mp 163.8-167.2 °C (DSC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 2.8 Hz, 1H), 7.50-7.45 (m, 2H), 7.17 (d, J = 2.5 Hz, 1H), 6.92-6.86 (m, 3H), 6.80-6.75 (m, 2H), 6.64 (bs, 1H), 4.26-4.21 (m, 4H), 4.03 (q, J = 7.0, 2H), 1.42 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1,150.6, 143.6, 142.8, 140.3, 140.0, 139.5, 139.3, 134.0, 130.8, 123.2, 117.2, 115.1, 113.6, 109.4, 64.6, 64.0, 15.1; IR (ATR) 3403 cm^{-1}; ESI MS *m/z* 383 $[C_{20}H_{19}FN_4O_3 + H]^+$; HPLC (Method A) 98.1% (AUC), t_R = 12.0 min. Anal. Calcd for $C_{20}H_{19}FN_4O_3$: C, 62.82; H, 5.01; N, 14.65. Found: C, 62.06; H, 5.01; N, 14.35.

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Section Number	Name of compound and reference number	Experimental
7.3.697	(R920671): N4-(4-n-Butyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine	In like manner to the preparartion **of** N4-(4-ethyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(4-n-butyloxyphenyl)-5-fluoro-4-pyrimidineamine with 3,4-ethylenedioxyaniline gaveN4-(4-n-butyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine. The crude product was purified by chromatography (2:1 $CHCl_3$/EtOAc) ; (0.17 g, 52%) as a tan solid: R_f 0.51 (4:1 $CHCl_3$/EtOAc); mp 149.6-151.4 °C (DSC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 3.4 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 2.4 Hz, 1H), 6.91-6.86 (m, 3H), 6.78-6.75 (m, 2H), 6 62 (bs, 1H), 4.26-4.22 (m, 4H), 3.96 (t, J = 6.5, 2H), 1.82-1.73 (m, 2H), 1.56-1.44 (m, 2H), 0.98 (t, J = 7 4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1,150.8, 143.6, 142.8, 140.2, 139.9, 139 5, 139.2, 133.9, 130.7, 123.1, 117.1, 115.0, 113.5, 109.4, 68.2, 64.6, 31.6, 19.4, 14.0; IR (ATR) 3365 cm^{-1}; ESI MS *m/z* 411 $[C_{22}H_{23}FN_4O_3 + H]^+$; HPLC (Method A) 99.0% (AUC), t_R = 13.2 min. Anal. Calcd for $C_{22}H_{23}FN_4O_3$: C, 64.38; H, 5.65; N, 13.65. Found: C, 63.63; H, 5.60; N, 13.38.
7.3.698	(R920672): N4-(4-n-Hexyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine	In like manner to the preparartion **of** N4-(4-ethyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(4-n-hexyloxyphenyl)-5-fluoro-4-pyrimidineamine with 3,4-ethylenedioxyaniline gave N4-(4-n-hexyloxyphenyl)-N2-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyridinediamine. The crude product was purified by chromatography (2:1 $CHCl_3$/EtOAc) (0.22 g, 69%) as a tan solid: R_f 0.54 (4:1 $CHCl_3$/EtOAc); mp 124.0-125.2 °C (DSC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 3.2 Hz, 1H), 7.47 (d, J = 8.9 Hz, 2H), 7.18 (d, J = 2.4 Hz, 1H), 6.91-6.86 (m, 3H), 6.78-6.74 (m, 2H), 6.62 (d, J = 1.8 Hz, 1H), 4.26-4.22 (m, 4H), 3.96 (t, J = 6.5, 2H), 1.83-1.74 (m, 2H), 1.51-1.42 (m, 2H), 1.36-1.32 (m, 4H), 0.93-0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 150.5, 143.5, 143.0, 142.8, 140.2, 139.9, 139.5, 139.2, 133.9, 130.7, 123.1, 117.1, 115.0, 113.5, 109.3, 68.5, 64.7, 64.5, 31.8, 29.5, 25.9, 22.8, 14.2; IR (ATR) 3378 cm^{-1}; ESI MS *m/z* 439 $[C_{24}H_{27}FN_4O_3 + H]^+$; HPLC (Method A) >99% (AUC), t_R = 14.6 min. Anal. Calcd for $C_{24}H_{27}FN_4O_3$: C, 65.74; H, 6.21; N, 12.78. Found: C, 65.52; H, 6.23; N, 12.66.

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Section Number	Name of compound and reference number	Experimental
7.3.699	(R920818): 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	To a mixture of 4-amino-[(1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene (1.2 g, 6.2 mmol), 1-propanol (40 mL) and trifluoroacetic acid (1 mL) was added 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyridineamine (1.5 g, 6.2 mmol). The mixture was heated at 110 °C for 17 h and then cooled to room temperature. The purple solid that formed was collected by filtration, washing with 1-propanol (30 mL) to afford 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (1.6 g, 65%) as an off-white solid: R_f 0.55 (6:3:1 $CHCl_3/CH_3OH/NH_4OH$); mp (DSC) 191.2-193.7 °C, 257.2-260.0 °C, 344.7-345.2 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.39 (s, 1H), 9.21 (s, 1H), 9.10 (s, 1H), 8.04 (d, J = 3.8 Hz, 1H), 7.59 (d, J = 9.1 Hz, 2H), 7.38 (s, 1H), 7.23 (t, J = 8.1 Hz, 1H), 7 17 (d, J = 1.8 Hz, 1H), 7.05 (t, J = 8.1 Hz, 1H), 6.93 (d, J = 9.1 Hz, 2H), 6.50 (dd, J = 1.8, 8.1 Hz, 1H), 5.40 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.3, 155.3, 153.5, 151.9, 149.8, 149.7, 141.0 (d, J_{C-F} = 150.0 Hz), 139.7, 138.7, 135.0, 128.9, 120.2, 114.8, 110.3, 108.7, 59.6; IR (ATR) 3338, 2923, 2581, 1724, 1661, 1580, 1557 cm^{-1}; ESI MS m/z 395 $[C_{18}H_{15}FN_8O_2 + H]^+$; HPLC (Method A) 96.5% (AUC), t_R = 6.9 min.
7.3.700	(R920819): N4-(3-Hydroxyphenyl)-N2-[4-(1H,1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	To a mixture of 4-amino-[(1H,1,2,3,4-tetrazolyl)methyleneoxy]benzene (0.1 g, 0.5 mmol), 1-propanol (2 mL) and trifluoroacetic acid (0.2 mL) was added 2-chloro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (0.1 g, 0.5 mmol). The mixture was heated at 110 °C for 17 h and then cooled to room temperature. The purple solid that formed was collected by filtration, washing with 1-propanol (5 mL) to afford N4-(3-hydroxyphenyl)-N2-[4-(1H,1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (59.4 mg, 30%) as an off-white solid: R_f 0.51 (6:3:1 $CHCl_3/CH_3OH/NH_4OH$); mp 292-295°C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.34 (s, 2H), 9.13 (s, 1H), 7.95 (d, J = 5.8 Hz, 1H), 7.64 (d, J = 8.9 Hz, 2H), 7.39 (s, 1H), 7.19 (t, J = 8.1 Hz, 1H), 7.05 (t, J = 8.1 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H), 6.43 (dd, J = 1.4, 8.1 Hz, 1H), 6.20 (d, J = 5.8 Hz, 1H), 5.40 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.4, 158.5, 157.5, 154.0, 153.7, 152.2, 140.6, 134.4, 129.1, 120.9, 114.7, 111.0, 109.5, 107.2, 98.4, 59.6; IR (ATR) 3321, 2920, 2581, 1649, 1605, 1487 cm^{-1}; ESI MS m/z 377 $[C_{18}H_{16}N_8O_2 + H]^+$; HPLC (Method A) 97.6% (AUC), t_R = 7.6 min.

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Section Number	Name of compound and reference number	Experimental
7.3.701	(R920820): N4-(3-Hydroxyphenyl)-5-methyl-N2-[4-(1H, 1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine	To a mixture of 4-amino-[(1H,1,2,3,4-tetrazolyl)methyleneoxy]benzene (0.2 g, 0.9 mmol), 1-propanol (4 mL) and trifluoroacetic acid (0.2 mL) was added 2-chloro-N4-(3-hydroxyphenyl)-5-methyl-4-pyrimidineamine (0.2 g, 0.9 mmol). The mixture was heated at 110 °C for 17 h and then cooled to room temperature. The purple solid that formed was collected by filtration, washing with 1-propanol (10 mL) to afford N4-(3-hydroxyphenyl)-5-methyl-N2-[4-(1H,1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine (0.3 g, 89%) as an off-white solid: R_f 0.44 (6:3:1 $CHCl_3/CH_3OH/NH_4OH$); mp (DSC) 255.3-262.4 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.65 (s, 2H), 7.85 (s, 1H), 7.38 (d, J = 10.5 Hz, 2H), 7.17 (s, 1H), 7.12 (t, J = 7.9 Hz, 1H), 7.06 (s, 1H), 6.90 (d, J = 10.5 Hz, 2H), 6.68 (d, J = 7.9 Hz, 1H), 5.45 (s, 2H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.6, 157.9, 154.5, 153.7, 151.2, 140.4, 138.2, 130.1, 129.4, 123.3, 115.9, 115.4, 113.5, 112.4, 107.5, 59.8, 13.7; IR (ATR) 3214, 3051, 2157, 1632, 1596, 1547 cm^{-1}; ESI MS m/z 391 $[C_{19}H_{18}N_8O_2 + H]^+$; HPLC (Method A) >99% (AUC), t_R = 7.9 min.
7.3.702	N4-(3-Benzyloxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine [NEED R NO.]	A mixture of N4-(3-benzyloxyphenyl)-2-chloro-4-pyrimidineamine (0.25 g, 0.82 mmol), 4-amino-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (0.17 g, 0.82 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (10 mL) was heated to 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol, the crude product was preadsorbed onto silica gel using 95.5 methylene chloride /methanol and purified by flash chromatography (95:5 methylene chloride /methanol) to give N4-(3-benzyloxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a tan solid (0.20 g, 52%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (br s, 1H), 7.86 (d, J = 6.1 Hz, 1H), 7.53-7.20 (m, 13H), 7.14 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 6.1 Hz, 1H), 6.13 (d, J = 6.1 Hz, 1H), 5.27 (s, 2H), 4.04 (s, 3H); ESI MS m/z 481 $[C_{26}H_{24}N_8O_2 + H]^+$

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Section Number	Name of compound and reference number	Experimental
7.3.703	(R920917): N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine	A mixture of N4-(3-benzyloxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine (0.20 g, 0.42 mmol) and 5% Pd/C (0.10 g) in 14:1 ethanol/concentrated hydrochloric acid (40 mL) was at room temperature was shaken in a hydrogen atmosphere at 50 psi. After 3 h no further hydrogen uptake was observed. The reaction mixture was filtered through diatomaceous earth, the solids washed with 95:5 methylene chloride/methanol and the filtrate concentrated to afford N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine (0.16 g, 95%) as a tan solid: R_f 0.23 (95:5 methylene chloride/methanol); mp (DSC) 207.1-212.8, 287.4-295.7 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.87 (br s, 1H), 10.81 (br s, 1H), 9 62 (br s, 1H), 8.08-8.06 (m, 1H), 7.72 (d, J = 9.0 Hz, 2H), 7.24 (br s, 1H), 7.20-7.00 (m, 3H), 6.61 (m, 2H), 6.46, (d, J = 6.0 Hz, 1H), 5.38 (s, 2H), 4.40 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.3, 160.1, 157.0, 154.3, 151.6, 141.7, 137.6, 129.1, 128.6, 123.4, 114.4, 111.9, 111.5, 108.3, 98.6, 59.6, 38.0; IR (ATR) 2975, 1639, 1602, 1521cm^{-1}; ESI MS *m/z* 391 $[C_{19}H_{18}N_8O_2 + H]^+$; HPLC (Method A) 94.9 % (AUC), t_R =8.19 min.
7.3.704	N4-(3-Benzyloxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine [NEED R NO.]	A mixture of N4-(3-benzyloxyphenyl)-2-chloro-4-pyrimidineamine (0.52 g, 1.69 mmol), 4-amino-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene (0.34 g, 1.69 mmol) and trifluoroacetic acid (0.4 mL) in 1-propanol (10 mL) was heated to 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride /methanol and purified by flash chromatography (95:5 methylene chloride /methanol) affording the requisite product N4-(3-benzyloxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl)-2,4-pyrimidineamine as a tan solid (0.41 g, 51%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.85 (d, J = 6.1 Hz, 1H), 7.49-7.04 (m, 14H), 6.93 (d, J = 9.0 Hz, 2H), 6.60-6.72 (m, 1H), 6.11 (d, J = 6.1 Hz, 1H), 5.14 (s, 2H), 4.34 (s, 3H); ESI MS *m/z* 481 $[C_{26}H_{24}N_8O_2 + H]^+$

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Section Number	Name of compound and reference number	Experimental
7.3.705	(R920910): N4-(3-Hydroxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine	A mixture of N4-(3-benzyloxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine (0.40 g, 0.42 mmol) and 5% Pd/C (0.10 g) in 14:1 ethanol/concentrated hydrochloric acid (40 mL) at room temperature was shaken in an atmosphere of hydrogen at 50 psi. After 3 h no further hydrogen uptake was observed. The reaction mixture was filtered through diatomaceous earth, the solids washed with 95:5 methylene chloride/methanol and the filtrate concentrated to afford N4-(3-hydroxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine (0.29 mg, 89%) as a beige solid: R_f 0.43 (95:5 methylene chloride/methanol); mp 140-152 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.24 (br s, 1H), 9.98 (br s, 1H), 9.52 (br s, 1H), 7.94 (d, J = 6.6 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.43 (s, 1H), 7.26 (s, 1H), 7.18-7.01 (m, 3H), 6.53, (d, J = 7.5 Hz, 1H), 6.37, (d, J = 6.6 Hz, 1H), 5.52 (s, 2H), 4.13 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.2, 157.2, 154.5, 153.0, 151.2, 146.8, 139.9, 131.8, 128.7, 122.3, 114.7, 111.4, 110.5, 107.5, 99.5, 59.5, 33.3; IR (ATR) 3042, 1578, 1504, 1459 cm^{-1}; ESI MS *m/z* 391 [$C_{19}H_{18}N_8O_2$ + H]$^+$; HPLC (Method A) 95.8 % (AUC), t_R =8.82 min.
7.3.706	(R920861): 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine	A mixture of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (0.22 g, 0.93 mmol, 4-amino-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (0.19 g, 0.93 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (8 mL) was heated to 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride/methanol and purified by flash chromatography (95:5 methylene chloride /methanol) affording the requisite product 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a purple solid (0.18 g, 49%): R_f 0.47 (95:5 methylene chloride/methanol); mp 219-224 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.36 (s, 1H), 9.18 (s, 1H), 9.06 (s, 1H), 8.05 (d, J = 6.0 Hz, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 9.0 Hz, 1H), 7.09 (t, J = 8.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 6.49 (dd, J = 8.0, 2.1 Hz, 1H),, 5.45 (s, 2H), 4.11 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.4, 155.5, 151.7, 151.6, 149.6, 149.5, 142.0, 142.0, 139.3 (d, J_{C-F} = 127.5 Hz), 135.3, 128.9, 120.1, 114.9, 112.3, 110.3, 108.5, 58.5, 33.9; IR (ATR) 3278, 1586, 1542, 1508 cm^{-1}; ESI MS *m/z* 409 [$C_{19}H_{17}FN_8O_2$+H]$^+$; HPLC (Method A) 98.2 % (AUC), t_R =7.69 min. Anal. Calcd for $C_{19}H_{17}FN_8O_2 \cdot 0.5\ H_2O$: C, 54.74; H, 4.23; N, 26.88. Found: C, 54.55; H, 4.02; N, 26.62.

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Section Number	Name of compound and reference number	Experimental
7.3.707	(R920860): 5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine	A mixture of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine (0.31 g, 1.28 mmol), 4-amino-[(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (0.26 g, 1.28 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (8 mL) was heated at 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride/methanol and purified by flash chromatography (95:5 methylene chloride /methanol) to give 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a purple solid (0.20 g, 37 %): R_f 0.63 (95:5 methylene chloride/methanol); mp 220-224 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.36 (s, 1H), 9.17 (s, 1H), 9.02 (s, 1H), 8.05 (d, J = 2.8 Hz, 1H), 7.57 (d, J = 9.1 Hz, 2H), 7.27 (d, J = 8.0 Hz, 1H), 7.10 (dt, J = 2.8, 8.0 Hz, 2H), 6.91 (d, J = 9.1 Hz, 2H), 6.49 (dd, J = 8.0, 2.8 Hz, 1H), 5.29 (s, 2H), 4.39 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.2, 157.4, 155.5, 152.1, 149.6, 149.5, 140.9 (d, $J_{C\text{-}F}$ = 142.0 Hz), 140.5, 140.2, 138.7, 134.8, 128.9, 120.2, 114.5, 112.2, 110.2, 108.5, 60.5, 38.5; IR (ATR) 3274, 1587, 1507 cm^{-1}; ESI MS m/z 409 [$C_{19}H_{17}FN_8O_2$ + H]$^+$; HPLC (Method A) 97.2 % (AUC), t_R =8.04 min. Anal. Calcd for $C_{19}H_{17}FN_8O_2$: C, 55.88; H, 4.20; N, 27.44. Found: C, 55.56; H, 4.10; N, 27.17.
7.3.708	(R920894): N4-(3-Hydroxyphenyl)-5-methyl-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine	A mixture of 2-chloro-N4-(3-hydroxyphenyl)-5-methyl-4-pyrimidineamine (0.20 g, 0.85 mmol, 4-amino-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (0.17 g, 0.85 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (8 mL) was heated at 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride/methanol and purified by flash chromatography (95:5 methylene chloride /methanol) to give N4-(3-hydroxyphenyl)-5-methyl-N2-[4-(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a purple solid (0.18 g, 52%): R_f 0.61 (95:5 methylene chloride/methanol); mp 209-211 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.30 (s, 1H), 8.82 (s, 1H), 8.13 (s, 1H), 7.83 (s, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.18-7.05 (m, 3H), 6.89 (d, J = 9.0 Hz, 2H), 6.48 (t, J = 7.1 Hz, 1H), 5.27 (s, 2H), 4.39 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.7, 158.6, 157.5, 156.7, 154.7, 151.2, 140.2, 134.6, 134.6, 128.1, 119.3, 114.0, 112.6, 109.4, 108.9, 104.7, 59.8, 38.0, 12.9; IR (ATR) 3003, 1602, 1581, 1531, 1507 cm^{-1}; ESI MS m/z 405 [$C_{20}H_{20}N_8O_2$ + H]$^+$; HPLC (Method A) 96.8 % (AUC), t_R =8.23 min.

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Section Number	Name of compound and reference number	Experimental
7.3.709	(R920893): N4-(3-Hydroxyphenyl)-5-methyl-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine	A mixture of 2-chloro-N4-(3-hydroxyphenyl)-5-methyl-4-pyrimidineamine (0.20 g, 0.85 mmol), 4-amino-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (0.17 g, 0.85 mmol) and trifluoroacetic acid (0.2 mL) in 1-propanol (8 mL) was heated at 110 °C for 24 h. The reaction was concentrated to remove most of the 1-propanol. The crude product was preadsorbed onto silica gel using 95:5 methylene chloride/methanol and purified by flash chromatography (95:5 methylene chloride /methanol) to give N4-(3-Hydroxyphenyl)-5-methyl-N2-[4-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidineamine as a purple solid (0.14 g, 42%): R_f 0.44 (95:5 methylene chloride/methanol); mp 219-221 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.32 (s, 1H), 8 85 (s, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.64 (d, J = 9.0 Hz, 2H), 7.20-7.07 (m, 3H), 6.91 (d, J = 9.0 Hz, 2H), 6.50 (dd, J =8.0, 1.2 Hz, 1H), 5.45 (s, 2H), 4.12 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.0, 157.0, 156.1, 154.3, 150.6, 150.0, 139.6, 134.6, 127.5, 118.6, 113.7, 112.0, 108.8, 108.2, 104.2, 57.4, 32.7, 12.3; IR (ATR) 3428, 1595, 1567, 1509 cm^{-1}; ESI MS m/z 405 [$C_{20}H_{20}N_8O_2$ + H]$^+$; HPLC (Method A) 98.5 % (AUC), t_R =7.89 min. Anal. Calcd for $C_{20}H_{20}N_8O_2$. H_2O: C, 57.00; H, 5.02; N, 26.59. Found: C, 56.86; H, 4.92; N, 26.50.
7.3.710	N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-(1,2,3,4-tetrazol-5-yl)-2,4-pyrimidinediamine (R925810)	In a manner similar to experiment #, N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-cyano-2,4-pyrimidinediamine and sodium azide were reacted to yield N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-(1,2,3,4-tetrazol-5-yl)-2,4-pyrimidinediamine. LCMS: ret. time: 25.8 min.; purity: 95%; MS: 535 (MH$^+$).
7.3.711	N2-[4-(N-Cyclopropylmethylamino) carbonylmethyleneoxyphenyl]-5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925838)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-(methoxycarbonylmethyleneoxyphenyl)-2,4-pyridinediamine with cyclopropylmethylamine gave N2-[4-(N-cyclopropylmethylamino)carbonylmethyleneoxyphenyl]- 5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: MS (m/e): 478 (MH$^+$).
7.3.712	5-Ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R925839)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-(methoxycarbonylmethyleneoxyphenyl)-2,4-pyridinediamine with methylamine hydrochloride gave 5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-[4-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. LCMS: MS (m/e): 438 (MH$^+$).

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Section Number	Name of compound and reference number	Experimental
7.3.713	N2-[4-(N-2,3-Dihydroxypropylamino) carbonylmethyleneoxyphenyl]-5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925840)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-N2-(methoxycarbonylmethyleneoxyphenyl)-2,4-pyridinediamine with 3-amino-1,2-propanediol gave N2-[4-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-5-ethoxycarbonyl-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: MS (m/e): 498 (MH^+).
7.3.714	N2,N4-Bis[4-[N-(3-methoxybenzylamino) carbonylmethyleneoxy]phenyl]-5-bromo-2,4-pyrimidinediamine (R925841)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2,N4-bis[4-ethoxycarbonylmethyleneoxyphenyl)-5-bromo-2,4-pyrimidinediamine with 3-methoxybenzylamine gave N2,N4-bis[4-[N-(3-methoxybenzylamino) carbonylmethyleneoxy]phenyl]-5-bromo-2,4-pyrimidinediamine. LCMS: ret. time: 25.94 min.; purity: 95 %; MS (m/e): 727 (MH^+).
7.3.715	5-Bromo-N4-[4-[(N-cyclopropylmethylamino) carbonylmethyleneoxyphenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R925842)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-bromo-N4-(4-ethoxycarbonylmethyleneoxyphenyl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine with cyclopropylmethylamine gave 5-bromo-N4-[4-(N-cyclopropylmethylamino)carbonylmethyleneoxyphenyl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 20.63 min.; purity: 100 %; MS (m/e) 485 (MH^+).
7.3.716	5-Bromo-N2-(3-hydroxyphenyl)-N4-[4-(N-3-methoxybenzylamino)carbonylmethyleneoxyphenyl] -2,4-pyrimidinediamine (R925843)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-bromo-N4-(4-ethoxycarbonylmethyleneoxyphenyl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine with 3-methoxybenzylamine gave 5-bromo-N2-(3-hydroxyphenyl)-N2-(3-hydroxyphenyl)-N4-[4-(N-3-methoxybenzylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 22.34 min.; purity: 90 %; MS (m/e): 551 (MH^+).
7.3.717	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-carboxybenzofuran-5-yl)-2,4-pyrimidinediamine (R926698)	In a manner similar to the preparation of N4-(4-*tert*-butylphenyl)-5-fluoro-N2-(2,3-dihydro-2-carboxybenzofuran-5-yl)-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine and LiOH were reacted to yield N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-carboxybenzofuran-5-yl)-2,4-pyrimidinediamine.

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Section Number	Name of compound and reference number	Experimental
7.3.718	N2,N4-Bis(4-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926016)	In a manner similar to the preparation of N2-N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-trifluoromethylaniline gave N2,N4-bis(4-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.06 (bs, 1H), 7.75 (d, 2H, J= 9 Hz), 7.67 (d, 2H, J= 9Hz), 7.63 (d, 2H, J= 9Hz), 7.54 (d, 2H, J= 9 Hz), 7.19 (bs, 1H), 6.96 (s, 1H); ^{19}F NMR ($CDCl_3$): δ –17598 (s, 3F), -17676 (s, 3F), -46549 (s, 1F); HPLC: 85% pure.
7.3.719	N2-(3,4-Ethylenedioxyphenyl)-N4-(3,4-methylenedioxyphenylhydrazinyl)-5-fluoro-2-pyrimidineamine (R926406)	In a manner similar to the preparation of N2-(3-hydroxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro N4-(3,4-methylenedioxyphenylhydrazinyl)-4-pyrimidineamine with 3,4-ethylenedioxyaniline gave N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(3,4-methylenedioxyphenylhydrazinyl)-2-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 7.82 (d, 1H, J= 3.6 Hz), 7.52 (dd, 1H, J= 1.8 and 7.5 Hz), 7.40 (d, 1H, J= 1.2 Hz), 7.14 (d, 1H, J= 2.4 Hz), 6.92 (d, 1H, J= 8.4 Hz), 6.85 (dd, 1H, J= 2.1 and 8.7 Hz), 6.45 (d, 1H, J= 9Hz), 6.06 (s, 2H), 4.10 (s, 4H); LCMS: ret. time: 12.14 min.; purity: 88%; MS (m/e): 426 (MH^+).
7.3.720	N2,N4-Bis(4-ethoxycarbonylmethylenedioxyphenyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine (R926566)	To a solution of 2,4-dichloro-5-nitropyrimidine (0.264 g, 1 mmol) in EtOAc (10 mL) at 0 °C was added diisopropylethyl amine (0.200 mL) followed by ethyl 4-aminophenoxy acetate (0.585 g, 3 mmol) and then shaken at room temperature for 2h. The reaction was quenched with water and extracted with EtOAc. The EtOAc extract was washed with 2N HCl and water. The solvent was evaporated and the residue was purified by crystallization using EtOAc/hexanes to afford N2,N4-bis(4-ethoxycarbonylmethylenedioxyphenyl)-6-ethoxycarbonyl-5-nitro-2,4-pyrimidinediamine (**R926566**). ^{1}H NMR ($CDCl_3$): 10.32 (s, 1H), 7.42 (s, 1H), 7.40 (d, 2H, J= 8.7 Hz), 7.32 (d, 2H, J= 8.7 Hz), 6.93 (d, 2H, J= 8.7 Hz), 6.82 (d, 2H, J= 8.7 Hz), 4.67 (s, 2H), 4.62 (s, 2H), 4.47 (q, 2H, J= 7.5 Hz), 4.30 (m, 4H), 1.42 (t, 3H, J= 6.9 Hz), 1.31 (m, 6H); LCMS: ret. time: 32.10 min.; purity: 100%; MS (m/e): 584 (MH^+).
7.3.721	N2,N4-Bis[2-(methylthio)-1,3-benzothiaz-6-yl]-5-fluoro-2,4-pyrimidinediamine (R950202)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-fluoropyrimidine and 2-(methylthio)-1,3-benzothiazol-6-amine were reacted to prepare N2,N4-bis[2-(methylthio)-1,3-benzothiaz-6-yl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 24.98 min.; purity: 84.6%; MS (m/e): 486.80 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.722	N4-[3-(2-Hydroxyethyleamino)phenyl]-N2-[3-(N-(N-methyl)-piperazino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950240)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethylamino)phenyl]-2,4-pyrimidinediamine and N-methylpiperazine were reacted to give N4-[3-(2-hydroxyethylenoxy)phenyl]-N2-[3-(N-(N-methyl)-piperazino)carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 13.36 min.; purity: 97.6%; MS (m/e): 495.42 (MH^+).
7.3.723	N4-[3-(2-Hydroxyethyleamino)phenyl]-N2-[3-(N-piperazino)-carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine (R950241)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-(carboxymethyleneaminophenyl)-5-fluoro-N4-[3-(2-hydroxyethyleneamino)phenyl]-2,4-pyrimidinediamine and piperazine were reacted to give N4-[3-(2-hydroxyethyleneamino)phenyl]-N2-[3-(N-piperazino)-carbonylmethyleneaminophenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 13.21 min.; purity: 100%; MS (m/e): 481.40 (MH^+).
7.3.724	(±)-N4-(3-Aminophenyl)-5-fluoro-N2-(3-(3-carboxy-3-D,L-N-phtaloylamino)propylenecarbonylaminophenyl)-2,4-pyrimidinediamine (R950251)	N2,N4-Bis(4-aminophenyl)-5-fluoro-2,4-pyrimidinediamine and N-phtaloyl-DL-glutamic anhydride were reacted in DMF to give N4-(3-aminophenyl)-5-fluoro-N2-(3-(3-carboxy-3-D,L-N-phtaloylamino)propylenecarbonylaminophenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 19.41 min.; purity: 95.7%; MS (m/e): 569.98 (MH^+).
7.3.725	(±)-N4-(3-Aminophenyl)-5-fluoro-N2-[3-(3-carboxy-3-amino)propylenecarbonylaminophenyl]-2,4-pyrimidinediamine (R950255)	(±)-N4-(3-Aminophenyl)-5-fluoro-N2-[3-(3-carboxy-3-D,L-N-phtaloylamino)propylenecarbonylaminophenyl]-2,4-pyrimidinediamine was reacted with hydrazine to give N4-(3-aminophenyl)-5-fluoro-N2-[3-(3-carboxy-3-amino)propylenecarbonylaminophenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 11.98 min.; purity: 90.1%; MS (m/e): 440.3 (MH^+).
7.3.726	5-Methoxycarbonyl-N2,N4-bis[4-(N-pyrrolidino) carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R926559)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-ethoxycarbonyl-N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with pyrrolidine gave 5-methoxycarbonyl-N2,N4-bis[4-(N-pyrrolidino) methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. The ethyl ester at 5-position was exchanged to methyl ester in methanol as a solvent. MS (m/e): 575 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.727	N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyridinediamine (R925565)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with ethyl 4-aminophenoxyacetate gave N2,N4-bis(4-ethoxycarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyridinediamine. MS (m/e): 485 (MH^+).
7.3.728	N2-(3-Ethoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(3,4-tetrafluoroethylenedioxyphenyl)-2,4-pyrimidinediamine (R926799)	In a manner similar to the preparation of N2-(3-hydroxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of ethyl 3-aminophenoxyacetate with 2-chloro-5-ethoxycarbonyl-N4-(3,4-tetrafluoroethylenedioxyphenyl)-4-pyrimidineamine gave N2-(3-ethoxycarbonylmethyleneoxyphenyl)-5-ethoxycarbonyl-N4-(3,4-tetrafluoroethylenedioxyphenyl)-2,4-pyrimidinediamine. MS (m/e): 567 (MH^+).
7.3.729	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[N-2-(D)-(+)-biotinylethylamino]carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926811)	To a solution of D-(+)-biotin and N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DMF at –20 °C was added diisopropylethylamine and the mixture was shaken for 10 minutes. To this mixture was added benzotriazole-1-yl-oxy-tris(dimethylamino)-phosphoniumhexafluorophosphate (BOP) and shaken at room temperature for 24 h. The reaction was quenched with water and extracted with ethyl acetate. The ethyl acetate extract was washed with aqueous solution of NaHCO3 and finally with water. The residue obtained after the removal of solvent was purified by preparative TLC to obtain the desired N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[N-2-(D)-(+)-biotinylethylamino] carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 19.29 min.; purity: 99%; MS (m/e): 682 (M^+).
7.3.730	5-Fluoro-N4-(3-hydroxyphenyl)-N2[2-(N-methyl-N-2-hydroxyethyl)carbonylbenzofuran-5-yl)-2,4-pyrimidinediamine (R926725)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 5-fluoro-N4-(3-hydroxyphenyl)-N2[2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine with 2-(N-methyl)ethanolamine gave 5-fluoro-N4-(3-hydroxyphenyl)-N2[2-(N-methyl-N-2-hydroxyethyl)carbonylbenzofuran-5-yl)-2,4-pyrimidinediamine. LCMS: ret. time: 14.87 min.; purity: 98%; MS: 438 (MH^+).
7.3.731	N2,N4-Bis(3-ethoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926228)	In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, the reaction of 2,4-dichloro-5-fluoropyrimidine and 3-ethoxycarbonylaniline gave N2,N4-bis(3-ethoxycarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 26.55 min.; purity: 100%; MS (m/e): 425 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.732	N2-(3-chloro-4-methylbenzyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R908696)	In a manner similar to the preparation of N2-(3-hydroxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of 2-chloro-N4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 3-chloro-4-methylbenzylamine gave N2-(3-chloro-4-methylbenzyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 25.38 min.; purity: 99 %; MS (m/e): 401 (MH^+).
7.3.733	(±)-N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-phenylethyl)-2,4-pyrimidinediamine (R908697)	In a manner similar to the preparation of N2-(3-hydroxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidineamine, the reaction of 2-chloro-N4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with (±)-2-aminoethylbenzene gave (±)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-phenylethyl)-2,4-pyrimidinediamine. LCMS: ret. time: 23.48 min.; purity: 99 %; MS (m/e): 367 (MH^+).
7.3.734	N2-(3-Ethoxycarbonylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R925745)	In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-ethoxycarbonylaniline gave N2-(3-ethoxycarbonylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 8.04 (bs, 1H), 7.94 (bs, 1H), 7.90 (bd, 1H), 7.68 (bd, 1H, J= 7.5 Hz), 7.35 (t, 1H, J= 8.1 Hz), 7.28 (d, 1H, J= 2.4 Hz), 7.07 (s, 1H), 6.93 (dd, 1H, J= 3 and 8.7 Hz), 6.83 (d, 1H, J= 9 Hz), 6.64 (bs, 1H), 4.36 (q, 2H, J= 7.2 Hz), 4.26 9s, 4H), 1.35 (t, 3H, J= 7.5 Hz); ^{19}F NMR ($CDCl_3$): - 47247; LCMS: ret. time: 15.88.; purity: 100%; MS (m/e): 411 (MH^+).
7.3.735	N4-(3,4-Difluorophenyl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920394)	A solution of N-methyl 3-aminophenoxyacetamide (1 equivalent) and 2-chloro-N4-(3,4-difluorophenyl)-5-fluoro-4-pyrimidineamine (1.2 equivalents) in MeOH was shaken in a sealed tube at 100 °C for 24 hours for 24 h. Upon cooling to the room temperature, it was diluted with ethyl acetate. The resulting solid was filtered and washed with a mixture of ethyl acetate: n-hexanes (1:1; v/v) to obtain N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 10.05 (bs, 1H), 9.83 (bs, 1H), 8.23 (d, 1H, J= 2.7 Hz), 7.98 (m, 2H), 7.52 (m, 1H), 7.39 9m, 1H), 7.20 (m, 3H), 6.60 (m, 1H), 4.37 (s, 2H0, 2.63 (d, 3H, J= 3.3 Hz); LCMS: purity: 94%; MS (m/e): 404 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.736	N4-(4-Chlorophenyl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920396)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.21 (bs, 1H), 10.00 (bs, 1H), 8.26 (d, 1H, J= 4.8 Hz), 8.00 (bd, 1H, J= 4.2 Hz), 7.77 (dd, 2H, J= 2.1 and 7.6 Hz), 7.37 (dd, 2H, J= 2.1 and 7.6 Hz), 7.17 9m, 3H), 8.63 (dd, 1H, J= 1.8 and 8.1 Hz), 4.37 (s, 2H), 2.64 (d, 3H, 4.5 Hz); LCMS: purity: 92%; MS (m/e): 402 (MH^+).
7.3.736.1	N4-(3,4-Dichlorophenyl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920397)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(3,4-dichlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.02 (bs, 1H), 9.76 (bs, 1H), 8.24 (d, 1H, J= 4.2 Hz), 8.08 (m, 1H), 7.97 (bd, 1H, J= 4.8 Hz), 7.77 (m, 1H), 7.55 (d, 1H, J= 8.7 Hz), 7.18 (m, 3H), 6.58 (m, 1H), 4.36 (s, 1H), 2.63 (d, 1H, J= 2.7 Hz); LCMS: purity: 91%; MS: 434 (MH^+).
7.3.737	5-Fluoro-N4-(5-methylpyridin-2-yl)-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920398)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(5-methylpyridin-2-yl)-4-pyrimidineamine gave 5-fluoro-N4-(5-methylpyridin-2-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.35 (bs, 1H), 10.70 (bs, 1H), 8.58 (s, 1H), 8.42 (d, 1H, J= 3.0 Hz), 8.12 (bd, 1H, J= 9.3 Hz), 8.03 (bd, 1H, J= 4.2 Hz), 7.82 (d, 1H, J= 8.7 Hz), 7.56 (s, 1H), 7.30 (bdd, 1H, J= 8.1 Hz), 7.19 (t, 1H, J= 8.1 Hz), 6.55 (dd, 1H, J= 1.8 and 8.1 Hz), 4.41 (s, 2H), 2.63 (d, 3H, J= 3.6 Hz), 2.36 (s, 3H); LCMS: purity: 99%; MS (m/e): 382 (M^+).
7.3.738	5-Fluoro-N4-(6-methylpyridin-2-yl)-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920399)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(6-methylpyridin-2-yl)-4-pyrimidineamine gave 5-fluoro-N4-(6-methylpyridin-2-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.00 (bs, 1H), 9.60 (bs, 1H), 8.25 (s, 1H), 7.95 (m, 3H), 7.30 (s, 1H), 7.10 (m, 3H), 6.55 (d, 1H, J= 7.2 Hz), 4.40 (s, 2H), 2.62 (d, 3H, J= 3.6 Hz), 2.45 (s, 3H); LCMS: purity: 92%; MS (m/e): 383 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.739	N4-(5-Chloropyridin-2-yl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R920405)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(5-chloropyridin-2-yl)-5-fluoro-4-pyrimidineamine gave N4-(5-chloropyridin-2-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.04 (bs, 1H), 9.53 (bs, 1H), 8.40 (d, 1H, J= 2.4 Hz), 8.22 (m, 2H), 7.88 (bd, 1H, J= 4.5 Hz), 7.86 (dd, 1H, J= 2.4 and 8.7 Hz), 7.40 (d, 1H, J= 1.8 Hz), 7.19 (m, 2H), 6.51 (bdd, 1H, J= 1.2 and 9 Hz), 4.38 (s, 2H), 2.64 (d, 3H, J= 3.3 Hz); LCMS: purity: 95%; MS (m/e): 403 (MH^+).
7.3.740	N4-(6-Chloropyridin-3-yl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R920406)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(6-chloropyridin-3-yl)-5-fluoro-4-pyrimidineamine gave N4-(6-chloropyridin-3-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.72 (s, 1H), 9.38 (s, 1H), 8.93 (t, 1H, J= 3.0 Hz), 8.28 (m, 1H), 8.18 (d. 1H, J= 3.6 Hz), 7.95 (m, 1H), 7.45 (d, 1H, J= 8.7 Hz), 7.39 (m, 1H), 7.21 (m, 1H), 7.14 (t, 1H, J= 4.8 Hz), 6.50 (bdd, 1H, J= 7.8 Hz), 4.4 (s, 2H, 2.63 (d, 3H); LCMS: purity: 100%; MS (m/e): 403 (MH^+).
7.3.741	5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(4-methylpyridin-2-yl)-2,4-pyrimidinediamine (R927016)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-methylpyridin-2-yl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(4-methylpyridin-2-yl)-2,4-pyrimidinediamine. LCMS: purity: 95%; MS (m/e): 383 (MH^+).
7.3.742	5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R920407)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(3-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]- N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.835 (bs, 1H), 9.54 (bs, 1H), 8.20 (d, 1H, J= 3.6 Hz), 7.94 (m, 2H), 7.78 (bs, 1H), 7.43 (t, 1H, J= 8.4 Hz), 7.25 (m, 2H), 7.15 (t, 1H, J= 7.5 Hz), 7.03 (bd, 1H, J= 9.3 Hz), 6.55 (bd, 1H, J= 7.5 Hz), 4.36 (s, 2H), 2.63 (d, 3H, J= 4.5 Hz); LCMS: purity: 91%; MS (m/e): 452 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.743	N4-(3,4-Difluoromethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920408)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro- N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.91 (bs, 1H), 9.64 (bs, 1H), 8.19 (d, 1H, J= 3.9 Hz), 8.03 (s, 1H), 7.96 (bd, 1H, J= 4.8 Hz), 7.46 (m, 1H), 7.36 (d, 1H, J= 8.7 Hz), 7.27 (bs, 1H), 7.17 (m, 2H), 6.57 (bdd, 1H, J= 7.2 Hz), 4.36 (s, 1H), 2.62 (d, 3H, J= 4.5 Hz); LCMS: purity: 96%; MS (m/e): 448 (MH^+).
7.3.744	N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R920410)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.08 (d, 1H, J= 5.4 Hz), 7.99 (d, 1H, J= 3.6 Hz), 7.67 (dd, 1H, J= 2.4 and 9.0 Hz), 7.40 (m, 3H), 7.06 (m, 2H), 6.92 (dd, 1H, J= 2.4 and 8.4 Hz), 4.44 (s, 2H), 2.80 (s, 3H); ^{19}F NMR (CD_3OD): -16973 and - 45983; LCMS: purity: 96%; MS (m/e): 486 (MH^+).
7.3.745	N4-(4-Ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926827)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-ethoxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 96%; MS: 412 (MH^+).
7.3.746	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[4-methoxy-3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926828)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-amino-6-methoxyphenoxyacetamide with 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[4-methoxy-3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.83 (s, 1H), 7.80 (d, 1H, J= 4.2 Hz), 7.30 (d, 1H, 2.4 Hz), 7.23 (d, 1H, J= 2.4 Hz), 7.06 (m, 2H), 6.90 (d, 1H, J= 5.7 Hz), 6.73 (d, 1H, J= 5.2 Hz), 4.32 (s, 2H), 4.22 (s, 4H), 3.86 (s, 3H), 2.83 (s, 3H); LCMS: purity: 97%; MS (m/e): 455 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.747	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-methoxy-3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926829)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-amino-4-methoxyphenoxyacetamide with 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-methoxy-3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.86 (d, 1H, J= 4.2 Hz), 7.35 (d, 1H, J= 2.4 Hz), 7.19 (m, 1H), 7.12 (m, 3H), 6.93 (d, 1H, J= 8.7 Hz), 6.52 (m, 1H), 4.37 (s, 2H), 3.85 (s, 3H), 2.82 (s, 3H); ^{19}F NMR (CD_3OD): - 47650, LCMS: purity: 100%; MS: 414 (MH^+).
7.3.748	N4-(3-Chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926832)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of 3 N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3-chlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(3-chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.12 (s, 1H), 9.93 (s, 1H), 8.27 (d, 1H, J= 4.2 Hz), 7.98 (d, 1H, J= 4.9 Hz), 7.85 (s, 1H), 7.73 (d, 1H, J= 8.1 Hz), 7.35 (t, 1H, J= 8.4 Hz), 7.19 (m, 3H), 6.62 (m, 1H), 4.36 (s, 2H), 2.63 (d, 3H, J= 4.2 Hz); LCMS: purity: 95%; MS: 402 (MH^+).
7.3.749	5-Fluoro-N4-(3-methoxy-5-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926833)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(3-methoxy-5-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(3-methoxy-5-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 95%; MS (m/e): 466 (MH^+).
7.3.750	5-Fluoro-N4-(3-hydroxy-4-methoxyphenyl)-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926834)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(3-hydroxy-4-methoxyphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(3-hydroxy-4-methoxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.70 (bs, 2H), 8.12 (d, 1H, J= 4.8 Hz), 7.96 (m, 1H), 7.12 (m, 5H), 6.85 (d, 1H, J= 8.7 Hz), 6.57 (bd, 1H, J= 8.1 Hz), 4.35 (s, 2H), 3.74 (s, 3H), 2.63 (d, 3H, J= 4.5 Hz); LCMS: purity: 99%; MS (m/e): 414 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.751	5-Fluoro-N4-(4-methoxy-3-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926835)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-methoxy-3-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(4-methoxy-3-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.9 Bs, 1H), 9.62 (bs, 1H), 8.17 (d, 1H, J= 4.2 Hz), 8.04 (bdd, 1H, J= 7.2 Hz), 7.82 (t, 1H, 2.7 Hz), 7.18 (m, 3H), 7.11 (t, 1H, J= 8.1 Hz), 6.55 (bd, 1H, J= 6.9 Hz); 4.33 (s, 2H), 3.86 (s, 3H), 2.61 (d, 3H, J= 4.0 Hz); LCMS: purity: 93%; MS: 466 (MH^+).
7.3.752	5-Fluoro-N4-(4-fluoro-3-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926838)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-fluoro-3-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N4-(4-fluoro-3-trifluoromethylphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.80 (s, 1H), 9.44 (s, 1H), 8.25 (m, 1H), 8.18 (d, 1H, J= 3.9 Hz), 8.00 (m, 1H), 7.97 (m, 1H), 7.47 (t, 1H, J= 9.6 Hz), 7.26 (s, 1H), 7.21 (m, 1H), 7.11 (t, 1H, J= 8.4 Hz), 6.51 (bd, 1H, J= 9.9 Hz), 4.34 (s, 2H), 2.62 (d, 3H, J= 4.8 Hz); LCMS: purity: 88%; MS: 454 (MH^+).
7.3.753	N4-(3-Chloro-4-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926839)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(3-chloro-4-methylphenyl)-4-pyrimidineamine gave N4-(3-chloro-4-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.69 (s, 1H), 9.52 (s, 1H), 8.16 (d, 1H, J= 4.2 Hz), 7.96 (bs, 1H), 7.81 (d, 1H, J= 2.1 Hz), 7.67 (bd, 1H, J= 8.4 Hz), 7.26 (m, 3H), 7.15 (t, 1H, J= 8.1 Hz), 6.54 (bd, 1H, J= 7.2 Hz), 4.34 (s, 2H), 2.63 (d, 3H, J= 4.2 Hz), 2.27 (s, 3H); LCMS: purity: 80%; MS (m/e): 415 (M^+).
7.3.754	N4-(2-Chloro-5-methylphenyl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926840)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(2-chloro-5-methylphenyl)-4-pyrimidineamine gave N4-(2-chloro-5-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.80 (bs, 2H), 8.21 (d, 1H, J= 4.8 Hz), 7.92 (d, 1H, J= 4.8 Hz), 7.46 (m, 1H), 7.31 (m, 2H), 7.04 (m, 2H), 6.53 (bd, 1H, J= 8.1 Hz), 4.30 (s, 1H), 2.18 (s, 3H); LCMS: purity: 93%; MS (m/e): 416 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.755	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-isopropylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926830)	The reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(ethoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with isopropylamine (5 equivalents) in the presence of diisopropylethylamine (5 equivalents) in MeOH in a sealed tube at 80 °C for 24 hours gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-isopropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.15 (s, 1H), 8.04 (d, 1H, J= 4.2 Hz), 7.77 (d, 1H, J= 7.5 Hz), 7.28 (m, 4H), 7.08 (t, 1H, J= 8.1 Hz), 6.78 (d, 1H, J= 8.7 Hz), 6.45 (dd, 1H, J= 1.8 and 7.8 Hz), 4.30 (s, 2H), 4.20 (s, 4H), 3.92 (m, 1H), 1.06 (d, 6H, J= 6.6 Hz); LCMS: purity: 95%; MS (m/e): 454 (MH^+).
7.3.756	N2-[3-(N-Cyclopropylamino)carbonylmethyleneoxyphenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926848)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-isopropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(ethoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine with cyclopropylamine gave 5-fluoro-N4-(3,4-ethylenedioxyphenyl)-N2-[3-(N-cyclopropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.17 (bs, 2H), 8.05 (m, 2H), 7.27 (m, 4H), 7.08 (t, 1H, J= 8.1 Hz), 7.67 (d, 1H, J= 8.7 Hz), 6.42 (dd, 1H, J= 2.4 and 8.1 Hz), 4.3 (s, 2H), 4.2 (bs, 4H), 2.65 (m, 1H), 0.6 (m, 2H), 0.45 (m, 2H); LCMS: purity: 91%; MS (m/e): 452 (MH^+).
7.3.757	N4-(4-Cyano-3-methylphenyl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926851)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-cyano-3-methylphenyl)-4-pyrimidineamine gave N4-(4-cyano-3-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.7 (s, 1H), 9.40 (s, 1H), 8.2 (s, 1H), 8.00-7.50 (m, 3H), 7.40-7.00 (m, 3H), 6.50 (bm, 1H), 4.35 (s, 2H), 2.60 (s, 3H), 2.35 (s, 3H); LCMS: purity: 91%; MS (m/e): 407 (MH^+).
7.3.758	5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926855)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.04 (bs, 1H), 9.65 (bs, 1H), 8.35 (s, 1H), 8.23 (d, 1H, J= 3.9 Hz), 8.00 (bd, 1H, J= 6.6 Hz), 7.91 (bd, J= 3.6 Hz), 7.77 (d, 1H, J= 8.1 Hz), 7.57 (t, 1H, J= 8.1 Hz), 7.23 (m, 2H), 6.95 (t, 1H, J= 8.4 Hz), 6.46 (bdd, 1H, J= 1.8 and 8.1 Hz), 4.22 (s, 2H), 2.62 (d, 3H, 4.2 Hz); LCMS: purity: 83%; MS (m/e): 436 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.759	5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(N-methylphthalimido-4-yl)-2,4-pyrimidinediamine (*R926856*)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(N-methylphthalimido-4-yl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(N-methylphthalimido-4-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.95 (s, 1H), 9.44 (s, 1H), 8.29 (m, 1H), 8.25 (m, 1H), 8.18 (d, 1H, J= 1.8 Hz), 7.88 (bd, 1H, J= 4.5 Hz), 7.75 (d, 1H, J= 6.6 Hz), 7 38 (bs, 1H), 7.22 (bd, 1H, J= 8.1 Hz), 7.14 (t, 1H, J= 7.8 Hz), 6.50 (dd, 1H, J= 1.8 and 9.0 Hz), 4.28 (s, 2H), 2.99 (s, 3H), 2.60 (d, 3H, J= 4.5 Hz); LCMS. purity: 92%; MS (m/e): 451 (MH^+)
7.3.760	N4-(2,5-Dimethoxy-4-chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926859)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with N4-(2,5-dimethoxy-4-chlorophenyl)-2-chloro-5-fluoro-4-pyrimidineamine gave N4-(2,5-dimethoxy-4-chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.05 (d, 1H, J= 5.4 Hz), 7.29 (s, 1H), 7.24 (t, 1H, J= 8.1 Hz), 7.18 (s, 1H), 7.02 (t, 1H, J= 2.1 Hz), 6.92 (dd, 1H, J= 1.8 and 8.1 Hz), 6.83 (dd, 1H, J= 2.4 and 8.4 Hz), 4.29 (s, 2H), 3.81 (s, 3H), 3.59 (s, 3H), 2.81 (s, 3H); LCMS: purity: 96%; MS (m/e): 460 (MH)-; 462 (MH^-).
7.3.761	5-Fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-N4-(3-methoxycarbonyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926862)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(3-methoxycarbonyl-5-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(3-methoxycarbonyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.95 (s, 1H), 9.41 (s, 1H), 8.57 (s, 1H), 8.33 (s, 1H), 8.23 (d, 1H, J= 3 Hz), 7.83 (s and d, 2H), 7.22 (m, 2H), 7.02(t, 1H, J= 8.7 Hz), 6 48 (1H, J= 2.4 and 7.5 Hz), 4.27 (s, 2H), 3.80 (s, 3H), 2.60 (d, 3H, J= 4.8 Hz); ^{19}F NMR (DMSO-d6): - 17446; LCMS: purity: 94%; MS (m/z): 494 (MH^+).
7.3.762	5-Fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926870)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-2,4-pyrimidinediamine. LCMS: purity: 86%; MS (m/e): 512 (MH+).

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Section Number	Name of compound and reference number	Experimental
7.3.763	N4-[3-(2-(3-Chlorophenyl)-1,3,4-oxadiazol-5-yl)phenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926871)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-[3-(2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl)phenyl]-4-pyrimidineamine gave N4-[3-(2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl)phenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 100%; MS (m/e): 546 (MH^+).
7.3.764	5-Fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-N4-[4-trifluoromethoxyphenyl]-2,4-pyrimidinediamine (R926879)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-trifluoromethoxyphenyl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[4-trifluoromethoxyphenyl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 10.05 (bs, 1H), 9.74 (bd, 1H, J= 1.5 Hz), 8.22 (d, 1H, J= 4.2 Hz), 7.99 (bd, 1H, J= 4.5 Hz), 7.86 (m, 2H), 7.32 (d, 2H, J= 8.1 Hz), 7.26 (s, 1H), 7.16 (m, 2H), 6.58 (m, 1H), 4.36 (s, 2H), 2.65 (bd, 3H); LCMS: purity: 92%; MS (m/e): 452 (MH^+).
7.3.765	5-Fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-N4-[4-trifluoromethylphenyl]-2,4-pyrimidinediamine (R926880)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(4-trifluoromethylphenyl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[4-trifluoromethylphenyl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 10.10 (bs, 1H), 9.72 (d, 1H, J= 1.2 Hz), 8.26 (d, 1H, J= 4.2 Hz), 8.00 (m, 3H), 7.65 (d, 2H, J= 8.1 Hz), 7.31 (bs, 1H), 7.17 (d, 2H, J= 5.4 Hz), 6.59 (m, 1H), 4.36 (s, 2H), 2.62 (d, 3H, J= 4.8 Hz); LCMS: purity: 92%; MS (m/e): 436 (MH^+).
7.3.766	N4-(4-Chloro-3-trifluoromethylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R926881)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-chloro-3-trifluoromethylphenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chloro-3-trifluoromethylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 10.20 (bs, 1H), 9.81 (bs, 1H), 8.28 (d, 1H, J= 3.9 Hz), 8.23 (bdd, 1H, J= 8.7 Hz), 8.11 (d, 1H, J= 2.4 Hz), 7.98 (bd, 1H, J= 4.5 Hz), 7.65 (d, 1H, J= 8.7 Hz), 7.17 (m, 3H), 6.59 (m, 1H), 4.35 (s, 2H), 2.63 (d, 3H, J= 4.2 Hz); LCMS: purity: 87%; MS (m/e): 470 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.767	5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-N4-(quinolin-6-yl)-2,4-pyrimidinediamine (R926883)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of 3 N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(quinolin-6-yl)-4-pyrimidineamine gave 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-N4-(quinolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.17 (bs, 1H), 9.83 (s, 1H), 8.24 (d, 1H, J= 4.8 Hz), 8.17 (m, 1H), 7.94 (m, 2H), 7.86 (m, 1H), 7.39 (d, 1H, J= 9.3 Hz), 7.25 (s, 1H), 7.16 (m, 2H), 6.60 (m, 1H), 6.50 (d, 1H, J= 9.6 Hz), 4.32 (s, 2H), 2.60 (d, 3H, J= 3.6 Hz); LCMS: purity: 98%; MS 9m/e): 436 (MH^+).
7.3.768	5-Fluoro-N4-(2-methoxypyridin-5-yl)-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R926886)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro-N4-(2-methoxypyridin-5-yl)-4-pyrimidineamine gave 5-fluoro-N4-(2-methoxypyridin-5-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.36 (bs, 1H), 9.19 (s, 1H), 8.59 (d, 1H, J= 3 Hz), 8.05 (m, 3H), 7.38 (m, 1H), 7.24 (bd, 1H, J= 8.1 Hz), 7.08 (t, 1H, J= 8.4 Hz), 6.79 (d, 1H, J= 8.7 Hz), 6.46 (dd, 1H, J= 2.4 and 7.8 Hz), 4.34 (s, 2H), 3.82 (s, 3H), 2.63 (d, 3H, J= 4.5 Hz); LCMS: purity: 95%; MS (m/e): 399 (MH^+).
7.3.769	5-Fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R927023)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-5-fluoro- N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-4-pyrimidineamine gave 5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl] -2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.65 (bs, 1H), 9.45 (bs, 1H), 8.55 (s, 1H), 8.12 (d, 1H, J= 3.6 Hz), 7.99 (m, 2H), 7.28 (m, 1H), 7.19 (m, 2H), 7.11 (t, 1H, J= 8.4 Hz), 6.81 (d, 1H, J= 8.7 Hz), 6.52 (m, 2H), 4.35 (s, 2H), 4.23 (t, 2H, J= 5.1 Hz), 3.69 (t, 2H, J= 4.5 Hz), 2.63 (d, 3H, J= 2.7 Hz); LCMS: purity: 95%; MS (m/e): 429 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.770	N4-(2,6-Dimethoxypyridin-3-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R920404)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(2,6-dimethoxypyridin-3-yl]-5-fluoro-4-pyrimidineamine gave N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.05 (d, 1H, J= 1.8 Hz), 8.62 (s, 1H), 8.01 (d, 1H, J= 3.6 Hz), 7.91 (bd, 1H, J= 4.8 Hz), 7.77 (m, 1H), 7.18 (m, 2H), 6.96 (t, 1H, J= 8.1 Hz), 6.40 (d, 2H, J= 8.1 Hz), 4.29 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.63 (d, 3H, J= 4.5 Hz); LCMS: purity: 86%; MS (m/e): 429 (MH^+).
7.3.771	N4-(4-Chloro-3-methoxyphenyl))-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R927042)	In like manner to preparation of N4-(3,4-difluorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine the reaction of N-methyl 3-aminophenoxyacetamide with 2-chloro-N4-(4-chloro-3-methoxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.89 (bs, 1H), 9.66 (bs, 1H), 8.20 (d, 1H, J= 4.2 Hz), 7.95 (bd, 1H), 7.48 (m, 2H), 7.33 (d, 1H, J= 9.1 Hz), 7.26 (bs, 1H), 7.17 (m, 2H), 6.57 (bd, 1H, J= 7.8 Hz), 4.34 (s, 2H), 3 72 (s, 3H), 2.62 (d, 3H); LCMS: purity: 97%; MS (m/e): 432 (MH^+).
7.3.772	N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R920411)	A solution of 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine (1.1 equivalents) and 3-hydroxyaniline (1 equivalent) in a sealed tube was heated at 100 °C for 24 hours. The resulting solution was diluted with EtOAc and the solid obtained was filtered, washed with a mixture of EtOAc:n-hexanes (1:1; v/v), dried and analyzed to give N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 8.02 (d, 1H, J= 5.1 Hz), 7.98 (d, 1H, J= 3.0 Hz), 7.72 (dd, 1H, J= 3.0 and 9.3 Hz), 7.42 (dd, 1H, J= 1.2 and 9.0 Hz), 7.22 (t, 1H, J= 8.4 Hz), 6.85 (m, 2H), 6.73 (dd, 1H, J= 2.4 and 8.7 Hz); ^{19}F NMR (CD_3OD): - 16967 and - 46027; LCMS: purity: 97%; MS (m/e): 415 (MH^+).
7.3.773	5-Fluoro-N2-(3-hydroxyphenyl)-N4-[3-(3-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926866)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-5-fluoro-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-4-pyrimidineamine gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.72 (bs, 1H), 7.96 (bd, 3H), 7.85 (m, 2H), 7.56 (m, 4H), 7.14 (d, 1H, J= 2.1 Hz), 6.91 (m, 2H), 6.28 (dd, 1H, J= 1.8 and 6.9 Hz); LCMS: purity: 80%; MS (m/e): 441 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.774	N4-(3,4-Difluoromethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926794)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. LCMS: purity: 85%; MS (m/e): 377 (MH^+).
7.3.775	5-Fluoro-N2-(3-hydroxyphenyl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R926885)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-5-fluoro-N4-(3-trifluoromethoxyphenyl)-4-pyrimidineamine gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 9.99 (bs, 1H), 9.61 (bs, 1H), 8.21 (d, 1H, J= 4.2 Hz), 7.93 (bd, 1H, J= 7.5 Hz), 7.78 (s, 1H), 7.43 (t, 1H, J= 8.4 Hz), 7.03 (m, 4H), 6.43 (m, 1H); ^{19}F NMR (DMSO-d6): -16097; LCMS: purity· 85%; MS (m/e): 381 (MH^+).
7.3.776	N4-(2,6-Dimethoxypyridin-3-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926887)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-4-pyrimidineamine gave N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 9.98 (bs, 2H), 8.20 (d, 1H, J= 5.4 Hz), 7.72 9m, 1H), 6.90 (t, 1H, J= 7.8 Hz), 6.81 (m, 2H), 6.42 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H); LCMS: purity: 94%; MS (m/e): 358 (MH^+).
7.3.777	5-Fluoro-N2-(3-hydroxyphenyl)-N4-(5-methylpyridin-2-yl)-2,4-pyrimidinediamine (R927017)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-5-fluoro-N4-(5-methylpyridin-2-yl)-4-pyrimidineamine gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-(5-methylpyridin-2-yl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6)· δ 11.39 (bs, 1H), 10.59 (bs, 1H), 8.58 (s, 1H0, 8.41 (d, 1H, J= 3 Hz), 8.12 (d, 1H, J= 8.7 Hz), 7.82 (d, 1H, J= 8.7 Hz), 7.29 (s, 1H), 7.16 (d, 1H, J= 9 Hz), 7.05 (t, 1H, J= 8.4 Hz), 6.38 (dd, 1H, 1.2 and 6.9 Hz); LCMS: purity: 99%; MS (m/e): 312 (MH^+).
7.3.778	N4-(6-Chloropyridin-3-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R927018)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-N4-(6-chloropyridin-3-yl)-5-fluoro-4-pyrimidineamine gave N4-(6-chloropyridin-3-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 10.10 (bs, 1H), 9.64 (bs, 1H), 8.85 (m, 1H), 8.30 (m, 2H), 8.22 (d, 1H, J= 4.2 Hz), 7.43 (d, 1H, J= 8.7 Hz), 7.01 (m, 3H), 6.42 (bd, 1H, J= 8.4 Hz); LCMS: purity: 93%; MS (m/e): 332 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.779	5-Fluoro-N2-(3-hydroxyphenyl)-N4-(quinolin-6-yl)-2,4-pyrimidinediamine (R927019)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-5-fluoro-N4-(quinolin-6-yl)-4-pyrimidineamine gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-(quinolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.50 (s, 1H), 10.14 (s, 1H), 8.29 (d, 1H, J= 4.8 Hz), 8.14 (d, 1H, J= 1.8 Hz), 7.96 (d, 1H, J= 9.3 Hz), 7.83 (dd, 1H, J= 2.4 and 9.0 Hz), 7.40 (d, 1H, J= 8.7 Hz), 7.04 (t, 1H, J= 8.1 Hz), 6.93 (m, 2H), 6.52 (m, 2H); LCMS: purity: 93%; MS (m/e): 365 (MH^+).
7.3.780	N4-(5-Chloropyridin-2-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R927020)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-N4-(5-chloropyridin-2-yl)-5-fluoro-4-pyrimidineamine gave N4-(5-chloropyridin-2-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.80 (bs, 1H), 9.77 (bs, 1H), 8.45 (bd, 1H), 8.26 (d, 1H, J= 3.9 Hz), 8.15 (d, 1H, J= 8.7 Hz), 7.85 (dd, 1H, J= 2.4 and 8.7 Hz), 7.06 (m, 3H), 6.43 (bd, 1H, J= 7.2 Hz); LCMS: purity: 97%; MS (m/e): 332 (MH^+).
7.3.781	N4-(4-Chloro-2,5-dimethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-primidinediamine (R926860)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 3-hydroxyaniline with 2-chloro-N4-(4-chloro-2,5-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chloro-2,5-dimethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-primidinediamine. ^{1}H NMR (CD_3OD): δ 7.96 (d, 1H, J= 4.8 Hz), 7.66 (s, 1H), 7.13 (s, 1H), 7.07 (t, 1H, J= 8.7 Hz), 8.86 (m, 2H), 6.57 (dd, 1H, J= 3.2 and 8.1 Hz), 3.48 (s, 3H), 3.66 (s, 3H); ^{19}F NMR (CD_3OD): - 46968.
7.3.782	N4-(4-Chlorophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine (R927026)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 5-amino-2-methoxycarbonylbenzofuran with 2-chloro-N4-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(4-chlorophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.28 (bs, 1H), 10.18 (bs, 1H), 8.25 (d, 1H, J= 4.5 Hz), 7.96 (bs, 1H), 7.84 (m, 1H), 7.67 (m, 3H), 7.57 (m, 1H), 7.37 (bd, 2H, J= 9.0 Hz), 3.88 (s, 3H); LCMS: purity: 96%; MS (m/e): 413 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.783	N4-(3,4-Dichlorophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine (R927027)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 5-amino-2-methoxycarbonylbenzofuran with 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine gave N4-(3,4-dichlorophenyl)-5-fluoro-N2-(2-methoxycarbonylbenzofuran-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.70 (bs, 1H), 9.50 (bs, 1H), 8.20 (d, 1H, J= 4.5 Hz), 8.09 (m, 1H), 7.80 (m, 3H), 7.62 (m, 2H), 7.53 (m, 1H), 7.38 (m, 1H), 3.88 (s, 3H); LCMS: purity: 94%; MS (m/e): 448 (MH^+).
7.3.784	5-Fluoro-N4-(3-hydroxyphenyl)-N2-(3-methoxycarbonyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926863)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-methoxycarbonyl-5-trifluoromethylaniline gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-methoxycarbonyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.98 (s, 1H), 9.52 (s, 1H), 8.53 (s, 1H), 8.38 (s, 1H), 8.20 (d, 1H, J= 4.2 Hz), 7.69 (s, 1H), 7.27 (d, 1H, J= 8.1 Hz), 7.14 (s, 1H), 7.05 (t, 1H, 7.8 Hz), 6.49 (dd, 1H, J= 1.8 and 8.4 Hz), 3.80 (s, 3H); LCMS: purity: 82%; MS (m/e): 423 (MH^+).
7.3.785	N2-(4-Chloro-2,5-dimethoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926857)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 4-chloro-2,5-dimethoxyaniline gave N2-(4-chloro-2,5-dimethoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.04 (d, 1H, J= 5.4 Hz), 7.46 (s, 1H), 7.17 (m, 2H), 7.03 (m, 2H), 6.72 (dd, 1H, J= 1.8 and 7.8 Hz), 3.85 (s, 3H), 3.52 (s, 3H); LCMS: purity: 98%; MS (m/e): 390 (MH^+).
7.3.786	N2-(3-Bromo-5-trifluorophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926846)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-bromo-5-trifluoromethylaniline gave N2-(3-bromo-5-trifluorophenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.70 (s, 1H), 9.36 (s, 1H), 9.34 (s, 1H), 8.31 (s, 1H), 8.18 (d, 1H, J= 3.6 Hz), 8 02 (s, 1H), 7.35 (s, 1H), 7.28 (bd, 1H, J= 7.2 Hz), 7.11 (t, 1H, J= 8.4 Hz), 7.02 (m, 1H), 6.49 (dd, 1H, J= 1.8 and 7.8 Hz); LCMS: purity: 94%; MS (m/e): 442 (MH^+).
7.3.787	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(1H-pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine (R926841)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-(1H-pyrazol-3-yl)aniline gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(1H-pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine. LCMS: purity: 84%; MS 363 (MH^+)

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Section Number	Name of compound and reference number	Experimental
7.3.788	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926842)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-(tetrazol-5-yl)aniline gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.05 (bs, 1H), 9.80 (bs, 1H), 8.27 (s, 1H), 8.23 (d, 1H, J= 3.3 Hz), 7.86 (d, 1H, J= 8.1 Hz) 7.65 (d, 1H, J= 6.9 Hz), 7.44 (t, 1H, J= 7.5 Hz), 7.19 (m, 2H), 6.93 (t, 1H, J= 7.5 Hz), 6.49 (dd, 1H, J= 2.4 and 8.1 Hz); LCMS: purity: 89%; MS (m/e): 364 (MH^+).
7.3.789	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(1,3-oxazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926831)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-(1,3-oxazol-5-yl)aniline gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-(1,3-oxazol-5-yl)phenyl]-2,4-pyrimidinediamine. LCMS: purity: 76%; MS (m/e): 364 (MH^+).
7.3.790	N2-(3-Chloro-4-trifluoromethylphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinedimine (R926844)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-chloro-4-trifluoromethoxyaniline gave N2-(3-chloro-4-trifluoromethylphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinedimine. ^{1}H NMR (DMSO-d6): δ 9.70 (bs, 1H), 9.48 (bs, 1H), 8.15 (bd, 1H, J= 3.6 Hz), 8.06 (s, 1H), 7.62 (dd, 1H, J= 2.4 and 9.3 Hz), 7.37 (d, 1H, J= 9.0 Hz), 7.20 9m, 1H), 7.11 (m, 3H), 6.53 (bd, 1H, J= 8 1 Hz); LCMS: purity: 93%; MS (m/e): 414 (MH^+).
7.3.791	5-Fluoro-N4-(3,4-ethylenedioxyphenyl)-N2-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine (R926843)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine with 3-(tetrazol-5-yl)aniline gave 5-fluoro-N4-(3,4-ethylenedioxyphenyl)-N2-[3-(tetrazol-5-yl)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.91 (s, 1H), 9.74 (s, 1H), 8.29 (s, 1H), 8.18 (d, 1H, J= 4.5 Hz), 7.76 (bdd, 1H, J= 1.5 and 8.1 Hz), 7.64 (d, 1H, J= 8.1 Hz), 7.46 (t, 1H, J= 8.1 Hz), 7.29 (m, 1H), 7.13 (dd, 1H, J= 2.4 and 8.7 Hz), 6.64 (d, 1H, J= 8.7 Hz), 4.11 (m, 4H); LCMS: purity: 91%; MS (m/e): 407 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.792	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(4-methoxy-2-methylphenyl)-2,4-pyrimidinediamine (R926845)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine with 4-methoxy-2-methylaniline gave N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(4-methoxy-2-methylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.30 (bs, 1H), 9.10 (bs, 1H), 8.22 (d, 1H, J= 5.1 Hz), 7.55 (m, 1H), 7.15 (m, 1H), 7.07 (m, 1H), 6.92 (m, 2H), 6.82 (d, 1H, J= 8.7 Hz), 4.22 (bs, 4H), 3.80 (s, 3H), 2.15 (s, 3H); LCMS: purity: 94%; MS (m/e): 383 (MH^+).
7.3.793	N2-[5-(N-Aminocarbonylmethylene-2-oxo-1,3-oxazol-3(2H)-yl)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrmidinediamine (R926847)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine with 2-[5-amino-2-oxo-1,3-benzoxazol-3(2H)-yl)acetamide gave N2-[5-(N-aminocarbonylmethylene-2-oxo-1,3-oxazol-3(2H)-yl)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrmidinediamine. ^{1}H NMR (CD_3OD): δ 7.95 (d, 1H, J= 8.4 Hz), 7.32 (dd, 1H, J= 2.4 and 8.1 Hz), 7.24 (d, 1H, J= 2.4 Hz), 7.19 (m, 2H), 6.95 (dd, 1H, J= 2.7 and 9 Hz), 6.80 (d, 1H, J= 9 Hz), 4.51 (s, 2H), 4.21 (m, 4H).
7.3.794	N2-[3-(2-Ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)phenyl-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926874)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine with 3-(2-ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)aniline gave N2-[3-(2-ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)phenyl-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.52 (s, 1H), 9.31 (s, 1H), 9.28 (s, 1H), 8.30 (s, 1H), 8.12 (d, 1H, J= 3.6 Hz), 8.00 (m, 1H), 7.49 (d, 1H, J= 7.5 Hz), 7.42 (d, 1H, J= 8.4 Hz), 7.30 (m, 1H), 7.12 (bs, 1H), 7.03 (t, 1H, J= 8.1 Hz), 6.46 (m, 1H), 4.21 (s, 2H), 4.15 (q, 2H, J= 6.9 Hz), 1.19 (t, 3H, J= 7.2 Hz); LCMS: purity: 90%; MS (m/e): 451 (MH^+).
7.3.795	N2,N4-Bis(3-boronylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926836)	A mixture of 2,4-dichloro-5-fluoro-pyrimidine (1 equivalents) and 3-aminophenylboronic acid (3 equivalents) in MeOH was heated in a sealed tube at 100 °C for 24 hours. The resulting mixture was cooled to room temperature, acidified with 2N HCl and the solid obtained was filtered, washed with water, dried and analyzed to give N2,N4-sis(3-boronylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.40 (s, 1H), 10.07 (s, 1H), 8.25 (d, 8.4 Hz), 7.85 (s, 1H), 7.73 (d, 1H, J= 7.5 Hz), 7.63 (bt, 3H), 7.48 (d, 1H, J= 6.9 Hz), 7.30 (t, 1H, J= 8.4 Hz), 7.12 (t, 1H, J= 2.5 Hz); LCMS: purity: 85%; MS (m/e): 368 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.796.	N2-(3-Boronylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926837)	In like manner to the preparation of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidineamine, the reaction of 2-chloro-5-fluoro-N4-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine with 3-aminophenylboronic acid gave N2-(3-boronylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 99%; MS (m/e): 383 (MH^+).
7.3.797	(±)-N4-(3,4-Difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine (R927030)	A mixture of equivalent amount of 2-chloro-N4-(3,4-difluorophenyl)-5-fluoro-4-pyrimidineamine and (±)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran in MeOH was shaken in a sealed tube at 80 °C for 48 h, cooled to room temperature and diluted with a mixture of n-hexanes:EtOAc (1:1; v/v). The resulting solid formed was filtered, washed with a mixture of EtOAc:n-hexanes (1:1; v/v), dried and analyzed to give (±)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.21 (bs, 1H), 9.80 (bs, 1H), 8.20 (d, 1H, J= 4.8 Hz), 7.94 (bs, 1H), 7.43 (m, 3H0, 7.15 (bd, 1H, J= 8.4 Hz), 6.81 (d, 1H, J= 8.1 Hz), 5.35 (dd, 1H, J= 6.0 and 6.3 Hz), 3 69 (s, 3H), 3.52 (dd, 1H, J= 10.5), 3.22 (dd, 1H, J= 9.0 and 6.0 Hz); LCMS: purity: 99%; MS (m/e): 417 (MH^+).
7.3.798	(±)-N4-(4-Chlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine (R927024)	In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (±)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-N4-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine gave (±)-N4-(4-chlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.29 (bs, 1H), 9.89 (bs, 1H), 8.21 (d, 1H, J= 4.8 Hz), 7.69 (m, 2H), 7.38 (m, 3H), 7.13 (bd, 1H, J= 8.1 Hz), 6.83 (d, 1H, J= 8.4 Hz), 5.36 (dd, 1H, J= 6.3 and 5.7 Hz), 3.70 (s, 3H), 3.52 (dd, 1H, J= 10.5 Hz), 3.20 (dd, 1H, J= 5.4 and 5.7 Hz); LCMS: purity: 98%; MS (m/e): 415 (MH^+).
7.3.799	(±)-N4-(3,4-Dichlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine (R927031)	In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (±)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine gave (±)-N4-(3,4-dichlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.13 (bs, 1H), 9.70 (bs, 1H), 8.21 (d, 1H, J= 4.8 Hz), 8.04 (d, 1H, J= 2.4 Hz), 7.68 (m, 1H), 7.54 (d, 1H, J= 9.0 Hz), 7.37 (bs, 1H), 7.19 (m, 1H), 6.80 (d, 1H, J= 8.7 Hz), 5.35 (dd, 1H, J= 6.6 Hz), 3.69 (s, 3H), 3.53 (dd, 1H, J= 10.5 and 11.1 Hz), 3.21 (dd, 1H, J= 6.0 Hz); LCMS: purity: 100%; MS (m/e): 450 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.800	(±)-N2-(2,3-Dihydro-2-methoxycarbonylbenzofuran-5-yl)-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-2,4-pyrimidinediamine (R927032)	In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (±)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-4-pyrimidineamine gave (±)--N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.03 (bs, 2H), 8.18 (d, 1H, J= 4.8 Hz), 7.68 (bd, 1H, J= 8.1 Hz), 7.27 (bs, 1H), 6.98 (bd, 1H, J= 8.1 Hz), 6.69 (d, 1H, J= 8.7 Hz), 6.44 (d, 1H, J= 8.1 Hz), 5.33 (dd, 1H, J= 5.7 Hz), 3.88 (s, 3H), 3.86 (s, 3H), 3.69 (s, 3H), 3.42 (dd, 1H, J= 10.8 and 11.1 Hz), 3.10 (dd, 1H, J= 6.3 and 6.6 Hz); LCMS: purity: 99%; MS (m/e): 442 (MH^+).
7.3.801	(±)-N2-(2,3-Dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927025)	In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (±)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-4-pyrimidineamine gave (±)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.10 (bs, 1H), 9.70 (bs, 1H), 8.46 (m, 1H), 8.13 (d, 1H, J= 4.8 Hz), 7.92 (m, 1H), 7.41 (bs, 1H), 7.12 (bdd, 1H, J= 8.4 Hz), 6.79 (m, 2H), 5.35 (dd, 1H, J= 5.7 and 6.0 Hz), 4.24 (t, 2H, J= 5.1 Hz), 3.70 (s, 3H), 3.69 (t, 2H, J= 5.1 Hz), 3.52 (dd, 1H, J= 11.1 Hz), 3.24 (dd, 1H, J= 6.6 Hz); LCMS: purity: 92%; MS (m/e): 442 (MH^+).
7.3.802	(±)-N2-(2,3-Dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-(3-trifluorophenyl)-2,4-pyrimidinediamine (R927028)	In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (±)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-5-fluoro-N4-(3-trifluorophenyl)-4-pyrimidineamine gave (±)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-(3-trifluorophenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.32 (bs, 1H), 9.90 (bs, 1H), 8.23 (d, 1H, J= 4.8 Hz), 7.80 (bd, 1H, J= 6.9 Hz), 7.73 (bs, 1H), 7.43 (t, 1H, J= 8.1 Hz), 7.36 (bs, 1H), 7.16 (m, 2H), 6.79 (d, 1H, J= 8.1 Hz), 5.33 (dd, 1H, J= 6.0 and 6.6 Hz), 3.69 (s, 3H), 3.51 (dd, 1H, J= 10.5 Hz), 3.20 (dd, 1H, J= 6.0 Hz); LCMS: purity: 98%; MS (m/e): 465 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.803	(±)-N2-(2,3-Dihydro-2-methoxycarbonylbenzofuran-5-yl)-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927029)	In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, the reaction of (±)-5-amino-2,3-dihydro-2-methoxycarbonylbenzofuran with 2-chloro-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine gave (±)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.36 (bs, 1H), 9.93 (bs, 1H), 8.22 (d, 1H, J= 4.8 Hz), 7.91 (bs, 1H), 7.38 (m, 3H), 7.15 9bd, 1H, J= 8.7 Hz), 6.79 (d, 1H, J= 6.0 Hz), 5.33 (dd, 1H, J= 6.3 and 6.6 Hz), 3.69 (s, 3H), 3.50 (dd, 1H, J= 10.5 and 10.8 Hz), 3 22 (dd, 1H, J= 6.0 Hz); LCMS: purity: 100%; MS (m/e): 461 (MH^+).
7.3.804	(±)-N4-(3,4-Difluorophenyl)-5-fluoro-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine (R927035)	A mixture of (±)-N4-(3,4-difluorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine, methylamine Hydrogen Chloride (5 equivalents) and diisopropylethylamine (5 equivalents) in MeOH was shaken in a sealed tube at 80 °C for 24 h. The resulting solution was diluted with water and the precipitate obtained was filtered, washed with water, dried and analyzed to afford (±)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.46 (s, 1H), 9.07 (s, 1H), 8.05 (m, 3H), 7.48 (m, 2H), 7.35 (m, 1H), 7.22 (m, 1H), 6.72 (d, 1H, J= 8.1 Hz), 5.07 (dd, 1H, J= 6.6 and 6.3 Hz), 3.40 (dd, 1H), 3.15 (dd, 1H), 2.60 (d, 3H, J= 4.5 Hz); LCMS: purity: 98%; MS (m/e): 416 (MH^+).
7.3.805	(±)-N4-(4-Chlorophenyl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927036)	In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (±)-N4-(4-chlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine gave (±)-N4-(4-chlorophenyl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.40 (s, 1H), 9.02 (s, 1H), 8.05 (m, 2H), 7.84 (dd, 2H, J= 2.7 and 9.3 Hz), 7.51 (bs, 1H), 7.32 (bd, 2H, J= 8.7 Hz), 7.23 (bd, 1H, J= 8.7 Hz), 6.72 (d, 1H, J= 8.7 Hz), 5.07 (dd, 1H, J= 6.0 and 6.3 Hz), 3.39 (dd, 1H), 3.17 (dd, 1H), 2.60 (d, 3H, J= 4.8 Hz); LCMS: purity: 99%; MS (m/e): 414 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.806	(±)-N4-(3,4-Dichlorophenyl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927037)	In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (±)-N4-(3,4-dichlorophenyl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine gave (±)-N4-(3,4-dichlorophenyl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine . ^{1}H NMR (DMSO-d6): δ 9.52 (s, 1H), 9.09 (s, 1H), 8.08 (m, 3H), 7.76 (bd, 1H, J= 9.3 Hz), 7.50 (d, 1H, J= 9.0 Hz), 7.43 (bs, 1H), 7.24 (bd, 1H, J= 8.7 Hz), 6.73 (d, 1H, J= 8.1 Hz), 5.07 (dd, 1H, J= 6.3 and 6.6 Hz), 3 39 (dd, 1H, J= 10.5 Hz), 3.15 (dd, 1H, J= 6.3 Hz), 2.60 (d, 3H, J= 4.8 Hz); LCMS: purity: 99%; MS (m/e): 450 (MH^+).
7.3.807	(±)-N4-(2,6-Dimethoxypyridin-3-yl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927038)	In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (±)-N4-(2,6-dimethoxypyridin-3-yl)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediamine gave (+)-N4-(2,6-dimethoxypyridin-3-yl)-N2-[2,3-dihydro-2-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.98 (d, 1H, J= 8.1 Hz), 7.81 (d, 1H, J= 3.6 Hz), 7.39 (bd, 1H, J= 2.4 Hz), 7.06 (dd, 1H, J= 2.4 and 8.7 Hz), 6.72 (d, 1H, J= 8.1 Hz), 6.31 (d, 1H, J= 8.7 Hz), 5.07 (dd, 1H, J= 6.3 Hz), 3.96 (s, 3H), 3.93 (s, 3H), 3.46 (dd, 1H, J= 7.8 and 10.5 Hz), 3.19 (dd, 1H, J= 5.7 and 6.3 Hz), 2.77 (d, 3H, J= 4.8 Hz); LCMS: purity: 98%; MS (m/e): 441 (MH^+).
7.3.808	(±)-N2-[2,3-Dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-2,4-pyrimidinediamine (R927039)	In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (±)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-2,4-pyrimidinediamine gave (±)-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.26 (s, 1H), 8.99 (s, 1H), 8.50 (bd, 1H, J= 3.0 Hz), 8.02 (bd, 2H, J= 3.6 Hz), 7.94 (dd, 2H, J= 2.7 and 5.1 Hz), 7.52 (bs, 1H), 7.20 (bd, 1H, J= 8.7 Hz), 6.78 (d, 1H, J= 8.7 Hz), 6.67 (d, 1H, J= 8.7 Hz), 5.05 (dd, 1H, J= 6.3 and 6.6 Hz), 4.80 (t, 1H), 4.23 (t, 2H, J= 5.1 Hz), 3.69(q, 2H, J= 5.4 Hz), 3.40 (dd, 1H), 3.15 (dd, 1H, J= 6.3 and 9.9 Hz), 2.60 (d, 3H, J= 4.5 Hz); LCMS: purity: 86%; MS (m/e): 441 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.809	(±)-N2-[2,3-Dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R927040)	In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (±)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine gave (±)-N2-[2,3-dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. LCMS: purity: 94%; MS (m/e): 464 (MH^+).
7.3.810	(±)-N2-[2,3-Dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-N4-(3,4-difluoromethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927041)	In like manner to the preparation of (±)-N4-(3,4-difluorophenyl)-5-fluoro-N2-[2-(N-methylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine, the reaction of methyl amine Hydrogen Chloride with (±)-N2-(2,3-dihydro-2-methoxycarbonylbenzofuran-5-yl)-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine gave (±)-N2-[2,3-dihydro-(N-methylamino)carbonylbenzofuran-5-yl]-N4-(3,4-difluoromethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. 1H NMR (DMSO-d6): d 9.46 (s, 1H), 9.05 (s, 1H), 8.05 (m, 3H), 7.43 (m, 2H), 7.31 (d, 1H, J= 8.7 Hz), 7.23 (bd, 1H, J= 7.5 Hz), 6.70 (d, 1H, J= 9.0 Hz), 5.04 (dd, 1H, J= 6.6 Hz), 3.40 (dd, 1H), 3.14 (dd, 1H, J= 5.7 and 6.6 Hz), 2.60 (d, 3H, J= 3.9 Hz); LCMS: purity: 94%; MS (m/e): 460 (MH^+).
7.3.811	N2-(4-Carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926238)	The reaction of N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine with LiOH in THF:H_2O at room temperature gave N2-(carboxymethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 8.16 (d, 1H, J= 4.8 Hz), 7.37 (bd, 2H, J= 9 Hz), 7.25 9d, 1H, J= 3Hz), 7.08 (m, 1H), 6.83 (m, 3H), 4.64 (s, 2H), 4.23 (s, 4H); LCMS: ret. time: 19.15 min.; purity: 100%; MS (m/e): 413 (MH^+).
7.3.812	N4-(1,4-Benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt (R920395)	To a solution of N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (1 equivalent) in MeOH at 0 °C was added HCl (4M, dioxane, 1.1 equivalents) dropwise and shaken for 5 minutes. The resulting solution was diluted with EtOAc and the solid obtained was filtered washed with EtOAc, dried and analyzed to give N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt. ^1H NMR (DMSO-d6): δ 9.80 (bs, 2H), 8.12 (d, 1H, J= 4.8 Hz), 7.89 (bd, 1H, J= 4.5 Hz), 7.18 (m, 3H), 8.24 (m, 2H), 6.60 (bd, 2H, J= 8.1 Hz), 4.36 (s, 2H), 4.10 (t, 2H, J= 3.9 Hz), 3.27 (t, 2H, J= 3.9 Hz), 2.62 (d, 3H, J= 4.5 Hz); LCMS: purity: 98%, MS (m/e): 425 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.813	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Trifluoro Acetic Acid Salt (R926826)	In like manner to the synthesis of N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Hydrogen Chloride Salt the reaction of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine with trifluoroacetic acid gave N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine Trifluoro Acetic Acid Salt. ^{1}H NMR (DMSO-d6): δ 9.40 (bs, 1H), 9.36 (bs, 1H), 8.07 (d, 1H, J= 4.2 Hz), 7.94 (bd, 1H), 7.22 (m, 4H), 7.11 (t, 1H, J= 7.5 Hz), 6.79 (d, 1H, J= 8.7 Hz), 6.51 (bd, 1H, J= 7.5 Hz), 4.33 (s, 2H), 4.21 (bs, 4H), 2.63 (d, 3H, 3.3 Hz).
7.3.814	5-Fluoro-N4-[(1H)-indol-6-yl]-N2-[4-methoxy-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926752)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 4-methoxy-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce 5-fluoro-N4-[(1H)-indol-6-yl]-N2-[4-methoxy-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.83 (d, 1H, J= 3.6 Hz), 7.73 (d, 1H, J= 0.9 Hz), 7.49 (d, 1H, J= 8.1 Hz), 7.39 (d, 1H, J= 3.0 Hz), 7.20 (d, 1H, J= 3.6 Hz), 7.15 (dd, 1H, J= 1.8 and 8.1 Hz), 7.05 (dd, 1H, J=2.1 and 8.7 Hz), 6.81 (d, 1H, J= 8.7 Hz), 6.41 (d, 1H, J= 4.2 Hz), 4.09 (s, 2H), 3.81 (s, 3H), 2.76 (s, 3H); LCMS: purity: 100%; MS (m/e): 437(MH^+).
7.3.815	5-Fluoro-N4-(3-hydroxy-4-methylphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926753)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(2-hydroxy-4-methylphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy] aniline were reacted to produce 5-fluoro-N4-(3-hydroxy-4-methylphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.95 (bs, 1H), 9.83 (bs, 1H), 9.38 (bs, 1H), 8.17 (d, 1H, J= 4.4 Hz), 7.97 (d, 1H, J= 4.8 Hz), 7.24-7.17 (m, 2H), 7.16 (d, 1H, J= 8.4 Hz), 7.10 (dd, 1H, J=1.8 and 8.4 Hz), 7.03 (d, 1H, J= 2.4 Hz), 7.00 (d, 1H, J= 9.0 Hz), 6.61 (d, 1H, J= 8.7 Hz), 4.34 (s, 2H), 2.63 (d, 3H, J= 4.5 Hz), 2.08 (s, 3H); LCMS: purity: 96%; MS (m/e): 398(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.816	5-Fluoro-N4-(3-dihydroxyborylphenyl)- N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926754)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-dihydroxyborylphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce 5-fluoro-N4-(3-dihydroxyborylphenyl)- N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.38 (bs, 1H), 9.22 (bs, 1H), 8.08 (d, 1H, J= 3.6 Hz), 8.06-7.81 (m, 4H), 7.51 (d, 1H, J= 8.1 Hz), 7.33-7.28 (m, 3H), 7.06 (t, 1H, J= 8.1 Hz), 6.44 (dd, 1H, J= 2.4 and 7.5 Hz), 4.33 (s, 2H), 2.63 (d, 3H, J= 4.8 Hz); LCMS: purity: 95%; MS (m/e): 412(MH^+).
7.3.817	5-Fluoro-N4-(3-dihydroxyborylphenyl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926755)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-dihydroxyborylphenyl)-4-pyrimidineamine and 3-hydroxyaniline were reacted to produce 5-Fluoro-N4-(3-dihydroxyborylphenyl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.68 (bs, 1H), 9.35 (bs, 1H), 9.22 (bs, 1H), 8.10 (d, 1H, J= 3.9 Hz), 7.88-7.80 (m, 2H), 7.54 (d, 1H, J= 7.2 Hz), 7.31 (t, 1H, J= 7.2 Hz), 7.08 (d, 1H, J= 8.4 Hz), 6.98-6.93 (m, 2H), 6.35 (d, 1H, J= 8.4 Hz); LCMS: purity: 96%; MS (m/e): 341(MH^+).
7.3.818	N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-(3-hydroxyborylphenyl)-2,4-pyrimidinediamine (R926756)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-dihydroxyborylphenyl)-4-pyrimidineamine and 3,4-ethylenedioxyaniline were reacted to produce N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(3-hydroxyborylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.46 (bs, 1H), 9.11 (bs, 1H), 8.05 (d, 1H, J= 4.2 Hz), 7.95 (bs, 1H), 7.88 (s, 1H), 7.78 (d, 1H, J= 7.5 Hz), 7.52 (d, 1H, J= 7.5 Hz), 7.29 (t, 1H, J= 7.5 Hz), 7.16 (s, 1H), 7.02 (d, 1H, J= 8.7 Hz), 6.65 (d, 1H, J= 8.7 Hz), 3.40 (s, 4H); LCMS: purity: 98%; MS (m/e): 383(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.819	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926757)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.32 (s, 1H), 9.17 (s, 1H), 9.04 (s, 1H), 8.04 (d, 1H, J= 4.2 Hz), 7.76 (d, 1H, J= 4.8 Hz), 7.32 (td, 2H, J= 1.8 and 8.1 Hz), 7.13-7.04 (m, 3H), 6.95 (d, 1H, J= 8.4 Hz), 6.46 (dd, 1H, J= 1.8 and 8.4 Hz), 4.31 (s, 2H), 2.65 (d, 3H, J= 4.8 Hz), 2.14 (s, 3H); LCMS: purity: 99%; MS (m/e): 398(MH^+).
7.3.820	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro- N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926758)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce N4-(3,4-ethylenedioxyphenyl)-5-fluoro- N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.13 (bs, 1H), 9.05 (s, 1H), 8.01 (d, 1H, J= 4.2 Hz), 7.76 (d, 1H, J= 4.8 Hz), 7.32 (d, 1H, J= 2.4 Hz), 7.27 (dd, 1H, J= 2.4 and 8.1 Hz), 7.21 (dd, 1H, J= 2.4 and 8.7 Hz), 7.13 (d, 1H, J= 1.8 Hz), 6.95 (d, 1H, J= 8.1 Hz), 6.76 (d, 1H, J= 8.7 Hz), 4.28 (s, 2H), 4.20 (s, 4H), 2.65 (d, 3H, J= 4.8 Hz), 2.15 (s, 3H); LCMS: purity: 97%; MS (m/e): 440(MH^+).
7.3.821	5-Fluoro-N4-(3-hydroxy-4-methylphenyl)-N2-[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926759)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(2-hydroxy-4-methylphenyl)-4-pyrimidineamine and 4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce 5-fluoro-N4-(3-hydroxy-4-methylphenyl)-N2-[4-methyl-3-[(N-methylamino)carbonylmethylene oxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.09 (bs, 1H), 9.96 (bs, 1H), 9.44 (bs, 1H), 8.16 (d, 1H, J= 4.8 Hz), 7.81 (d, 1H, J= 4.8 Hz), 7.13-6.94 (m, 6H), 4.29 (s, 2H), 2.64 (d, 3H, J= 4.5 Hz), 2.17 (s, 3H), 2.07 (s, 3H); LCMS: purity: 99%; MS (m/e): 412(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.822	5-Fluoro-N2,N4-bis[4-methyl-3-[(N-methylamino) carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926760)	In a like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N2,N4-bis[4-methyl-3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.30 (s, 1H), 9.02 (s, 1H), 8.06 (d, 1H, J= 3.6 Hz), 7.94 (d, 1H, J= 4.5 Hz), 7.80 (d, 1H, J= 4.2 Hz), 7.58 (bs, 1H), 7.31-7.22 (m, 3H), 7.05 (d, 1H, J= 9.0 Hz), 6.97 (d, 1H, J= 7.5 Hz), 4.41 (s, 2H), 4.27 (s, 2H), 2.66 (d, 3H, J= 4.2 Hz), 2.63 (d, 3H, J= 4.2 Hz), 2.18 (s, 3H), 2.14 (s, 3H); LCMS: purity: 100%; MS (m/e): 483(MH$^+$).
7.3.823	5-Fluoro-N4-(3-hydroxyphenyl)-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (R926761)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3,4,5-trimethoxyaniline were reacted to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.33 (s, 1H), 9.17 (s, 1H), 8.99 (s, 1H), 8.06 (d, 1H, J= 3.3 Hz), 7.27 (d, 1H, J= 7.5 Hz), 7.08-7.02 (m, 4H), 6.46 (dd, 1H, J= 1.8 and 7.8 Hz), 3.60 (s, 6H), 3.57 (s, 3H); LCMS: purity: 99%; MS (m/e): 387(MH$^+$).
7.3.824	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (R926762)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3,4,5-trimethoxyaniline were reacted to produce N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine ^{1}H NMR (DMSO-d_6): δ 8.08 (d, 1H, J= 4.8 Hz), 7.29 (d, 1H, J= 2.4 Hz), 7.15 (dd, 1H, J=3.0 and 9.0 Hz), 6.91 (s, 1H), 6.76 (d, 1H, J= 8.7 Hz), 4.20 (s, 4H), 3.61 (s, 6H), 3.59 (s, 3H); LCMS: purity: 97%; MS (m/e): 429(MH$^+$).
7.3.825	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3,5-dichloro-4-hydroxyphenyl)-2,4-pyrimidinediamine (R926763)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3,5-dichloro-4-hydroxyaniline were reacted to produce N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3,5-dichloro-4-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.50 (bs, 1H), 9.26 (bd, 2H, J= 7.5 Hz), 8.06 (d, 1H, J= 3.9 Hz), 7.65 (s, 2H), 7.18-7.13 (m, 2H), 6.80 (d, 1H, J= 9.0 Hz), 4.20 (s, 4H); LCMS: purity: 100%; MS (m/e): 424(MH$^+$).

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Section Number	Name of compound and reference number	Experimental
7.3.826	5-Fluoro-N2-(3,5-dichloro-4-hydroxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926890)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3,5-dichloro-4-hydroxyaniline were reacted to produce 5-Fluoro-N2-(3,5-dichloro-4-hydroxyphenyl)-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.47 (bs, 1H), 9.35 (bs, 1H), 9.22 (bs, 2H), 8.09 (d, 1H, J= 3.6 Hz), 7.70 (s, 2H), 7.31 (dd, 1H, J= 1.2 and 9.3 Hz), 7.10 (t, 1H, J= 7.5 Hz), 7.00 (bs, 1H), 6.48 (dd, 1H, J= 1.2 and 6.9 Hz); LCMS: purity: 93%; MS (m/e): 382(MH^+).
7.3.827	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926891)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to produce N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.85 (bs, 1H), 9.70 (bs, 1H), 8.17 (d, 1H, J= 4.8 Hz), 7.98 (d, 1H, J= 3.9 Hz), 7.79 (d, 1H, J= 2.4 Hz), 7.65 (dd, 1H, J= 3.0 and 9.3 Hz), 7.24-7.09 (m, 4H), 6.57 (d, 1H, J= 5.7 Hz), 4.34 (s, 2H), 3.82 (s, 3H), 2.62 (d, 3H, J= 4.8 Hz); LCMS: purity: 95%; MS (m/e): 433(MH^+).
7.3.828	5-Fluoro-N4-(3-fluoro-4-methoxyphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926892)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-fluoro-4-methoxyphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethylene oxy]aniline were reacted to produce 5-fluoro-N4-(3-fluoro-4-methoxyphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.68 (bs, 1H), 9.53 (bs, 1H), 8.13 (d, 1H, J= 4.2 Hz), 7.97 (d, 1H, J= 4.8 Hz), 7.76 (dd, 1H, J= 2.4 and 13.5 Hz), 7.47 (d, 1H, J= 7.5 Hz), 7.27-7.08 (m, 4H), 6.54 (d, 1H, J= 8.4 Hz), 4.35 (s, 2H), 3.80 (s, 3H), 2.63 (d, 3H, J= 4.8 Hz); LCMS: purity: 94%; MS (m/e): 416(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.829	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-(3-hydroxy-5-methylphenyl)-2,4-pyrimidinediamine (R926893)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 4-amino-*m*-cresol hydrogenchloride salt, and diisopropylethylamine were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(3-hydroxy-5-methylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.06 (s, 1H), 8.94 (s, 1H), 8.11 (s, 1H), 7.86 (d, 1H, J= 3.9 Hz), 7.21-7.15 (m, 2H), 7.03 (d, 1H, J= 8.1 Hz), 6.59 (bd, 2H, J= 8.7 Hz), 6.52 (dd, 1H, J= 3.0 and 8.1 Hz), 4.17 (s, 4H), 2.05 (s, 3H); LCMS: purity: 99%; MS (m/e): 369(MH^+).
7.3.830	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3-fluoro-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926894)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-amino-5-fluorobenzotrifluoride were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-fluoro-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.75 (s, 1H), 9.32 (d, 1H, J= 1.2 Hz), 8.13 (d, 1H, J= 3.6 Hz), 7.99 (d, 1H, J= 12.3 Hz), 7.77 (s, 1H), 7.21 (d, 1H, J= 2.4 Hz), 7.13 (dd, 1H, J= 2.1 and 8.7 Hz), 7.03 (d, 1H, J= 9.0 Hz), 6.80 (d, 1H, J= 8.7 Hz), 4.21 (s, 4H); LCMS: purity: 97%; MS (m/e): 425(MH^+).
7.3.831	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3-methyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926895)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-amino-5-methylbenzotrifluoride were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-methyl-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.57 (bs, 1H), 9.39 (bs, 1H), 8.12 (d, 1H, J= 3.6 Hz), 7.77 (s, 2H), 7.25-7.13 (m, 2H), 7.02 (s, 1H), 6.79 (d, 1H, J= 9.0 Hz), 4.20 (s, 4H), 2.27 (s, 3H); LCMS: purity: 100%; MS (m/e): 421(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.832	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(5-methoxy-2-methylphenyl)-2,4-pyrimidinediamine (R926896)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 5-methoxy-2-methylaniline were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(5-methoxy-2-methylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.91 (bs, 1H), 7.61 (d, 1H, J= 2.1 Hz), 7.17 (d, 1H, J= 3.0 Hz), 7.05 (d, 1H, J= 9.3 Hz), 7.03 (dd, 1H, J= 3.0 and 8.7 Hz), 6.82 (d, 1H, J= 8.1 Hz), 6.68-6.60 (m, 2H), 6.55 (dd, 1H, J= 2.1 and 8.1 Hz), 4.26 (s, 4H), 3.70 (s, 3H), 2.22 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): -47450; LCMS: purity: 99%; MS (m/e): 383(MH^+).
7.3.833	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(2-fluoro-5-methylphenyl)-2,4-pyrimidinediamine (R926897)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 2-fluoro-5-methylaniline were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(2-fluoro-5-methylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.11 (dd, 1H, J= 1.8 and 8.1 Hz), 7.94 (d, 1H, J= 2.7 Hz), 7.08-6.84 (m, 4H), 6.74-6.67 (m, 1H), 6.64-6.59 (m, 1H), 4.27 (s, 4H), 2.28 (s, 3H) ; ^{19}F NMR (282 MHz, $CDCl_3$): -38659, -47267; LCMS: purity: 100%; MS (m/e): 371(MH^+).
7.3.834	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(3,5-difluorophenyl)-2,4-pyrimidinediamine (R926898)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3,5-difluoroaniline were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3,5-difluorophenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.94 (d, 1H, J= 3.3 Hz), 7.20-7.11 (m, 3H), 7.02 (s, 1H), 6.92-6.90 (m, 2H), 6.65 (s, 1H), 6.39 (tt, 1H, J= 2.4 and 9.0 Hz), 4.31 (s, 4H); ^{19}F NMR (282 MHz, $CDCl_3$): -31142, -47002; LCMS: purity: 97%; MS (m/e): 375(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.835	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(4-trifluoromethylthiophenyl)-2,4-pyrimidinediamine (R926899)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-(trifluoromethylthio)aniline were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(4-trifluoromethylthiophenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.73 (s, 1H), 9.47 (s, 1H), 8.13 (d, 1H, J= 3.6 Hz), 7.79 (d, 2H, J= 9.0 Hz), 7.51 (d, 2H, J= 9.0 Hz), 7.28 (d, 1H, J= 2.1 Hz), 7.12 (dd, 1H, J= 2.4 and 9.0 Hz), 6.83 (d, 1H, J= 8.7 Hz), 4.23 (s, 4H); ^{19}F NMR (282 MHz DMSO-d_6): -12306; LCMS: purity: 97%; MS (m/e): 439(MH^+).
7.3.836	N4-[3-(Benzothiazol-2-yl)-4-chlorophenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl)-2,4-pyrimidinediamine (R926900)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[3-(Benzothiazol-2-yl)-4-chlorophenyl)-2-chloro-5-fluoro-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide N4-[3-(benzothiazol-2-yl)-4-chlorophenyl)-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.77 (s, 1H), 9.30 (s, 1H), 8.49 (d, 1H, J= 3.0 Hz), 8.25 (dd, 1H, J= 3.0 and 9.0), 8.21-8.16 (m, 2H), 8.06 (d, 1H, J= 7.8 Hz), 7.92 (d, 1H, J= 4.8 Hz), 7.63-7.48 (m, 3H), 7.30 (t, 1H, J= 1.8 Hz), 7.22 (dd, 1H, J= 1.8 and 7.5 Hz), 6..95 (t, 1H, J= 8.1 Hz), 6.32 (dd, 1H, J= 1.2 and 8.1 Hz), 4.29 (s, 2H), 2.62 (d, 1H, J= 4.8 Hz); LCMS: purity: 100%; MS (m/e): 536(MH^+).
7.3.837	5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-methoxy-4-methylphenyl)-2,4-pyrimidinediamine (R926902)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-Chloro-5-fluoro-N4-(3-methoxy-4-methylphenyl)-4-pyrimidineamine and 3-methoxy-4-methylaniline were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-methoxy-4-methylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.78 (bs, 1H), 9.63 (bs, 1H), 8.15 (d, 1H, J= 4.5 Hz), 7.94 (d, 1H, J= 4.5 Hz), 7.94 (d, 1H, J= 4.5 Hz), 7.30 (dd, 1H, J= 1.8 and 8.4 Hz), 7.25-7.04 (m, 5H), 6.57 (d, 1H, J= 8.1 Hz), 4.31 (s, 2H), 3.66 (s, 3H), 2.62 (d, 1H, J= 4.8 Hz), 2.09 (s, 3H); LCMS: purity: 95%; MS (m/e): 412(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.838	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(methoxycarbonyl)-(1H)-indol-6-yl])-2,4-pyrimidinediamine (R926903)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 6-amino-2-(methoxycarbonyl)-(1H)-indole were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(methoxycarbonyl)-(1H)-indol-6-yl])-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 11.53 (s, 1H), 9.37 (s, 1H), 9.18 (d, 2H, J= 9.9 Hz), 8.08 (d, 1H, J= 3.6 Hz), 7.96 (bs, 1H), 7.46 (d, 1H, J= 9.0 Hz), 7.39-7.35 (m, 2H), 7.16 (t, 1H, J= 2.4 Hz), 7.10-7.04 (m, 2H), 6.48 (dd, 1H, J= 2.4 and 7.5 Hz), 3.82 (s, 3H); LCMS: purity: 95%; MS (m/e): 394(MH^+).
7.3.839	5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-2,4-pyrimidinediamine (R926904)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro N4-[2-(methoxycarbonyl)-(1H)-indol-6-yl])-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 9.05 (bs, 1H), 8.35 (s, 1H), 8.00 (bs, 1H), 7.66-7.62 (m, 2H), 7.27-7.17 (m, 3H), 7.01-6.90 (m, 3H), 6.64 (dd, 1H, J= 2.4 and 8.1 Hz), 6.40 (bs, 1H). 4.49 (s, 2H), 3.94 (s, 3H), 2.75 (d, 3H, J= 5.1 Hz); LCMS: purity: 86%; MS (m/e): 465(MH^+).
7.3.840	N4-[3-[[4-(Ethoxycarbonyl)piperidino]methyl]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl-2,4-pyrimidinediamine (R926905)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[3-[[4-(ethoxycarbonyl)piperidino]methyl]phenyl]-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-[3-[[4-(ethoxycarbonyl)piperidino]methyl]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): 9.33 (s, 1H), 9.20 (s, 1H), 8.09 (d, 1H, J= 4.2 Hz), 7.93 (d, 1H, J= 4.8 Hz), 7.82 (d, 1H, J= 8.1 Hz), 7.55 (s, 1H), 7.35 (t, 1H, J= 2.4 Hz), 7.29-7.22 (m, 2H), 7 09 (t, 1H, J= 8.1 Hz), 6.96 (d, 1H, J= 7.8 Hz), 6.47 (dd, 1H, J= 2.4 and 8.1 Hz), 4.32 (s, 2H), 4.02 (q, 2H, J= 6.9 Hz), 3.39 (s, 2H), 2.73 (bd, 2H, J=11.1 Hz), 2.63 (d, 3H, J= 4.5 Hz), 2.30-2.20 (m, 1H), 1.94 (t, 2H, J= 11.1 Hz), 1.74 (d, 2H, J= 9.9 Hz), 1.60-1.50 (m, 2H), 1.14 (t, 3H, J= 6.9 Hz); LCMS: purity: 99%; MS (m/e): 537(M - CH_2^+).

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Section Number	Name of compound and reference number	Experimental
7.3.841	N2-[3-(Ethoxycarbonyl-1,1-dimethylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926906)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-(ethoxycarbonyl-1,1-dimethylmethyleneoxy)aniline were reacted to provide N2-[3-(ethoxycarbonyl-1,1-dimethylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.91 (d, 1H, J= 4.8 Hz), 7.20-7.03 (m, 6H), 6.67 (td, 1H, J= 2.1 and 7.5 Hz), 6.57-6.53 (m, 1H), 4.19 (q, 2H, J= 6.9 Hz), 1.53 (s, 6H), 1.20 (t, 3H, J= 6.9 Hz); ^{19}F NMR (282 MHz, CD_3OD): -46120; LCMS: purity: 91%; MS (m/e): 427(MH^+).
7.3.842	N2-[3-(Ethoxycarbonyl-1,1-dimethylmethyleneoxy)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926907)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-(ethoxycarbonyl-1,1-dimethylmethyleneoxy)aniline were reacted to provide N2-[3-(ethoxycarbonyl-1,1-dimethylmethyleneoxy)phenyl]-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.92 (d, 1H, J= 3.0 Hz), 7.21-7.08 (m, 4H), 7.00 (dd, 1H, J= 2.4 and 8.4 Hz), 6.93 (bs, 1H), 6.86 (d, 1H, J= 8.7 Hz), 6.99 (d, 1H, J= 2.4 Hz), 6.45 (ddd, 1H, J= 1.2, 1.2, and 7.8 Hz), 4.27 (s, 4H), 4.23 (q, 2H, J= 6.9 Hz), 1.60 (s, 6H), 1.23 (t, 3H, J= 6.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): -47216; LCMS: purity: 85%; MS (m/e): 469(MH^+).
7.3.843	N2-[3-(Ethoxycarbonyl-1,1-dimethylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxy-4-methylphenyl)-2,4-pyrimidinediamine (R926908)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(2-hydroxy-4-methylphenyl)-4-pyrimidineamine and 3-(ethoxycarbonyl-1,1-dimethylmethyleneoxy)aniline were reacted to provide N2-[3-(ethoxycarbonyl-1,1-dimethylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxy-4-methylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.86 (bs, 1H), 7.80 (bs, 1H), 7.53 (s, 1H), 7.16-6.86 (m, 4H), 6.54 (d, 2H, J= 7.5 Hz), 4.21 (q, 2H, J= 6.9 Hz), 3.48 (s, 2H), 2.20 (s, 3H), 1.60 (s, 6H), 1.22 (t, 3H, J= 6.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): -46808; LCMS: purity: 96%; MS (m/e): 441(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.844	N2-[3-(Ethoxycarbonyl-1,1-dimethylmethyleneoxy)phenyl]-5-fluoro-N4-[(1H)-indol-6-yl]-2,4-pyrimidinediamine (R926909)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 3-(ethoxycarbonyl-1,1-dimethylmethyleneoxy)aniline were reacted to provide N2-[3-(Ethoxycarbonyl-1,1-dimethylmethyleneoxy)phenyl]-5-fluoro-N4-[(1H)-indol-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 9.43 (bs, 1H), 8.64 (s, 1H), 7.92 (d, 1H, J= 3.6 Hz), 7.66 (t, 1H, J= 2.4 Hz), 7.54 (d, 1H, J= 8.4 Hz), 7.44 (s, 1H), 7.19 (t, 1H, J= 3.0 Hz), 7.15 (d, 1H, J= 8.1 Hz), 6.96 (d, 1H, J= 3.0 Hz), 6.80 (dd, 1H, J= 1.8 and 7.5 Hz), 6.77 (dd, 1H, J= 1.8 and 8.1 Hz), 6.52 (dd, 1H, J= 1 8 and 7.5 Hz), 6.49-6.46 (m, 1H), 4.32 (q, 2H, J= 7.2 Hz), 1.57 (s, 6H), 1.31 (t, 3H, J= 7.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): -47190; LCMS. purity: 93%; MS (m/e): 450(MH^+).
7.3.845	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)carbonyl-1,1-dimethylmethyleneoxy]phenyl]- 2,4-pyrimidinediamine (R926913)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-(N-methylamino)carbonyl-1,1-dimethylmethyleneoxy)aniline were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)carbonyl-1,1-dimethylmethyleneoxy]phenyl]- 2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.35 (s, 1H), 9.20 (s, 1H), 9.17 (s, 1H), 8.07 (d, 1H, J= 3.3 Hz), 7.93 (d, 1H, J= 3.9 Hz), 7.40-7.29 (m, 3H), 7.13-7.02 (m, 3H), 6.47 (d, 1H, J= 7.5 Hz), 6.33 (d, 1H, J= 7.5 Hz), 2.60 (s, 3H), 1.37 (s, 6H); LCMS: purity: 97%; MS (m/e): 412(MH^+).
7.3.846	5-Fluoro-N4-(1,2,3,4-tetrahydroisoquin-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926914)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-(1,2,3,4-tetrahydroisoquin-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 7.90 (d, 1H, J= 3.3 Hz), 7.47 (d, 1H, J= 2.4 Hz), 7.42-7.37 (m, 2H), 7.16 (t, 1H, J= 8.4 Hz), 7.10-7.04 (m, 2H), 6.50 (ddd, 1H, J= 1.2, 2.4, and 8.1 Hz), 4.26 (s, 2H), 3.93 (s, 2H), 3.12 (t, 2H, J= 6.3 Hz), 2.84-2.76 (m, 5H), ; ^{19}F NMR (282 MHz, CD_3OD): -47489; LCMS: purity: 87%; MS (m/e): 423(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.847	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro- N2-[3-[(N-methylamino)carbonyl-1,1-dimethylmethyleneoxy]phenyl]- 2,4-pyrimidinediamine (R926915)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-(N-methylamino)carbonyl-1,1-dimethylmethyleneoxy)aniline were reacted to provide N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-[3-[(N-methylamino)carbonyl-1,1-dimethylmethyleneoxy]phenyl]- 2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.26 (t, 1H, J= 7.5 Hz), 7.19 (d, 1H, J= 9.3 Hz), 7.13 (d, 1H, J= 2.4 Hz), 7.06 (dd, 1H, J= 2.4 and 8.7 Hz), 7.04-7.03 (m, 1H), 6.83 (d, 1H, J= 9.0 Hz), 6.75 (d, 1H, J= 7.2 Hz), 4.25 (s, 4H), 2.76 (s, 3H), 1.43 (s, 6H); LCMS: purity: 97%; MS (m/e): 454(MH^+).
7.3.848	5-Fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]- 2,4-pyrimidinediamine (R926917)	A mixture of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-methylamino)carbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine (20 mg, 0.052 mmol), allyl isocyanate (13mg, 0.16 mmol), and 2-(N,N-dimethylamino)pyridine (18 mg, 0.15 mmol) in anhydrous THF (1 mL) were heated at 60°C in a sealed vial for 2 days. The reaction was diluted with ethyl acetate and washed with 1N HCl and brine. Concentration gave an oily residue which was purified by preparative TLC (5% methanol/dichloromethane) to give the product 5-fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethylene oxy]phenyl]- 2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.93 (d, 1H, J= 3.6 Hz), 7.62-7.55 (m, 2H), 7.32 (s, 1H), 7.30 (t, 1H, J= 8.1 Hz), 7.19-7.15 (m, 2H), 6.82 (dd, 1H, J= 2.4 and 8.1 Hz), 6.61 (m, 1H), 5.96-5.82 (m, 1H), 5.24 (dd, 1H, J= 1.8 and 16.8 Hz), 5.13 (dd, 1H, J= 1.8 and 11.7 Hz), 4.41 (s, 2H), 3.79 (d, 1H, J= 5.4 Hz), 2.80 (s, 3H); ^{19}F NMR (282 MHz, CD_3OD): -47357; LCMS: purity: 99%; MS (m/e): 468(MH^+).
7.3.849	5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-[3-[[(N-isopropylamino)carbonyl]-N-isopropylamino) carbonyloxy]phenyl]-2,4-pyrimidinediamine (R926916)	In a like manner to the preparation of 5-fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy] phenyl]- 2,4-pyrimidinediamine and isopropyl isocyanate were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-[3-[[(N-isopropylamino)carbonyl]-N-isopropylamino)carbonyloxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.40 (bs, 1H), 9.27 (bs, 1H), 8.12 (d, 1H, J= 3.6 Hz), 7.94 (d, 1H, J= 3.9 Hz), 7.78 (d, 1H, J= 8.7 Hz), 7.64 (d, 1H, J= 7.5 Hz), 7.46 (s, 1H), 7.36-7.26 (m, 3H), 7.12 (t, 1H, J= 8.1 Hz), 6.81-6.74 (m, 1H), 6.47 (dd, 1H, J= 2.4 and 8.1 Hz), 5.43 (d, 1H, J= 3.9 Hz), 4.36 (s, 2H), 3.65-3.55 (m, 2H), 3.14 (s, 2H), 2.63 (d, 3H, J= 3.9 Hz), 1.10 (d, 6H, J= 7.2 Hz), 0.97 (d, 6H, J= 6.6 Hz).

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Section Number	Name of compound and reference number	Experimental
7.3.850	N4-[3-[[N-(Ethoxycarbonylmethyl)amino]carbonyloxy]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]- 2,4-pyrimidinediamine (R926918)	In a like manner to the preparation of 5-fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy] phenyl]- 2,4-pyrimidinediamine and ethyl isocyanatoacetate were reacted to provide N4-[3-[[N-(ethoxycarbonylmethyl)amino]carbonyloxy]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]- 2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.94 (d, 1H, J= 3.3 Hz), 7.69 (t, 1H, J= 1.8 Hz), 7.56 (ddd, 1H, J= 1.2, 1.2, and 8.1 Hz), 7.35 (m, 1H), 7.31 (t, 1H, J= 8.1 Hz), 7.18 (d, 1H, J= 2.4 Hz), 7.17 (d, 1H, J= 1.2 Hz), 6.84 (dd, 1H, J= 2.4 and 8.1 Hz), 6.63-6.58 (m, 1H), 4.42 (s, 2H), 4.20 (q, 2H, J= 7.2 Hz), 3.93 (s, 2H), 2.80 (s, 3H), 1.27 (t, 3H, J= 7.2 Hz), ^{19}F NMR (282 MHz, CD_3OD): -47371; LCMS: purity: 89%; MS (m/e): 513(MH^+).
7.3.851	N4-[3-[(N-(Ethylamino)carbonyloxy]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]- 2,4-pyrimidinediamine (R926919)	In a like manner to the preparation of 5-fluoro-N4-[3-[(N-allylamino)carbonyloxy]phenyl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]- 2,4-pyrimidinediamine and ethyl isocyanate were reacted to provide N4-[3-[(N-(ethylamino)carbonyloxy]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]- 2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.94 (d, 1H, J= 3.3 Hz), 6.84-6.79 (m, 2H), 7.61-7.55 (m, 2H), 6.62-6.56 (m, 2H), 7.33-7.27 (m, 1H), 7.19-7.17 (m, 1H), 4.41 (s, 2H), 3.23 (q, 2H, J= 7.2 Hz), 2.80 (s, 3H), 1.17 (t, 3H, J= 7.2 Hz); ^{19}F NMR (282 MHz, CD_3OD): -47378; LCMS: purity: 100%; MS (m/e): 455(MH^+).
7.3.852	5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(4-methyl-3-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926922)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(4-methyl-3-trifluoromethylphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(4-methyl-3-trifluoromethylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.79 (bs, 1H), 9.48 (bs, 1H), 8.17 (d, 1H, J= 4.2 Hz), 8.10 (d, 1H, J= 6.3 Hz), 7.96 (d, 1H, J= 4.8 Hz), 7.89 (d, 1H, J= 2.1 Hz), 7.38 (d, 1H, J= 9.0 Hz), 7.26-7.20 (m, 2H), 7.11 (t, 1H, J= 8.4 Hz), 6.53 (d, 1H, J= 8.4 Hz), 4.33 (s, 2H), 2.62 (d, 3H, J= 4.8 Hz), 2.39 (s, 3H); LCMS: purity: 94%; MS (m/e): 450(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.853	5-Fluoro-N4-(4-fluoro-3-methylphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926923)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(4-fluoro-3-methylphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-Fluoro-N4-(4-fluoro-3-methylphenyl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.67 (bs, 1H), 9.51 (bs, 1H), 8.14 (d, 1H, J= 4.8 Hz), 7.95 (d, 1H, J= 4.2 Hz), 7.64 (dd, 1H, J= 2.7 and 6.9 Hz), 7.57-7.50 (m, 1H), 7.23-7.06 (m, 4H), 6.55 (d, 1H, J= 7.5 Hz), 4.33 (s, 2H), 2.63 (d, 3H, J= 4.8 Hz), 2.19 (s, 3H); LCMS: purity: 94%; MS (m/e): 400(MH^+).
7.3.854	5-Fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-trifluoromethylthiophenyl)-2,4-pyrimidinediamine (R926925)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-trifluoromethylthiophenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-trifluoromethylthiophenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.83 (bs, 1H), 9.49 (bs, 1H), 8.21-8.15 (m, 2H), 8.01 (s, 1H), 7.94 (bs, 1H), 7.49 (t, 1H, J= 7.8 Hz), 7.38 (d, 1H, J= 7.8 Hz), 7.29 (s, 1H), 7.22 (d, 1H, J= 7.5 Hz), 7.14 (t, 1H, J= 8.4 Hz), 6.54 (d, 1H, J= 9.9 Hz), 4.34 (s, 2H), 2.62 (d, 3H, J= 4.8 Hz); LCMS: purity: 98%; MS (m/e): 468(MH^+).
7.3.855	N2-[3,5-Bis(methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926926)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3,5-bis(methoxycarbonylmethyleneoxy)aniline were reacted to provide N2-[3,5-bis(methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.92 (d, 1H, J= 4.2 Hz), 7.20-7.10 (m, 3H), 6.92 (d, 2H, J= 2.4 Hz), 6.52 (ddd, 1H, J= 1.8, 1.8, and 7.5 Hz), 6.12 (t, 1H, J= 2.4 Hz), 4.55 (s, 4H), 3.77 (s, 6H); ^{19}F NMR (282 MHz, CD_3OD): -47342; LCMS: purity: 92%; MS (m/e): 473(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.856	5-Fluoro-N2-[3-hydroxy-5-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926927)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-hydroxy-5-(methoxycarbonylmethyleneoxy)aniline were reacted to produce 5-fluoro-N2-[3-hydroxy-5-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 8.13 (d, 1H, J= 4.8 Hz), 7.37-7.33 (m, 1H), 7.11 (t, 1H, J= 8.4 Hz), 7.07-7.05 (m, 1H), 6.73-6.65 (m, 2H), 6.51 (dd, 1H, J= 2.1 and 8.1 Hz), 5.97 ((s, 1H), 4.59 (s, 2H), 3.67 (s, 3H); LCMS: purity: 93%; MS (m/e): 401(MH^+).
7.3.857	N2-[3-[(N-Ethylamino)carbonyloxy]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926928)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-[(N-ethylamino)carbonyloxy]aniline were reacted to provide N2-[3-[(N-ethylamino)carbonyloxy]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.92 (d, 1H, J= 3.0 Hz), 7.67-7.55 (m, 2H), 7.24 (t, 1H, J= 7.5 Hz), 7.16 (t, 1H, J= 7.5 Hz), 7.07-6.98 (m, 2H), 6.84-6.79 (m, 2H), 6.67 (m, 2H), 6.60 (d, 1H, J= 7.5 Hz), 5.22-5.14 (m, 1H), 3.36-3.27 (m, 2H), 2.95 (s, 1H), 2.88 (s, 1H), 1.20 (t, 3H, J= 7.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): -47012; LCMS: purity: 99%; MS (m/e): 384(MH^+).
7.3.858	5-Fluoro-N2-[3-hydroxy-5-[(N-methylamino) carbonylmethyleneoxy]phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926929)	A solution of 5-fluoro-N2-[3-hydroxy-5-(methoxycarbonylmethyleneoxy)phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (56 mg, 0.13 mmol), methylamine hydrochloride (90 mg, 1.3 mmol), and diisopropylethylamine (0.12 mL, 0.70 mmol) in methanol (2 mL) was heated at 100°C for 8h. The cooled reaction mixture was poured into 1N HCl (20 mL) saturated with NaCl, and extracted with ethyl acetate. Purification by preparative TLC (5% methanol/dichloromethane) gave the product, 5-fluoro-N2-[3-hydroxy-5-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.29 (bs, 1H), 9.16 (s, 1H), 9.01 (s, 1H), 8.06 (d, 1H, J= 3.3 Hz), 7.87 (d, 1H, J= 4.8 Hz), 7.42 (dd, 1H, J= 1.5 and 8.1 Hz), 7.13-7.05 (m, 2H), 6.89-6.81 (m, 2H), 6.45 (dd, 1H, J= 2.4 and 8.4 Hz), 5.92 (t, 1H, J= 2.4 Hz), 4.28 (s, 2H), 3.30(bs, 1H), 2.63 (s, 3H); LCMS: purity: 94%; MS (m/e): 400(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.859	N2-[3,5-Bis[(N-methylamino)carbonylmethyleneoxy]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926930)	In a like manner to the preparation of 5-fluoro-N2-[3-hydroxy-5-[(N-methylamino)carbonylmethyleneoxy]phenyl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-[3,5-bis(methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine, methylamine hydrochloride, and diisopropylethylamine were reacted to give N2-[3,5-Bis[(N-methylamino)carbonylmethyleneoxy]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.91 (bs, 1H), 7.25 (t, 1H, J= 1.8 Hz), 7.14-7.11 (m, 1H), 6.98 (s, 1H), 6.97 (s, 1H), 6.55-6.50 (m, 1H), 6.26-6.23 (m, 1H), 4.39 (s, 4H), 2.81 (s, 6H); ^{19}F NMR (282 MHz, CD_3OD): -47307; LCMS: purity: 99%; MS (m/e): 471=(MH^+).
7.3.860	5-Fluoro-N4-[(1H)-indol-5-yl]-N2-[3-[(N-methylamino) carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926931)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)-indol-5-yl]-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-[(1H)-indol-5-yl]-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 11.09 (bs, 1H), 9.93 (bs, 1H), 9.67 (bs, 1H), 8.12 (d, 1H, J= 4.81 Hz), 7.94-7.82 (m, 2H), 7.37-7.22 (m, 4H), 7.13 (bs, 1H), 7.07 (t, 1H, J= 8.1 Hz), 6.58 (d, 1H, J= 7.8 Hz), 6.37 (s, 1H), 4.32 (s, 2H), 2.61 (d, 3H, J= 4.2 Hz); LCMS: purity: 92%; MS (m/e): 407(MH^+).
7.3.861	5-Fluoro-N2-(3-hydroxyphenyl)-N4-[(1H)-indol-5-yl]-2,4-pyrimidinediamine (R926932)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)-indol-5-yl]-4-pyrimidineamine and 3-hydroxyaniline were reacted to provide 5-fluoro-N2-(3-hydroxyphenyl)-N4-[(1H)-indol-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 11.13 (s, 1H), 10.25 (bs, 1H), 9.87 (bs, 1H), 9.43 (bs, 1H), 8.16 (d, 1H, J= 5.1 Hz), 7.89 (d, 1H, J= 0.09 Hz), 7.39-7.27 (m, 3H), 7.03-6.94 (m, 2H), 6.83 (s, 1H), 6.48 (d, 1H, J= 7.5 Hz), 6.40 (t, 1H, J= 2.1 Hz); LCMS: purity: 92%; MS (m/e): 336(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.862	5-Fluoro-N4-[(1H)-indol-6-yl]-N2-[3-[(N-methylamino)carbonyl]phenyl]-2,4-pyrimidinediamine (R926933)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 3-[(N-methylamino)carbonyl]aniline were reacted to provide 5-fluoro-N4-[(1H)indol-6-yl]-N2-[3-[(N-methylamino)carbonyl]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.99 (t, 1H, J= 1.8 Hz), 7.89 (d, 1H, J= 3.6 Hz), 7.78-7.76 (m, 1H), 7.70 (ddd, 1H, J= 1.2, 2.4, and 8.4 Hz), 7.50 (d, 1H, J= 9.0 Hz), 7.31 (td, 1H, J= 1.2 and 7.5 Hz), 7.23-7.17 (m, 3H), 6.43 (dd, 1H, J= 1.2 and 3.6 Hz), 2.73 (s, 3H); ^{19}F NMR (282 MHz, CD_3OD): -47513; LCMS: purity: 99%; MS (m/e): 377(MH^+).
7.3.863	5-Fluoro-N4-[(1H)-indol-6-yl]-N2-[3-(N-morpholinocarbonyl)phenyl]-2,4-pyrimidinediamine (R926934)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 3-(N-morpholinocarbonyl)aniline were reacted to provide 5-fluoro-N4-[(1H)-indol-6-yl]-N2-[3-(N-morpholinocarbonyl)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.96 (d, 1H, J= 4.8 Hz), 7.73 (t, 1H, J= 2.4 Hz), 7.66 (d, 1H, J= 1.2 Hz), 7.52 (d, 1H, J= 8.1 Hz), 7.49 (ddd, 1H, J= 0.09, 2.1, and 8.1 Hz), 7.33-7.26 (m, 2H), 7.19 (dd, 1H, J= 1.8 and 8.7 Hz), 7.12-7.06 (m, 1H), 6.45 (dd, 1H, J= 1.3 and 3.0 Hz), 3.62-3.15 (m, 8H); ^{19}F NMR (282 MHz, CD_3OD): -46545; LCMS: purity: 91%; MS (m/e): 433(MH^+).
7.3.864	N2-[3-[[4-(Ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N4-[(1H)-indol-6-yl]-2,4-pyrimidinediamine (R926935)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[(1H)indol-6-yl]-4-pyrimidineamine and 3-[4-(ethoxycarbonyl)piperidino]aniline were reacted to provide N2-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N4-[(1H)-indol-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.99 (d, 1H, J= 5.1 Hz), 7.64-7.58 (m, 2H), 7.52 (d, 1H, J= 8.7 Hz), 7.48 (ddd, 1H, J= 1.2, 2.4, and 8.1 Hz), 7.34-7.27 (m, 2H), 7.19-7.13 (m, 2H), 6.46 (dd, 1H, J= 1.2 and 4.2 Hz), 4.40-4.27 (m, 1H), 4.13 (q, 2H, J= 6.9 Hz), 3.56-3.41 (m, 1H), 2.95-2.82 (m, 2H), 2.58-2.47 (m, 1H), 1.98-1.82 (m, 1H), 1.75-7.60 (m, 1H), 1.58-1.39 (m, 2H), 1.24 (t, 3H, J= 6.9 Hz); ^{19}F NMR (282 MHz, CD_3OD): -46101; LCMS: purity: 90%; MS (m/e): 503(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.865	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)carbonyl]phenyl]-2,4-pyrimidinediamine (R926936)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-[(N-methylamino)carbonyl]aniline were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-methylamino)carbonyl]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.01 (d, 1H, J= 5.4 Hz), 7.84 (t, 1H, J= 1.8 Hz), 7.68-7.61 (m, 2H), 7.45 (t, 1H, J= 8.4 Hz), 7.16-7.03 (m, 3H), 6.68 (td, 1H, J= 1.2 and 8.7 Hz), 2.90 (s, 3H); LCMS: purity: 95%; MS (m/e): 354(MH^+).
7.3.866	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-propylamino)carbonyl]phenyl]-2,4-pyrimidinediamine (R926937)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-[(N-propylamino)carbonyl]aniline were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-[(N-propylamino)carbonyl]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.00 (d, 1H, J= 5.4 Hz), 7.84 (t, 1H, J= 1.8 Hz), 7.69-7.59 (m, 2H), 7.44 (t, 1H, J= 7.5 Hz), 7.16-7.05 (m, 3H), 6.67 (td, 1H, J= 2.4 and 7.2 Hz), 3.34-3.29 (m, 2H), 1.65-1.56 (m, 2H), 0.96 (t, 3H, J= 7.5 Hz); ^{19}F NMR (282 MHz, CD_3OD): -46049; LCMS: purity: 94%; MS (m/e): 382(MH^+).
7.3.867	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-morphonlinocarbonyl)phenyl]-2,4-pyrimidinediamine (R926938)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-(N-morpholinocarbonyl)aniline were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[3-(N-morphonlinocarbonyl)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.93 (d, 1H, J= 3.6 Hz), 7.84 (t, 1H, J= 1.8 Hz), 7.62 (ddd, 1H, J= 1.2, 2.4, and 8.1 Hz), 7.32 (t, 1H, J= 8.4 Hz), 7.19-7.10 (m, 3H), 6.96 (dd, 1H, J= 1.2 and 7.8 Hz), 6.56 (ddd, 1H, J= 1.2, 3.0, and 6.9 Hz), 3.78-3.34 (m, 8H); ^{19}F NMR (282 MHz, CD_3OD): -47323; LCMS: purity: 100%; MS (m/e): 410(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.868	N2-[3-[[4-(Ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926939)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-[[4-(ethoxycarbonyl)piperidino]carbonyl]aniline were reacted to provide N2-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.92 (d, 1H, J= 3.6 Hz), 7.82 (s, 1H), 7.62 (td, 1H, J= 1.2 and 8.4 Hz), 7.30 (t, 1H, J= 8.4 Hz), 7.19-7.09 (m, 3H), 6.93 (d, 1H, J= 7.5 Hz), 6.55 (td, 1H, J= 1.2 and 7.5 Hz), 4.43 (bd, 1H, J= 12.3 Hz), 4.13 (q, 2H, J= 6.9 Hz), 3.7 (bd, 1H, J= 11.7 Hz), 3.10-2.92 (m, 2H), 2.67-2.55 (m, 1H), 2.06-1.50 (m, 4H), 1.24 (t, H, J= 6.9 Hz); ^{19}F NMR (282 MHz, CD_3OD): -47299; LCMS: purity: 99%; MS (m/e): 480(MH^+).
7.3.869	N4-[3-[[4-(Ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926940)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-4-pyrimidineamine and 3-hydroxyaniline were reacted to provide N4-[3-[[4-(ethoxycarbonyl)piperidino] carbonyl]phenyl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.93 (d, 1H, J= 3.6 Hz), 7.89 (t, 1H, J= 1.8 Hz), 7.83 (td, 1H, J= 1.2 and 8.4 Hz), 7.41 (t, 1H, J= 7.8 Hz), 7.11-6.95 (m, 4H), 6.41 (td, 1H, J= 1.8 and 7.2 Hz), 4.44 (bd, 1H, J= 12.9 Hz), 4.10 (q, 2H, J= 7.2 Hz), 3.73 (bd, 1H, J= 12.3 Hz), 3.18-2.98 (m, 2H), 2.67-2.55 (m, 1H), 2.05-1.53 (m, 4H), 1.23 (t, 3H, J= 7.2 Hz); ^{19}F NMR (282 MHz, CD_3OD): -47483; LCMS: purity: 99%; MS (m/e): 480(MH^+).
7.3.870	N4-[3-[[4-(Ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926941)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide N4-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine.^{1}H NMR (CD_3OD): δ 7.95 (d, 1H, J= 3.3 Hz), 7.90 (t, 1H, J= 1.8 Hz), 7.80 (ddd, 1H, J= 0.09, 2.1, 8.1 Hz), 7.39 (t, 1H, J= 7.5 Hz), 7.31 (t, 1H, J= 1.2 Hz), 7.17-7.06 (m, 3H), 6.60-6.54 (m, 1H), 4.48-4.38 (m, 3H), 4.10 (q, 2H, J= 6.9 Hz), 3.78-3.65 (m, 1H), 3.17-2.95 (m, 2H), 2.79 (s, 3H), 2.65-2.53 (m, 1H), 2.01-1.52 (m, 4H), 1.22 (t, 3H, J= 6.9 Hz); ^{19}F NMR (282 MHz, CD_3OD): -47309; LCMS: purity: 99%; MS (m/e): 551(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.871	Reaction of 3-hydroxyaniline and 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-4-pyrimidineamine	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-4-pyrimidineamine and 3-hydroxyaniline were reacted to provide two products, R926942 and R926943.
7.3.872	N4-(1-Ethoxy-1,2,3,4-tetrahydronaphthalen-7-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926942)	^{1}H NMR (DMSO-d_6): δ 9.23 (bs, 1H), 9.14 (bs, 1H), 8.97 (bs, 1H), 8.04 (d, 1H, J= 3.6 Hz), 7.71 (dd, 1H, J= 2.4 and 7.5 Hz), 7.56 (bs, 1H), 7.14-6.98 (m, 3H), 6.93 (t, 1H, J= 8.1 Hz), 6.29 (bd, 1H, J= 7.2 Hz), 4.35 (bs, 1H), 3.59-3.36 (m, 2H), 2.69-2.60 (m, 2H), 1.89-1.78 (m, 2H), 1.72-1.56 (m, 2H), 1.08 (t, 3H, J= 6.9 Hz); LCMS: purity: 96%; MS (m/e): 395(MH$^+$).
7.3.873	5-Fluoro-N4-(3,4-dihydronaphthalen-7-yl)-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926943)	^{1}H NMR (DMSO-d_6): δ 9.19 (bs, 2H), 9.01 (s, 1H), 8.04 (d, 1H, J= 3.6 Hz), 7.56-7.46 (m, 2H), 7.16-7.03 (m, 3H), 6.94 (t, 1H, J= 8.1 Hz), 6.46 (d, 1H, J= 9.6 Hz), 6.03 (dd, 1H, J= 1.8 and 8.1 Hz), 6.09-6.01 (m, 1H), 2.69 (t, 2H, J= 8.4 Hz), 2.28-2.20 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6): -46541; LCMS: purity: 98%; MS (m/e): 349(MH$^+$).
7.3.874	5-Fluoro-N4-(3,4-dihydronaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926944)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-(3,4-dihydronaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 8.07 (d, 1H, J= 3.9 Hz), 7.53-7.45 (m, 2H), 7.32-7.29 (m, 2H), 7.11-7.01 (m, 2H), 6.49-6.40 (m, 2H), 6.08-6.00 (m, 1H), 4.32 (s, 2H), 2.69 (t, 2H, J= 8.4 Hz), 2.62 (s, 3H); LCMS: purity: 99%; MS (m/e): 420(MH$^+$).
7.3.875	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926945)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 3-hydroxyaniline were reacted to produce N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.91 (d, 1H, J= 5.4 Hz), 7.71 (d, 1H, J= 2.4 Hz), 7.58 (dd, 1H, J= 3.0 and 9.0 Hz), 7.15 (t, 1H, J= 8.4 Hz), 7.06 (d, 1H, J= 8.7 Hz), 6.92 (td, 1H, J= 1.8 and 9.9 Hz), 6.88 (t, 1H, J= 1.8 Hz), 6.61 (ddd, 1H, J= 1.2, 2.4, and 8.1 Hz), 3.89 (s, 3H), ; ^{19}F NMR (282 MHz, CD_3OD): -46612; LCMS: purity: 98%; MS (m/e): 362(MH$^+$).

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Section Number	Name of compound and reference number	Experimental
7.3.876	N2,N4-Bis(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926946)	In a like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloro-4-methoxyaniline were reacted to provide N2,N4-Bis(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.90 (bs, 1H), 9.68 (bs, 1H), 8.16 (d, 1H, J= 4.8 Hz), 7.72 (d, 1H, J= 2.4 Hz), 7.65 (d, 1H, J= 2.1 Hz), 7.58 (dd, 1H, J= 2.4 and 9.0 Hz), 7.38 (dd, 1H, J= 2.7 and 9.3 Hz), 7.12 (d, 1H, J= 8.7 Hz), 7.12 (d, 1H, J= 8.7 Hz), 7.05 (d, 1H, J= 8.7 Hz), 3.83 (s, 3H), 3.79 (s, 3H); LCMS: purity: 99%; MS (m/e): 410(MH^+).
7.3.877	5-Fluoro-N4-(1,2,3,4-tetrahydro-1-oxonaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926947)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxo-naphthalen-7-yl)-4-pyrimidineamine and 3-[(N-methylamino)carbonylmethyleneoxy]aniline were reacted to provide 5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxo-naphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethylene oxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.89 (bs, 1H), 9.55 (bs, 1H), 8.17 (d, 1H, J= 4.2 Hz), 8.04-7.93 (m, 3H), 7.32 (d, 1H, J= 8.7 Hz), 7.25-7.16 (m, 2H), 7.09 (t, 1H, J= 7.5 Hz), 6.52 (dd, 1H, J= 2.4 and 8.1 Hz), 4.28 (s, 2H), 2.90 (t, 2H, J= 6.0 Hz), 2.63 (d, 3H, J= 4.8 Hz), 2.59 (t, 2H, J= 6.6 Hz), 2.02 (t, 2H, J= 6.6 Hz); LCMS: purity: 93%; MS (m/e): 436(MH^+).
7.3.878	5-Fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxyiminonaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926948)	A solution of 5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxo-naphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (42 mg, 0.095 mmole) and hydroxylamine hydrochloride (8.5 mg, 0.12 mmole) in DMF (1 mL)was heated at 60°C for 12h. The reaction mixture was cooled to rt and then poured into brine (20 mL). A brown solid was collected by suction filtration and further purified by reverse phase chromatography to provide 5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxyiminonaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 8.13-8.05 (m, 2H), 7.99-7.92 (m, 2H), 7.77-7.72 (m, 1H), 7.33-7.21 (m, 2H), 7.14 (d, 1H, J= 8.7 Hz), 7.10-7.02 (m, 1H), 6.47 (dd, 1H, J= 2.4 and 7.5 Hz), 4.30 (s, 2H), 2.90 (t, 1H, J= 6.0 Hz), 2.70-2.40 (m, 6H), 2.07-1.98 (m, 1H), 1.74 (t, 1H, J= 6.6 Hz); LCMS: purity: 96%; MS (m/e): 451(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.879	5-Fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926949)	To a 0°C suspension of 5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxo-naphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (50mg, 0.11 mmol) in anhydrous THF (2.0 mL) was added lithiumborohydride (5 mg, 0.23 mmole). The reaction mixture was warmed to rt, stirred for 8h, and then quenched with methanol. The reaction mixture was poured into water and then extracted with ethyl acetate. Purification by preparative TLC (5% methanol/dichloromethane) provided 5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine. LCMS: purity: 96%; MS (m/e): 438(MH^+).
7.3.880	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[2-(methoxycarbonyl) benzofuran-5-yl]-2,4-pyrimidinediamine (R926950)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 5-amino-2-(methoxycarbonyl)benzofuran were reacted to produce N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.34 (bs, 2H), 8.10-8.07 (m, 2H), 7.78 (t, 1H, J= 2.7 Hz), 7.66-7.53 (m, 4H), 7.12 (d, 1H, J= 9.3 Hz), 3.87 (s, 3H), 3.85 (s, 3H); LCMS: purity: 99%; MS (m/e): 443(MH^+).
7.3.881	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2- (methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine (R926951)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 5-amino-2,3-dihydro-2-(methoxycarbonyl)benzofuran were reacted to produce N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.31 (bs, 1H), 10.04 (bs, 1H), 8.21 (d, 1H, J= 4.8 Hz), 7.75 (t, 1H, J= 3.0 Hz), 7.54 (td, 1H, J= 3.0 and 9.0 Hz), 7.34 (s, 1H), 7.20-7.15 (m, 2H), 6.80 (d, 1H, J= 8.1 Hz), 5.38-5.31 (m, 1H), 3.85 (s, 3H), 3.69 (s, 3H), 3.49 (dd, 1H, J= 11.1 and 16.5 Hz); LCMS: purity: 99%; MS (m/e): 446(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.882	N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine (R926953)	In a like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro -N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine and 5-amino-2,3-dihydro-2-(methoxycarbonyl)benzofuran were reacted to produce N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-(methoxycarbonyl)benzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.99 (bs, 1H), 9.49 (bs, 1H), 8.18 (d, 1H, J= 4.5 Hz), 8.08 (t, 1H, J= 2.4 Hz), 7.81-7.74 (m, 1H), 7.49 (d, 1H, J= 8.1 Hz), 7.42 (s, 1H), 7.20 (d, 1H, J= 8.1 Hz), 6.78 (d, 1H, J= 8.7 Hz), 5.36 (m, 1H), 3.80-3.47 (m, 4H), 3.20 (dd, 1H, J= 6.0 and 16.5 Hz); LCMS: purity: 100%; MS (m/e): 500(MH^+).
7.3.883	N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-2,4-pyrimidinediamine (R926954)	In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine, methylamine hydrogen chloride salt, and diisopropylethylamine were reacted to provide N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl] benzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.59 (s, 1H), 9.10 (s, 2H), 8.13-8.10 (m, 1H), 8.08-7.98 (m, 1H), 7.82 (d, 1H, J= 8.1 Hz), 7.48-7.42 (m, 2H), 7.24 (d, 1H, J= 8.7 Hz), 6.72 (d, 1H, J= 8.7 Hz), 5.06 (dd, 1H, J= 5.4 and 9.3 Hz), 3.39 (dd, 1H, J= 10.5 and 15.6 Hz), 3.15 (dd, 1H, J= 6.3 and 15.9 Hz), 2.59 (d, 3H, J= 4.5 Hz); LCMS: purity: 95%; MS (m/e): 499(MH^+).
7.3.884	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-2,4-pyrimidinediamine (R926955)	In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine, methylamine hydrochloride, and diisopropylethylamine were reacted to provide N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.24 (s, 1H), 8.99 (s, 2H), 8.02 (d, 1H, J= 3.0 Hz), 7.80-7.75 (m, 1H), 7.63 (d, 1H, J= 9.0 Hz), 7.47 (s, 1H), 7.23 (d, 1H, J= 8.1 Hz), 7.07 (d, 1H, J= 8.7 Hz), 6.69 (d, 1H, J= 8.1 Hz), 5.05 (dd, 1H, J= 2.1 and 9.9 Hz), 3.37 (dd, 1H, J= 10.5 and 15.9 Hz), 3.13 (dd, 1H, J= 6.0 and 15.9 Hz), 2.59 (d, 3H, J= 4.5 Hz); LCMS: purity: 95%; MS (m/e): 445(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.885	5-Fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R926956)	In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(4-isopropoxyphenyl)-4-pyrimidineamine, methylamine hydrochloride, and diisopropylethylamine were reacted to provide 5-fluoro-N2-[2,3-dihydro-2-[(N-methylamino)carbonyl]benzofuran-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.11 (s, 1H), 8.92 (s, 1H), 8.06-7.98 (m, 1H), 7.97 (d, 1H, J= 4.2 Hz), 7.60-7.52 (m, 3H), 7.20 (d, 1H, J= 8.1 Hz), 6.85 (d, 2H, J= 8.7 Hz), 6.67 (d, 1H, J= 9.0 Hz), 5.04 (dd, 1H, J= 5.7 and 9.9 Hz), 4.56 (quintet, 1H, J= 6.6 Hz), 3.36 (dd, 1H, J= 10.5 and 16.5 Hz), 3.10 (dd, 1H, J= 5.7 and 15.3 Hz), 2.59 (d, 1H, J= 4.5 Hz), 1.24 (d, 6H, J= 6.6 Hz); LCMS: purity. 96%; MS (m/e): 438(MH^+).
7.3.886	N2,N4-Bis(3-phenylphenyl)-2,4-pyrimidinediamine (R925809)	In a like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-aminobiphenyl were reacted to provide N2,N4-Bis(3-phenylphenyl)-2,4-pyrimidinediamine. LCMS: purity: 98%; MS (m/e): 415(MH^+).
7.3.887	2-Dimethylamine-5-fluoro-N4-(thyrosinyl methyl ester) pyrimidine (R940110)	A solution of 2,4-dichloro-5-fluoropyrimidine (0 .03 g, 0.18 mmol) and L-tyrosine methyl ester (0.14 g, 0.7 mmol) in DMF was heated at 100°C for 3 days. The reaction mixture was cool to room temperature and diluted with H_2O (10 mL). Upon saturation with sodium chloride it was extracted with ethyl acetate (3 x 15 mL), dried over anhydrous sodium sulfate and the solvent was removed. The resulting residue was filtered through a pad of silica gel (200-400 mesh, hexanes/EtOAc 2/8) to obtain 2-dimethylamine-5-fluoro-N4-(thyrosinyl methyl ester) pyrimidine **R940110.** ^{1}H NMR ($CDCl_3$): δ 7.76 (1H, d, *J*= 3.2 Hz), 7.00 (2H, d, *J*= 7.5 Hz), 6.76 (2H, d, *J*= 7.5 Hz), 5.20 (1H, d, *J*= 7.5 Hz), 4.90 (1H, q, *J*= 5.0 Hz), 3.71 (3H, s), 3.14 (2H, m), 3.08 (6H, s) ; purity: 98% ; MS (m/e) : 335 (M+H).

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Section Number	Name of compound and reference number	Experimental
7.3.888	5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine (R940299)	To a solution of 2-chloro-5-fluoro-N4-(3-aminocarbonylphenyl)-4-pyrimidineamine (0.050g, 0.18 mmol) in (2 mL) was added 3-(methylaminocarbonylmethyleneoxy)aniline (0.1g, 0.5 mmol). The mixture was heated in a sealed tube at 100 °C for 24h. The resulting reaction was diluted with H_2O (10 mL), acidified with 2N HCl (pH >2), saturated with sodium chloride and the resulting solid was filtered to give the desired product 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine **R940299**. Purification can be done by filtration through a pad of silica gel using 1-5% MeOH in CH_2Cl_2 or by crystallization using an appropriate solvent system. Alternatively, the reaction of equimolar amount of 2-chloro-5-fluoro-N4-(3-aminocarbonylphenyl)-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy) aniline in MeOH in a pressure tube at 110 °C for 24h or, in EtOH using microwave at 175 °C for 30-60 min followed by aqueous work up, also gave the desired product. ^{1}H NMR (DMSO-d6): δ 9.79 (1H, s), 9.49 (1H, s), 8.26 (1H, d, *J*= 3.9 Hz), 8.15 (1H, t, *J*= 1.8 Hz), 8.10-8.02 (3H, m), 7.68 (1H, d, *J*= 7.5 Hz), 7.51 (1H, t, *J*= 7.9 Hz), 7.48 (1H, s), 7.38 (2H, m), 7.20 (1H, t, *J*= 8.4 Hz), 6.60 (1H, d, *J*= 9.3 Hz), 4.45 (2H, s), 2.74 (3H, d, *J*= 4.8 Hz) ; purity: 95 % ; MS (m/e): 411 (MH+).
7.3.889	5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine (R940300)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine **R940300.** ^{1}H NMR (DMSO-d6): δ 9.66 (1H, s), 9.45 (1H, s), 8.21 (1H, d, *J*= 3.9 Hz), 8.06 (2H, m), 8.01 (1H, t, *J*= 2.7 Hz), 7.35 (2H, m), 7.23 (1H, d, *J*= 9Hz), 7.18 (1H, t, *J*= 8.1 Hz), 6.60 (1H, d, *J*= 7.8 Hz), 4.45 (2H, s), 3.91 (3H, s), 3.84 (3H, s), 2.74 (3H, d, *J*= 3.6 Hz) ; purity: 93% ; MS (m/e): 456 (MH+).

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Section Number	Name of compound and reference number	Experimental
7.3.890	5-Fluoro-N4-(3-hydroxyphenyl)-N2-(3-methyloxycarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine (R940301)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)-4-pyrimidineamine and 3-methyloxycarbonyl-4-methoxyaniline were reacted to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-(3-methyloxycarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine **R940301.** ^{1}H NMR (DMSO-d6): δ 9.93 (1H, s), 9.79 (1H, s), 9.54 (1H, s), 8.26 (1H, s, *J*= 4.5 Hz), 7.92 (1H, s), 7.81 (1H, dd, *J*= 9.3 Hz, *J*= 2.7 Hz), 7.32 (1H, d, *J*= 8.1 Hz), 7.20-7.13 (3H, m), 6.64 (1H, d, *J*= 8.1 Hz), 3.89 (3H, s), 3.84 (3H, s) ; purity: 97% ; MS (m/e): 385 (MH+).
7.3.891	5-Fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-N2-methyl-2,4-pyrimidinediamine (R940304)	A mixture of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine (0.15 g, 0.4 mmol), methylamine hydrochloride (0.324 g, 48 mmol) and diisopropylethylamine (0.84 mL, 48 mmol) in MeOH (2 mL) was heated in a sealed tube at 100 °C for 24h (followed by TLC). The reaction was cooled to room temperature and diluted with H_2O (20 mL). The solid was filtered, washed with H_2O and dried to obtain 5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-N2-methyl-2,4-pyrimidinediamine **R940304**. ^{1}H NMR (DMSO-d6): δ 10.65 (1H, s), 8.48 (1H, s), 8.29 (2H, m), 7.93 (1H, m), 7.28 (1H, d, *J*= 9 Hz), 4.00 (3H, s), 2.94 (3H, s), 2.90 (3H, d, *J*= 4.5 Hz) ; purity: 90% ; MS (m/e): 306 (MH+);
7.3.892	5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine (R940306)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine **R940306.** ^{1}H NMR (DMSO-d6): δ 9.28 (1H, s), 9.21 (1H, s), 8.12 (1H, d, *J*= 3.9 Hz), 8.06 (1H, d, *J*= 2.7 Hz), 7.99 (1H, m), 7.89 (1H, dd, *J*= 9.3 Hz, *J*= 2.7 Hz), 7.52 (1H, q, *J*= 4.9 Hz), 7.41 (1H, t, *J*= 2.1 Hz), 7.37 (1H, d, *J*= 7.5 Hz), 7.10 (1H, t, *J*= 8.1 Hz), 6.83 (1H, d, *J*= 9 Hz), 6.53 (1H, dd, *J*= 8.1 Hz, *J*= 1.8 Hz), 4.40 (2H, s), 3.82 (3H, s), 2.96 (3H, d, *J*= 5.1 Hz), 2.73 (3H, d, *J*= 4.5 Hz) ; purity: 93% ; MS (m/e): 455 (MH+).

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Section Number	Name of compound and reference number	Experimental
7.3.893	(R)-N2-[3-(dihydroxypropylaminocarbonylmethyleneoxy)-phenyl]-5-fluoro-N4-(3-isopropylphenyl)-2,4-pyrimidinediamine (R940307)	In like manner to the preparation of 5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-N2-methyl-2,4-pyrimidinediamine, 5-fluoro-N4-(3-isopropylphenyl)-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and (R)-3-amino-1,2-propanediol were reacted to give (R)-N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl)-5-fluoro-N4-(3-isopropylphenyl)-2,4-pyrimidinediamine **R940307**. ^{1}H NMR (DMSO-d6): δ 9.96 (1H, s), 9.80 (1H, s), 8.29 (1H d, *J*= 4.5 Hz), 7.98 (1H, t, *J*= 5.5 Hz), 7.77 (1H, d, *J*= 7.2 Hz), 7.57 (1H, s), 7.37 (1H, t, *J*= 7.8 Hz), 7.30-7.22 (3H, m), 7.12 (1H, d, *J*= 7.8 Hz), 6.70 (1H, d, *J*= 7.5 Hz), 4.47 (2H, s), 3.62 (1H, m), 3.38 (3H, m), 3.15 (1H, m), 2.94 (1H, quint, *J*= 6.9 Hz), 1.27 (6H, d, 6.9 Hz) ; purity: 99%; MS (m/e): 469 (M), 470 (MH+).
7.3.894	N4-(3-*tert*-Butylpheny)-5-fluoro-N2-[3-(1,1-dimethyl-2-hydroxyethylaminocarbonylmethyleneoxy)-phenyl]-2,4-pyrimidinediamine (R940308)	In like manner to the preparation of 5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-N2-methyl-2,4-pyrimidinediamine, N4-(3-*tert*-butylphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and 2-amino-2-methyl-1-propanol were reacted to give N4-(3-*tert*-butylpheny)-5-fluoro-N2-[3-(1,1-dimethyl-2-hydroxyethylaminocarbonylmethyleneoxy)-phenyl]-2,4-pyrimidinediamine **R940308.** ^{1}H NMR (DMSO-d6): δ 9.38 (1H, s), 9.28 (1H, s), 8.20 (1H, d, *J*= 3.9 Hz), 7.99 (1H, d, *J*= 7.5 Hz), 7.60 (1H, t, *J*= 2.1 Hz), 7.46 (1H, s), 7.37 (2H, t, *J*= 7.9 Hz), 7.30 (1H, s), 7.19 (2H, t, *J*= 7.9 Hz), 6.56 (1H, dd, *J*= 7.5 Hz, *J*= 1.5 Hz), 5.06 (1H, t, *J*= 5.7 Hz), 4.37 (2H, s), 3.40 (2H, m), 1.36 (9H, s), 1.32 (6H, s) ; purity: 93% ; MS (m/e): 482 (MH+).
7.3.895	N4-(3-Aminomethylenephenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940309)	A mixture of N4-[3-(N-*tert*-butoxycarbonyl-N-aminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline in MeOH was heated in a sealed tube at 100 °C for 12h. The reaction was cool to room temperature and the solvent was removed under reduce pressure. The resulting residue was filtered through a pad of silica gel (200-400 mesh, EtOAc/MeOH (2M NH_3) 95:5) to obtain the desired product N4-(3-aminomethylenephenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940309.** ^{1}H NMR (DMSO-d6): δ 9.41 (1H, s), 9.23 (1H, s), 8.20 (1H, d, *J*= 3.9 Hz), 8.00 (1H, m), 7.78 (1H, s), 7.72 (1H, d, *J*= 7.2 Hz), 7.46 (1H, s), 7.42-7.33 (2H, m), 7.21 (1H, t, *J*= 7.8 Hz), 7.14 (1H, d, *J*= 7.8 Hz), 6.59 (1H, dd, *J*= 8.1 Hz, *J*= 2.4 Hz), 4.42 (2H, s), 3.79 (2H, s), 2.74 (3H, d, *J*= 4.8 Hz) ; purity: 98% ; MS (m/e): 397 (MH+).

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Section Number	Name of compound and reference number	Experimental
7.3.896	N4-[3-(2-(N4-(3-aminomethylenephenyl)-5-fluoro-4-pyrimidineamine)-N-methylaminomethylene)-phenyl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidineamine (R940311)	A mixture of N4-[3-(N-methylaminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (0.05 g, 0.18 mmol) and 3-(methylaminocarbonylmethyleneoxy)aniline (0.04 g, 0 22 mmol) in EtOH (0.5 mL),was heated at 175 °C for 35 min using microwave. An aqueous work up gave the desired N4-[3-(2-(N4-(3-aminomethylenephenyl)-5-fluoro-4-pyrimidineamine)-N-methylaminomethylene)-phenyl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidineamine **R940311.** ^{1}H NMR (DMSO-d6): δ 9.48 (1H, s), 9.31 (1H, s), 9.26 (1H, s), 8.20 (1H, d, *J*= 3.6 Hz), 8.10-8.05 (4H, m), 7.62 (1H, s), 7.49 (2H, m), 7.41 (1H, t, *J*= 8.1 Hz), 7.36 (2H, m), 7.22 (1H, t, *J*= 8.4 Hz), 7.17 (1H, t, *J*= 8.4 Hz), 7.06 (1H, d, *J*= 7.5 Hz), 6.59 (1H, dd, *J*= 8.4 Hz, *J*= 2.4 Hz), 6.54 (1H, dd, *J*= 7.8 Hz, *J*= 2.4 Hz), 4.93 (2H, s), 4 46 (2H, s), 4.45 (2H, s), 3.28 (3H, d, *J*= 3Hz), 2.73 (6H, m) ; purity: 98%; MS (m/e) : 684 (M), 685 (MH+).
7.3.897	5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-*iso*-propylaminocarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine (R940312)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3- N-*iso*-propylaminomethylene-4-methoxyphenyl)-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-*iso*-propylaminocarbonyl-4-methoxyphenyl)-2,4-pyrimidinediamine **R940312.** ^{1}H NMR (DMSO-d6): δ 10.09 (1H, s), 9.88 (1H, s), 8.25 (1H, d, *J*= 4.8 Hz), 8.07 (1H, d, *J*= 2.7 Hz), 8.05 (1H, m), 7.81 (1H, dd, *J*= 9 Hz, *J*= 2.7 Hz), 7.63 (1H, s), 7.25 (2H, m), 7.17 (1H, t, *J*= 8.25 Hz), 6.91 (1H, d, *J*= 9 Hz), 6.68 (1H, d, *J*= 8.1 Hz), 4.42 (2H, s), 3.85 (1H, m), 3.81 (3H, s), 2.72 (3H, d, *J*= 4.2 Hz), 1.30 (6H, d, *J*= 6 Hz) ; purity: 97% ; MS (m/e): 483 (MH+).
7.3.898	5-Fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine (R940314)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, N2-chloro-5-fluoro-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine **R940314.** ^{1}H NMR (DMSO-d6): δ 9.33 (1H, s), 9.21 (1H, s), 8.15 (1H, d, *J*= 3.6 Hz), 8.04 (1H, d, *J*= 4.8 Hz), 7.82 (1H, dd, *J*= 9 Hz, *J*= 2.7 Hz), 7.57 (1H, d, *J*= 3 Hz), 7.47 (1H, t, *J*= 1.95 Hz), 7.34 (1H, m), 7.18 (1H, t, *J*= 8.1 Hz), 7.04 (1H, d, *J*= 9 Hz), 6.56 (1H, dd, *J*= 8.4 Hz, *J*= 2.1 Hz), 4.40 (2H, s), 3.86 (3H, s), 3.63 (4H, t, *J*= 4.5 Hz), 3.53 (2H, s), 2.74 (3H, d, *J*= 4.5 Hz), 2.46 (4H, m) ; purity: 97%; MS (m/e): 497 (MH+).

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Section Number	Name of compound and reference number	Experimental
7.3.899	N2-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine (R940316)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, N2-chloro-5-fluoro-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-4-pyrimidineamine and 4-amino-2-chloro-6-methylphenol were reacted to produce N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine R940316. ^{1}H NMR (DMSO-d6): δ 9.28 (1H, s), 9.01 (1H, s), 8.65 (1H, s), 8.11 (1H, d, *J*= 3.9 Hz), 7.76 (1H, dd, *J*= 9 Hz, *J*= 3 Hz), 7.61 (1H, d, *J*= 2.4 Hz), 7.50 (1H, d, *J*= 2.7 Hz), 7.30 (1H, d, *J*= 2.1 Hz), 7.04 (1H, d, *J*= 8.7 Hz), 3.87 (3H, s), 3.63 (4H, t, *J*= 4.3 Hz), 3.52 (2H, s), 2.45 (4H, m), 2.17 (3H, s) ; purity: 97% ; MS (m/e): 474 (MH+).
7.3.900	N4-(3-N-methylaminomethylenephenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940317)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, N4-[3-(N-*tert*-butoxycarbonyl-N-methylaminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-(3-N-methylaminomethylenephenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine R940317. ^{1}H NMR (DMSO-d6): δ 9.41 (1H, s), 9.31 (1H, s), 9.29 (1H, s), 8.20 (1H, d, *J*= 3 Hz), 8.05 (1H, m), 7.80 (1H, d, *J*= 7.8 Hz), 7.74 (1H, s), 7.45-7.35 (3H, m), 7.21 (1H, t, *J*= 8.1 Hz), 7.13 (1H, d, *J*= 7.5 Hz), 6.59 (1H, d, *J*= 9.6 Hz), 4.43 (2H, s), 3.71 (2H, s), 2.75 (3H, d, *J*= 4.2 Hz), 2.35 (3H, s) ; purity: 83.9% ; MS (m/e): 411 (MH+).
7.3.901	N2-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-[3-(N-piperazinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine (R940318)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, N4-[3-(N-piperazinomethylene)-4-methoxyphenyl]-2-chloro-5-fluoro-4-pyrimidineamine and 4-amino-2-chloro-6-methylphenol were reacted to produce N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-[3-(N-piperazinomethylene)-4-methoxyphenyl]-2,4-pyrimidinediamine **R940318.** ^{1}H NMR (DMSO-d6): δ 9.27 (1H, s), 9.00 (1H, s), 8.10 (1H, d, *J*= 3.6 Hz), 7.75 (1H, dd, *J*= 8.7 Hz, *J*= 2.7 Hz), 7.61 (1H, d, *J*= 2.4 Hz), 7.49 (1H, d, *J*= 2.4 Hz), 7.31 (1H, d, *J*= 2.4 Hz), 7.03 (1H, d, *J*= 9 Hz), 3.86 (3H, s), 3.49 (2H, s), 2.75 (4H, t, *J*= 4.65 Hz), 2.39 (4H, m), 2.17 (3H, s) ; purity: 95%; MS (m/e): 473 (MH+).

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Section Number	Name of compound and reference number	Experimental
7.3.902	N4-(3-(N-*tert*-Butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxyphenyl)-5-fluoro-N2-[3-(methylaminocarbonyl methyleneoxy)phenyl]-2,4-pyrimidinediamine (R940319)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, N4-(3-(N-*tert*-butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-(3-(N-*tert*-butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxyphenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940319.** ^{1}H NMR (DMSO-d6): δ 9.44 (1H, s), 8.95 (1H, s), 8.15 (1H, d, *J*= 3.6 Hz), 8.06 (1H, m), 7.83 (1H, m), 7.74 (1H, m), 7.56 (1H, m), 7.37 (1H, m), 7.20 (1H, t, *J*= 7.9 Hz), 7.02 (1H, d, *J*= 9.3 Hz), 6.57 (1H, d, *J*= 7.8 Hz), 4.44 (2H, s), 4.42 (1H, m), 4.33 (2H, s), 3.89 (3H, s), 2.74 (3H, d, *J*= 4.8 Hz), 1.52-1.30 (9H, m), 1.16 (6H, d, *J*= 6.9 Hz) ; purity: 98% ; MS (m/e): 569 (MH+).
7.3.903	N4-(3-N,N-Dimethylaminomethylene-4-methoxyphenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940321)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(3-N,N-dimethylaminomethylene-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-(3-N,N-dimethylaminomethylene-4-methoxyphenyl)-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940321.** ^{1}H NMR (DMSO-d6): δ 9.32 (1H, s), 9.23 (1H, s), 8.14 (1H, d, *J*= 3.9 Hz), 8.05 (1H, m), 7.83 (1H, dd, *J*= 8.7 Hz, *J*= 2.4 Hz), 7.55 (1H, d, *J*= 2.4 Hz), 7.45 (1H, s), 7.36 (1H, d, *J*= 8.4 Hz), 7.18 (1H, t, *J*= 8.1 Hz), 7.03 (1H, d, *J*= 9 Hz), 6.56 (1H, dd, *J*= 7.2 Hz, *J*= 1.5 Hz), 4.41 (2H, s), 3.86 (3H, s), 2.73 (3H, d, *J*= 4.5 Hz), 2.24 (6H, s) ; purity: 91.8% ; MS (m/e): 455 (MH+).
7.3.904	N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940323)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940323.** ^{1}H NMR (DMSO-d6): δ 10.70 (1H, s), 9.45 (1H, s), 9.19 (1H, s), 8.17 (1H, d, *J*= 3.9 Hz), 8.05 (1H, m), 7.43-7.34 (4H, m), 7.17 (1H, t, *J*= 8.25 Hz), 6.98 (1H, d, *J*= 8.4 Hz), 6.56 (1H, dd, *J*= 7.8 Hz, *J*= 2.1 Hz), 4.25 (2H, s), 2.74 (3H, d, *J*= 4.5 Hz), 1.5 (6H, s) ; purity: 98.7% ; MS (m/e): 467 (MH+).

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Section Number	Name of compound and reference number	Experimental
7.3.905	N4-[3-Dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940337)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940337.** ^{1}H NMR (DMSO-d6): δ 9.28 (1H, s), 9.20 (1H, s), 8.34 (1H, dd, *J*= 4.8 Hz, *J*= 1.2 Hz), 8.14 (1H, d, *J*= 3.8 Hz), 8.03 (1H, m), 7.64-7.60 (2H, m), 7.51-7.46 (3H, m), 7.37 (1H, d, *J*= 8.4 Hz), 7.17 (1H, t, *J*= 8.1 Hz), 6.94-6.91 (2H, m), 6.55 (1H, dd, *J*= 8.4 Hz, *J*= 3Hz), 4.42 (2H, s), 3.93 (2H, s), 2.74 (3H, d, *J*= 4.5 Hz), 1.32 (6H, s) ; purity: 98.2% ; MS (m/e): 530 (MH+);
7.3.906	N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine (R940338)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 5-amino-1-methyl-1-indazole were reacted to produce N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine **R940338.** ^{1}H NMR (DMSO-d6): δ 10.73 (1H, s), 9.39 (1H, s), 9.17 (1H, s), 8.21 (1H, s), 8.16 (1H, d, *J*= 3.9 Hz), 7.87 (1H. s), 7.56 (2H, m), 7.41 (1H, m), 7.32 (1H, s), 7.00 (1H, d, *J*= 8.4 Hz), 4.07 (3H, s), 1.51 (6H, s) ; purity: 99.2% ; MS (m/e): 434 (MH+).
7.3.907	N4-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R921303)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R921303.** ^{1}H NMR (DMSO-d6): δ 12.05 (1H, s), 9.67 (1H, s), 9.27 (1H, s), 8.24 (1H, d, *J*= 3.6 Hz), 8.05 (1H, m), 7.73-7.68 (1H, m), 7.56 (1H, t, *J*= 2.7 Hz), 7.50 (1H, s), 7.36 (2H, d, *J*= 8.7 Hz), 7.19 (1H, t, *J*= 8.2 Hz), 6.58 (1H, dd, *J*= 8.4 Hz, *J*= 2.4 Hz), 4.34 (2H, s), 2.74 (3H, d, *J*= 4.5 Hz); ^{19}F NMR (DMSO-d6): δ -21643, -46385 ; purity: 100% ; MS (m/e): 475 (MH+).

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Section Number	Name of compound and reference number	Experimental
7.3.908	N4-[(2,2-Dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-7-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940345)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-7-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-7-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940345.** ^{1}H NMR (DMSO-d6): δ 11.23 (1H, s), 9.69 (1H, s), 9.54 (1H, s), 8.50 (1H, s), 8.25 (1H, d, *J*= 3.3 Hz), 8.06 (1H, m), 7.96 (1H, t, *J*= 2.5 Hz), 7.41-7.36 (2H, m), 7.24 (1H, t, *J*= 8.25 Hz), 6.34 (1H, d, *J*= 8.7 Hz), 4.47 (2H, s), 2.74 (3H, d, *J*= 3.3 Hz), 1.53 (6H, s) ; purity: 98.4% ; MS (m/e): 468 (MH+).
7.3.909	N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R940346)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to produce N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine **R940346.** ^{1}H NMR (DMSO-d6): δ 10.75 (1H, s), 8.25 (1H, d, *J*= 4 5 Hz), 7.42-7.37 (1H, m), 7.34 (1H, s), 7.10 (3H, m), 7.00 (1H, d, *J*= 8.4 Hz), 6.53 (1H, m), 1.50 (6H, s) ; purity: 97.5% ; MS (m/e): 396 (MH+).
7.3.910	N4-[(2,2-Dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R940347)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-(methylaminocarbonylmethyleneoxy)aniline were reacted to produce N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine **R940347.** ^{1}H NMR (DMSO-d6): δ 11.20 (1H, s), 9.46 (1H, s), 8.26 (1H, d, *J*= 3.6 Hz), 8.06 (1H, s), 7.71 (1H, m), 7.49 (1H, d, *J*= 8.4 Hz), 7.45 (1H, s), 7.38 (1H, d, *J*= 9 Hz), 7.21 (1H, t, *J*= 8.1 Hz), 6.61 (1H, d, *J*= 8.7 Hz), 4.47 (2H, s), 2.74 (3H, s), 1.52 (6H, s); purity: 100% ; MS (m/e): 468 (MH+).

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Section Number	Name of compound and reference number	Experimental
7.3.911	N4-[3-Dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R940348)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to produce N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine **R940348.** ^{1}H NMR (DMSO-d6): δ 9.25 (1H, s), 9.23 (1H, s), 9.02 (1H, s), 8.34 (1H, d, *J*= 4.5 Hz), 8.11 (1H, d, *J*= 3.3 Hz), 7.62 (2H, m), 7.52 (2H, m), 7.22 (1H, s), 7.19 (1H, d, *J*= 7.5 Hz), 7.03 (1H, t, *J*= 7.9 Hz), 6.93 (2H, m), 6.38 (1H, d, *J*= 7.8 Hz), 3.93 (2H, s), 1.32 (6H, s) ; purity: 96.5%.
7.3.912	N4-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R940349)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to produce N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine **R940349.** ^{1}H NMR (DMSO-d6): δ 12.03 (1H, s), 9.63 (1H, s), 9.26 (1H, s), 9.09 (1H, s), 8.21 (1H, d, *J*= 3.6 Hz), 7.70 (1H, dd, *J*= 9 Hz, *J*= 2.4 Hz), 7.59 (1H, d, *J*= 2.7 Hz), 7.34 (1H, d, *J*= 9.3 Hz), 7.26 (1H, s), 7.16 (1H, d, *J*= 7.8 Hz), 7.04 (1H, t, *J*= 8.2 Hz), 6.41 (1H, d, *J*= 10.2 Hz) ; ^{19}F NMR (DMSO-d6): δ -21646, -46516 ; purity: 95.8% ; MS (m/e): 404 (MH+);
7.3.913	N2,N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine (R940350)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-5-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 6-amino-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one were reacted to produce N2,N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine **R940350.** ^{1}H NMR (DMSO-d6): δ 10.68 (1H, s), 10.62 (1H, s), 9.38 (1H, s), 9.04 (1H, s), 8.11 (1H, d, *J*= 3.6 Hz), 7.46 (1H, dd, *J*= 8.1 Hz, *J*= 1.8 Hz), 7.33-7.26 (3H, m), 6.95 (1H, d, *J*= 8.7 Hz), 6.84 (1H, d, *J*= 8.4 Hz), 1.49 (6H, s), 1.45 (6H, s) ; purity: 95.4% ; MS (m/e): 479 (MH+).

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Section Number	Name of compound and reference number	Experimental
7.3.914	N2-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine (R940351)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 6-amino-2,2-difluoro-4H-benzo[1,4]oxazin-3-one were reacted to produce N2-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine **R940351.** ^{1}H NMR (DMSO-d6): δ 11.99 (1H, s), 10.74 (1H, s), 9.64 (1H, s), 9.50 (1H, s), 8.19 (1H, d, *J*= 3.9 Hz), 7.50 (2H, m), 7.43 (1H, dd, *J*= 8.4 Hz, *J*= 1.8 Hz), 7.32 (1H, s), 7.20 (1H, d, *J*= 9.3 Hz), 6.98 (1H, d, *J*= 8.7 Hz), 1.49 (6H, s) ; purity: 94.77% ; MS (m/e): 487 (MH+).
7.3.915	N2,N4-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine (R940352)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and 6-amino-2,2-difluoro-4H-benzo[1,4]oxazin-3-one were reacted to produce N2,N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-2,4-pyrimidinediamine **R940352.** ^{1}H NMR (DMSO-d6): δ 12.08 (1H, s), 12.00 (1H, s), 9.72 (1H, s), 9.44 (1H, s), 8.23 (1H, d, *J*= 3.6 Hz), 7.73 (1H, dd, *J*= 11.1 Hz, *J*= 1.5 Hz), 7.6 (1H, s), 7.56 (1H, s), 7.51 (1H, dd, *J*= 9.6 Hz, *J*= 2.4 Hz), 7.35 (1H, d, *J*= 9 Hz), 7.24 (1H, d, *J*= 8.7 Hz); ^{19}F NMR (DMSO-d6): δ -21670, -21722, -4651 ; purity: 100% ; MS (m/e): 495 (MH+).
7.3.916	N4-[(2,2-Difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R940353)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and methyl 5-aminobenzofuran-2-carboxylate were reacted to produce N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine **R940353.** ^{1}H NMR (DMSO-d6): δ 12.05 (1H, s), 9.69 (1H, s), 9.43 (1H, s), 8.28 (1H, s), 8.25 (1H, d, *J*= 3.6 Hz), 7.40-7.64 (4H, m), 7.54 (1H, s), 7.38 (1H, d, *J*= 9 Hz), 3.97 (3H, s) ; ^{19}F NMR (DMSO-d6): δ -21707, -46489 ; purity: 97.77% ; MS (m/e): 486 (MH+).

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Section Number	Name of compound and reference number	Experimental
7.3.917	N4-[(2,2-Dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R940354)	In like manner to the preparation of 5-fluoro-N2-[3-(methylaminocarbonylmethyleneoxy)phenyl]-N4-(3-aminocarbonylphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine and methyl 5-aminobenzofuran-2-carboxylate were reacted to produce N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine **R940354.** ^{1}H NMR (DMSO-d6): δ 10.75 (1H, s), 9.67 (1H, s), 9.53 (1H, s), 8.25 (1H, s), 8.21 (1H, d, *J*= 4.2 Hz), 7.66 (2H, s), 7.59 (1H, s), 7.31 (1H, d, *J*= 8.7 Hz), 7.26 (1H, s), 7.03 (1H, d, *J*= 8.1 Hz), 3.97 (3H, s), 1.52 (6H, s) ; purity: 95.58% ; MS (m/e): 478 (MH+).
7.3.918	N2,N4-Bis(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950244)	N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 2:1) to give N2,N4-bis(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine. ^{1}H NMR (MeOD, 300 MHz): δ 8.65 (d, 1H, J = 2.4 Hz), 7.15-7.58 (m, 8H), 2.24 (s, 3H), 2.22 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H); LCMS: ret. time: 17 03 min.; purity: 87.0%; MS (m/e): 478.89 (MH^+).
7.3.919	N4-(3-N,N-Diacetylaminophenyl)-N2-(3-N-acetylaminopheny)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950245)	N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 2:1) to give N4-(3-N,N-diacetylaminophenyl)-N2-(3-N-acetylaminopheny)-5-fluoro-N2,N4-pyrimidinediacetylamine. ^{1}H NMR (MeOD, 300 MHz): δ 8.65 (d, 1H, J = 2.4 Hz), 7.03-7.66 (m, 8H), 2.21 (s, 6H), 2.14 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H); LCMS: ret. time: 19.27 min.; purity: 92.6%; MS (m/e): 521.01 (MH^+).
7.3.920	N4-(3-N-Acetylaminophenyl)-N2-(3-N,N-diacetylaminopheny)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950246)	N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 2:1) to give N4-[3-N-acetylaminophenyl]-N2-(3-N,N-diacetylaminopheny)-5-fluoro-N2,N4-pyrimidinediacetylamine. ^{1}H NMR (MeOD, 300 MHz): δ 8.66 (d, 1H, J = 2.4 Hz), 6.88-7.57 (m, 8H), 2.22 (s, 6H), 2.11 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H); LCMS: ret. time: 18.89 min.; purity: 83.0%; MS (m/e): 520.97 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.921	N2,N4-Bis(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950247)	N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 2:1) to give N2,N4-bis(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine. ^{1}H NMR (MeOD, 300 MHz): δ 8.58 (d, 1H, J = 2.4 Hz), 6.75-7.53 (m, 8H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 6H), 1.99 (s, 6H); LCMS: ret. time: 21.51 min.; purity: 91.8%; MS (m/e): 563.00 (MH^+).
7.3.922	N4-(3-Nitrophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950261)	A mixture of equimolar amounts of 2-chloro-N4-(3-nitrophenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-nitrophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 92.7%; MS (m/e): 412.94 (MH^+).
7.3.923	N4-(3-Aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine HCl salt (R950262)	N4-(3-Nitrophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine and Pd/C 10% (50% water content) were suspended in EtOH–10% aqueous HCl (1 : 1) and hydrogenated in a Parr apparatus for 2 hours (22 °C, 50 psi). The suspension was filtered over celite and carefully washed with MeOH. The combined filtrates were concentrated under reduced pressure to give the HCl salt of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.7%; MS (m/e): 383.07 ($M\text{-}Cl^+$, 100).
7.3.924	N4-(3-Aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950263)	The HCl salt of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine was neutralized with aqueous sodium carbonate solution and extracted with EtOAc. The organic phase was dried and concentrated to give N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a pale yellow solid. ^{1}H NMR (DMSO): δ 10.00 (s, 1H), 9.92 (s, 1H), 8.07 (d, 1H, J= 2.4 Hz), 8.15 (bs, 2H), 7.91-8.07 (m, 3H), 7.08-7.21 (m, 5H), 6.56 (d, 1H, J = 7.2 Hz), 4.32 (s, 2H), 2.72 (d, 3H, J = 4.8 Hz); LCMS: purity: 92.7%; MS (m/e): 383.17 (MH^+, 100).

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Section Number	Name of compound and reference number	Experimental
7.3.925	N4-(3-Bis-N-methylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950264)	A solution of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DME-DMF (1 : 1) was treated with 10 equivalents of MeI and sodium bicarbonate. The mixture was stirred for 1.5 hours at 70°C and purified by flash chromatography on silica gel to give N4-(3-bis-N-methylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 90.2%; MS (m/e): 411.04 (MH^+, 100).
7.3.926	N4-(3-N-Hydroxyethylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950265)	A solution of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DME-DMF (1 : 1) was treated with 10 equivalents of 2-bromoethanol and sodium bicarbonate. The mixture was stirred for 16 hours at 70°C and purified by flash chromatography on silica gel to give N4-(3-N-hydroxyethylaminophenyl)-5-fluoro. LCMS: purity: 90.2%; MS (m/e): 427.33 (MH^+, 100).
7.3.927	N4-(3-Bis(N-hydroxyethyl)aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950266)	A solution of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DME-DMF (1 : 1) was treated with 10 equivalents of 2-bromoethanol and sodium bicarbonate. The mixture was stirred for 16 hours at 70°C and purified by flash chromatography on silica gel to give N4-(3-bis(N-hydroxyethyl)aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 94.2%; MS (m/e): 471.46 (MH^+, 100).
7.3.928	N4-(3-N-Methylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950267)	A solution of N4-(3-aminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DME-DMF (1 : 1) was treated with 10 equivalents of MeI and sodium bicarbonate. The mixture was stirred for 1.5 hours at 70°C and purified by flash chromatography on silica gel to give N4-(3-N-methylaminophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.3%; MS (m/e): 397.02 (MH^+, 100).
7.3.929	N4-(3-Carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950290)	A mixture of equimolar amounts of 2-chloro-N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 97.8%; MS (m/e): 443.20 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.930	N4-(3-Carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-carboxymethyleneoxyphenyl]-2,4-pyrimidinediamine (R950291)	The reaction of N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (0.1 g) and LiOH (10 equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatment with aqueous HCl gave the solid. The resulting solid was filtered, washed with water and dried to give N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-carboxymethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 91.5%; MS (m/e): 415.16 (MH^+).
7.3.931	N4-(3-Methoxycarbonyl-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950293)	A solution of N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a 4 M solution of HCl in dioxane. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(3-methoxycarbonyl-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 96.8%; MS (m/e): 457.25 (MH^+).
7.3.932	N4-(4-Methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950294)	A mixture of equimolar amounts of 2-chloro-N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 92.1%; MS (m/e): 469.26 (MH^+).
7.3.933	N4-(4-Methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950295)	A mixture of equimolar amounts of 2-chloro-N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h followed by aqueous work up gave N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 87.6%; MS (m/e): 455.26 (MH^+).
7.3.934	N4-(4-Ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950296)	A solution of N4-(4-ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in EtOH was treated with the HCl salt of methylamine. The mixture was stirred for 4 hours at 100°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 87.4%; MS (m/e): 468.29 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.935	N4-(4-Carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950344)	A mixture of equimolar amounts of 2-chloro-N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 97.8%; MS (m/e): 456.32 (MH^+).
7.3.936	N4-(2,3-Dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950345)	A solution of N4-(4-Methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in TfOH was heated for 2 hours at 100°C. Aqueous work up followed by flash chromatography on silica gel gave N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.2%; MS (m/e): 435.95 (MH^+).
7.3.937	N4-(4-Methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950346)	A solution of N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a 4 M solution of HCl in dioxane. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 85.2%; MS (m/e): 468.01 (MH^+).
7.3.938	N4-(4-Hydroxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950347)	The reaction of N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and LiOH (10 equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatment with aqueous HCl gave a pale yellow solid. The resulting solid was filtered, washed with water and dried to give N4-(4-hydroxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 94.7%; MS (m/e): 382.03 (MH^+).
7.3.939	N4-(2,3-Dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950348)	A mixture N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 89.5%; MS (m/e): 451.00 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.940	N4-(4-Hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950349)	A solution of N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a sodiumcyanoborohydride. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-Hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 9.19 (s, 1H), 9.09 (s, 1H), 8.03 (d, 1H, J= 2.4 Hz), 7.28-7.93 (m, 5H), 7.07 (t, 1H, J = 7.2 Hz), 6.71 (d, 1H, J = 7.2 Hz), 6.44 (dd, 1H, J = 2.6, 7.2 Hz), 5.31 (d, 1H, J = 5.1 Hz), 4.14-4.59 (m, 3H), 4.30 (s, 2H), 2.63 (d, 3H, J = 4.8 Hz), 1.82-2.03 (m, 2H); LCMS: purity: 93.3%; MS (m/e): 440.15 (MH^+).
7.3.941	N4-(2,3-Dihydro-4-O-methyloxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950356)	A mixture N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and methoxyamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 85.5%; MS (m/e): 465.10 (MH^+).
7.3.942	N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950368)	A mixture N4-(4-azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and Pd/C (10%) in MeOH was hydrogenated at 22°C for 6 hours (40psi). The mixture was filtered and concentrated to dryness to give N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 9.60 (s, 1H), 9.46 (s, 1H), 8.73 (bs, 3H), 8.00-8.10 (m, 3H), 7.47 (s, 1H), 7.42 (m, 1H), 7.29 (d, 1H, J = 7.2 Hz), 7.11 (t, 1H, J = 7.2 Hz), 6.82 (d, 1H, J 7.0 Hz), 6.46 (m, 1H), 4.23-4.46 (m, 3H), 4.31 (s, 3H), 2.63 (d, 3H, J = 4.8 Hz), 2.09-2.29 (m, 2H); LCMS: purity: 97.6%; MS (m/e): 438.98 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.943	N4-(3-Methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950371)	A mixture of equimolar amounts of 2-chloro-N4-(3-methylcarbonylphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 10.16 (s, 1H), 9.82 (s, 1H), 8.24 (d, 1H, J= 2.4 Hz), 8.15 (s, 1H), 7.91-8.07 (m, 2H), 7.70 (d, 1H, J= 7.0 Hz), 7.49 (t, 1H, J = 7.2 Hz), 7.08-7.21 (m, 3H), 6.56 (d, 1H, J = 7.2 Hz), 4.30 (s, 3H), 2.62 (d, 3H, J = 4.8 Hz), 2.48 (s, 3H); LCMS: purity: 93.8%; MS (m/e): 410.50 (MH^+).
7.3.944	N4-(3-Phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950372)	A mixture of equimolar amounts of 2-chloro-N4-(3-phenylcarbonylphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 86.0%; MS (m/e): 472.50 (MH^+).
7.3.945	N4-(3-Methylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950373)	A mixture N4-(3-methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(3-methylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 11.21 (s, 1H), 10.11 (s, 1H), 9.85 (s, 1H), 6.54-8.23 (m, 9H), 4.32 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H), 2.47 (s, 3H); LCMS: purity: 92.4%; MS (m/e): 425.28 (MH^+).
7.3.946	N4-(3-Phenylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950374)	A mixture N4-(3-phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(3-phenylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 11.63 (s, 1H), 10.30 (s, 1H), 9.85 (s, 1H), 6.44-8.43 (m, 14H), 4.42 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H); LCMS: purity: 92.4%; MS (m/e): 487.31 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.947	N2,N4-Bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950376)	A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-acetophenone in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N2,N4-bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.1%; MS (m/e): 365.19 (MH^+).
7.3.948	N2,N4-Bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950377)	A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-benzophenone in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N2,N4-bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.7%; MS (m/e): 489.29 (MH^+).
7.3.949	N2,N4-Bis(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950378)	A solution of N2,N4-bis(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine in TfOH was heated for 2 hours at 100°C. Aqueous work up followed by flash chromatography on silica gel gave N2,N4-bis(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ^1H NMR (DMSO): δ 9.36 (s, 1H), 9.14 (s, 1H), 8.06 (d, 1H, J= 2.4 Hz), 7.72-7.99 (m, 3H), 6.97 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 4.42-4.52 (m, 4H), 2.70-2.78 (m, 4H); LCMS: purity: 94.3%; MS (m/e): 484.50 (MH^+).
7.3.950	N2,N4-Bis(3-methylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine (R950379)	A mixture of N2,N4-bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(3-methylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ^1H NMR (DMSO): δ 11.21 (s, 1H), 10.11 (s, 1H), 9.85 (s, 1H), 6.54-8.23 (m, 9H), 4.32 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H), 2.47 (s, 3H); LCMS: purity: 92.1%; MS (m/e): 393.06 ($M-H^-$).
7.3.951	N2,N4-Bis(3-phenylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine (R950380)	A mixture of N2,N4-bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(3-phenylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.3%; MS (m/e): 486.05 ($M-H^-$).
7.3.952	N2,N4-Bis(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950381)	A mixture of N2,N4-bis(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98.1%; MS (m/e): 449.03 ($M-H^-$).

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Section Number	Name of compound and reference number	Experimental
7.3.953	N4-(4-Acetyloxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950382)	A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in pyridine was treated with acetic anhydride at 22°C for 16 hours. Aqueous work up gave N4-(4-acetyloxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 10.43 (bs, 1H), 9.62 (bs, 1H), 8.03 (d, 1H, J = 2.4 Hz), 7.10-7.83 (m, 7H), 6.83 (d, 1H, J = 7.4 Hz), 6.52 (d, 1H, J = 7.2 Hz), 5.01 (m, 1H), 4.75 (s, 2H), 4.03-4.32 (m, 2H), 2.62 (s, 3H), 2.23 (s, 3H), 1.93-2.13 (m, 2H); LCMS: purity: 92.1%; MS (m/e): 393.06 ($M-H^-$).
7.3.954	N4-(4-Azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950383)	A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry THF was treated with 2 equivalents of DPPA and DBU. The mixture was stirred for 3 hours at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 10.09 (bs, 1H), 9.83 (bs, 1H), 8.18 (d, 1H, J = 2.4 Hz), 7.97 (m, 1H), 7.11-7.61 (m, 6H), 6.82 (d, 1H, J = 7.8 Hz), 6.62 (d, 1H, J = 7.2 Hz), 4.78 (s, 2H), 4.03-4.33 (m, 3H), 2.62 (s, 3H), 1.93-2.13 (m, 2H); LCMS: purity: 97.9%; MS (m/e): 463.07 (MH^+).
7.3.955	N4-(4-Benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950385)	A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in THF was treated with bortrifluoride etherate at 80°C for 8 hours. Aqueous work up gave N4-(4-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 9.18 (s, 1H), 9.14 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.93 (bs, 1H), 5.86-7.48 (m, 9H) 4.73-4.74 (m, 2H), 4.33 (s, 2H), 2.62 (s, 3H); LCMS: purity: 96.5%; MS (m/e): 420.07 ($M-H^-$).
7.3.956	N4-(3-Hydroxymethylen-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950386)	A mixture of equimolar amounts of 2-chloro-N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethylene oxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 89.2%; MS (m/e): 410.5 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.957	N4-(3-Amino-4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950388)	A mixture of 2-chloro-N4-(3-amino-4-ethoxyphenyl)-5-fluoro-4-aminopyridine and 3 equivalents of 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-amino-4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.1%; MS (m/e): 427.18 (MH^+).
7.3.958	N4-(4-Ethoxy-3-hydroxysulfonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950389)	A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in HOAc was treated with sodium nitrate followed by addition of concentrated aqueous HCl and copper dichloride. The mixture was stirred for 2 hours at 22°C for 8 hours and purified by aqueous work up followed by column chromatography on silica gel to give N4-(4-ethoxy-3-hydroxysulfonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 82.3%; MS (m/e): 474.09 ($M-H^-$).
7.3.959	N2,N4-Bis(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950391)	A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-methoxycarbonyl-4-trifluoromethoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up N2,N4-bis(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ^1H NMR (DMSO): δ 9.96 (s, 1H), 9.82 (s, 1H), 8.16-8.26 (m, 4H), 7.91 (dd, 1H, J = 3.0, 7.2 Hz), 7.42 (d, 1H, J= 7.2 Hz), 7.31 (d, 1H, J= 7.2 Hz), 3.77 (s, 3H), 3.75 (s, 3H); LCMS: purity: 93.0%; MS (m/e): 565.37 (MH^+).
7.3.960	N4-(3-Methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950392)	A mixture of equimolar amounts of 2-chloro-N4-(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.8%; MS (m/e): 510.41 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.961	N4-(4-Acetylamino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950393)	A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeCN was treated with concentrated sulfuric acid. The mixture was stirred for 3 hours at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-acetylamino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 10.46 (bs, 1H), 9.52 (bs, 1H), 7.98 (d, 1H, J = 2.4 Hz), 7.12-7.73 (m, 7H), 6.66 (d, 1H, J = 7.2 Hz), 6.49 (d, 1H, J = 7.2 Hz), 4.75 (s, 2H), 4.03-4.32 (m, 2H), 3.80 (m, 1H), 2.64 (s, 3H), 2.143 (s, 3H), 1.90-2.11 (m, 2H); LCMS: purity: 92.1%; MS (m/e): 393.06 (M-H$^-$). LCMS: purity: 96.2%; MS (m/e): 479.13 (M-H$^-$).
7.3.962	N4-[2,4-Dihydro-1-oxo-4H-imidazo[2,1-c][1,4]benzoxazin-8-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R945236)	N4-[2H-1,4-Benzoxazin-3(4H)-one-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (800 mg, 2.18 mmol) and phosphorus pentasulfide (800 mg, 1.80 mmol) were stirred in pyridine (5 mL) at 70 °C for 2h. The reaction solution was treated with 1N HCl solution to pH 5. The precipitation was collected with filtration, washed with water, dried to give N4-[2H-1,4-benzoxazin-3(4H)-thione-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine.
7.3.963	5-Fluoro-N2-(3-hydroxyphenyl)-N4-[1-oxo-1,2,3,6-tetrahydropyrimido[2,1-c][1,4]benzoxazin-9-yl]-2,4-pyrimidinediamine (R945237)	In a manner analogous to the preparation of N4-[2,4-dihydro-1-oxo-4H-imidazo[2,1-c][1,4]benzoxazin-8-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-[2H-1,4-benzoxazin-3(4H)-thione-6-yl]-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (400 mg, 1.04 mmol) and β-alanine (500 mg) gave 5-fluoro-N2-(3-hydroxyphenyl)-N4-[1-oxo-1,2,3,6-tetrahydropyrimido[2,1-c][1,4]benzoxazin-9-yl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (acetone-d_6): δ 2.68 (t, J= 7.2 Hz, 2H), 3.71 (t, J= 7.2 Hz, 2H), 4.62 (t, J= 1.2 Hz, 2H), 6.42 (ddd, J= 1.2 and 2.4 and 7.5 Hz, 1H), 6.98-7.08 (m, 3H), 7.38 (t, J= 2.4 Hz, 1H), 7.62 (dd, J= 2.4 and 8.7 Hz, 1H), 7.96 (d, J= 3.3 Hz, 1H), 8.12 (s, 1H), 8.16 (s, 1H), 8.52 (d, J= 2.7 Hz, 1H), 8.65 (s, 1H); ^{19}F NMR (282 MHz, acetone-d_6): δ - 168.04.

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Section Number	Name of compound and reference number	Experimental
7.3.964	5-Fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine (R945242)	2H-Pyrido[3,2-b]-1,4-oxazin-3(4H)-one (500 mg) was treated with nitric acid (5 mL) and sulfuric acid (5 mL). The reaction mixture was heated to 70 °C for 30 min and then poured into ice-water. The solution was neutralized with sodium bicarbonate to pH 6. The yellow precipitation was collected by filtration, washed with water and dried to give a mixture of nitrated products (regio-isomers). The mixture of nitrated compounds was reduced under hydrogenolysis conditions using 10% Pd-C in methanol at 40 psi for 30 min. The catalyst was filtered off. The filtrate was evaporated and treated with 2,4-dichloro-5-fluoropyrimidine (200 mg) in methanol (5 mL), water (5 mL). The reaction mixture was heated at 70 °C overnight, then evaporated. The residue was reacted with 3-methylaminocarbonylmethyleneoxyaniline (300 mg) in methanol (5 mL) and water (1 mL) at 100 °C overnight. The reaction mixture was diluted with 1N HCl solution (60 mL). The brown precipitation was collected by filtration, washed with water and dried to give 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 2.62 (d, J= 4.8 Hz, 3H), 4.33 (s, 2H), 4.63 (s, 2H), 6.48 (dd, J= 2.4 and 7.5 Hz, 1H), 7.11 (t, J= 8.1 Hz,1H), 7.27 (d, J= 7.8 Hz, 1H), 7.36 (s, 1H), 7.86 (d, J= 2.1 Hz, 1H), 7.97 (m, 1H), 8.12 (d, J= 3.6 Hz, 1H), 8.38 (d, J= 2.1 Hz, 1H), 9.33 (s, 1H), 9.46 (s, 1H), 11.18 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 164.49; LCMS: ret. time: 13.16 min.; purity: 79.30%; MS (m/e): 440.16 (MH^+).
7.3.965	5-Fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-7-yl]-2,4-pyrimidinediamine (R945263)	2H-Pyrido[3,2-b]-1,4-oxazin-3(4H)-one (1g, 6.66 mmol) was refluxed with boron hydride methyl sulfide complex (2 mL) in THF (10 mL) for 30 min to give 2H-pyrido[3,2-b]-1,4-oxazine. In a manner analogous to the preparation of 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine, 2H-pyrido[3,2-b]-1,4-oxazine was nitrated, reduced and reacted with 2,4-dichloro-5-fluoropyrimidine (400 mg) and 3-methylaminocarbonylmethyleneoxyaniline (500 mg) to give 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-7-yl]-2,4-pyrimidinediamine as a gray solid. ^{1}H NMR ($CDCl_3$): δ 2.91 (d, J= 4.8 Hz, 3H), 3.55 (t, J= 4.2 Hz, 2H), 4.24 (t, J= 4.5 Hz, 2H), 4.49 (s, 2H), 4.90 (br, 1H), 6.51 (dd, J= 2.7 and 8.1 Hz, 1H), 6.64 (s,1H), 6.90 (dd, J= 2.1 and 8.1 Hz, 1H), 7.08 (s, 1H), 7.14 (br, 1H), 7.18 (t, J= 8.1 Hz, 1H), 7.28 (d, J= 2.1 Hz, 1H), 7.51 (t, J= 2.1 Hz, 1H), 7 93 (d, J= 3.0 Hz, 1H), 7.95 (d, J= 2.4 Hz, 1H); LCMS: ret. time: 11.91 min.; purity: 100%; MS (m/e): 426.12 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.966	5-Fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-6-yl]-2,4-pyrimidinediamine (R921304)	2H-Pyrido[3,2-b]-1,4-oxazin-3(4H)-one (2.5 g) was dissolved in acetic acid (6 mL) and acetic anhydride (30 mL). Fuming nitric acid (3 mL) was added dropwise to the reaction solution in ice-bath. The reaction solution was stirred in ice-bath overnight. Solution was poured into crashed ice. The light yellow precipitation was collected by filtration, washed with water and dried to give a mixture of nitrated products (regio-isomers). The mixture was crystallized from dichloromethane to give 6-nitro-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (1 g) as a light yellow solid. 6-Nitro-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (1 g) was reduced under hydrogenolysis conditions using 10% Pd-C in methanol (50 mL) and 1N HCl solution (10 mL) at 50 psi for 2 h. The catalyst was filtered off and washed with methanol and 1N HCl solution. The filtrate was evaporated to give 6-amino-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one. In a manner analogous to the preparation of 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine, 6-amino-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one was reacted with 2,4-dichloro-5-fluoropyrimidine (500 mg) and 3-methylaminocarbonylmethyleneoxyaniline (500 mg) to give 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-6-yl]-2,4-pyrimidinediamine as a beige solid. ^{1}H NMR (DMSO-d_6): δ 2.63 (d, J= 4.5 Hz, 3H), 4.35 (s, 2H), 4.62 (s, 2H), 6.47 (dd, J= 1.8 and 8.1 Hz, 1H), 7.10 (t, J= 8.1 Hz, 1H), 7.25 (d, J= 8.1 Hz, 1H), 7.37 (m, 2H), 7.59 (d, J= 8.4 Hz, 1H), 7.96 (d, J= 5.1 Hz, 1H), 8.13 (d, J= 3.6 Hz, 1H), 9.26 (s, 1H), 9.29 (s, 1H), 11.13 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 163.20; LCMS: ret. time: 25.22 min.; purity: 97.55%; MS (m/e): 440.25 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.967	5-Fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-6-yl]-2,4-pyrimidinediamine (R945299)	6-Nitro-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (500 mg) was refluxed with boron hydride methyl sulfide complex (1 mL) in THF (10 mL) for 30 min to give 6-nitro-2H-pyrido[3,2-b]-1,4-oxazine. In a manner analogous to the preparation of 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-7-yl]-2,4-pyrimidinediamine, 6-nitro-2H-pyrido[3,2-b]-1,4-oxazine was reduced and reacted with 2,4-dichloro-5-fluoropyrimidine (500 mg) and 3-methylaminocarbonylmethyleneoxyaniline (500 mg) to give 5-fluoro-N2-(3-methylaminocarbonylmethyleneoxyphenyl)-N4-[2H-pyrido[3,2-b]-1,4-oxazin-6-yl]-2,4-pyrimidinediamine as a gray solid. ^{1}H NMR (CD_3OD): δ 2.81 (s, 3H), 3.48 (t, J= 4.5 Hz, 2H), 4.14 (t, J= 4.5 Hz, 2H), 4.44 (s, 2H), 6.60 (ddd, J= 1.5 and 2.7 and 7.5 Hz, 1H), 6.94 (d, J= 8.1 Hz, 1H), 7.14 (d, J= 3.0 Hz, 1H), 7.17 (t, J= 7.8 Hz, 1H), 7.40 (d, J= 8.9 Hz, 1H), 7.42 (t, J= 2.1 Hz, 1H), 7.92 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD): δ -168.20; LCMS: ret. time: 25.49 min.; purity: 97.56%; MS (m/e): 426.23 (MH^+).
7.3.968	N4-(1,4-Benzoxazin-3-on-7-yl))-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R908698):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,4-benzoxazin-3-on-7-yl)pyrimidineamine and 3-aminophenol were reacted to yield N4-(1,4-Benzoxazin-3-on-7-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.2 (d, 1H, J=4 Hz), 7.30 (m, 2H), 7.09 (m, 4H), 6.5 (m, 1H), 4.6 (s, 2H) purity 95 %; MS (m/e): 368 (MH+)
7.3.969	N2-(1,4-Benzoxazin-3-on-7-yl)- 5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R908699):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)] pyrimidineamine and 7-amino-1,4-benzoxazine-3-one were reacted to yield N2-(1,4-Benzoxazin-3-on-7-yl)- 5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.10 (m, 5H), 6.65 (m, 1H), 4.54 (s, 2H) purity 95 % MS (m/e): 368 (MH+)
7.3.970	N4-(1,4-Benzoxazine-3-on-7-yl)-5-fluoro-N2-((N-methyl acetamido-2)-3-phenoxy)-2,4-pyrimidinediamine (R908700):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-1,4-benzoxazin-3-on-7-yl)phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield N4-(1,4-Benzoxazine-3-on-7-yl)-5-fluoro-N2-((N-methyl acetamido-2)-3-phenoxy)-2,4-pyrimidinediamine 1H (DMSO-d6) 8.2 (d, 1H, J=4 Hz), 8 00 (m, 1H), 7.19 (m, 1H), 7.09 (m, 3H), 6.55 (m, 1H), 4.64 (s, 2H), 4.27 (s, 2H), 3.18 (s, 3H), 2.63 (m, 3H) purity 95 % MS (m/e):439 (MH+)

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Section Number	Name of compound and reference number	Experimental
7.3.971	N4-(1,4-Benzoxazine-3-on-6-yl)-5-fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy)]-2,4-pyrimidinediamine (R908701):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[6-(1,4-benzoxazin-3-onyl)]phenylpyrimidineamine and 3-(N- methylaminocarbonylmethyleneoxy)aniline were reacted to yield N4-(1,4-Benzoxazine-3-on-6-yl)-5-fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy]-2,4-pyrimidinediamine 1H (DMSO-d6) 8.2 (d, 1H, J=4 Hz), 8.00 (m, 1H), 7.13 (m, 3H), 6.95 (m, 1H), 6.55 (m, 1H), 4.64 (s, 2H), 4.27 (s, 2H), 3.18 (s, 3H), 2.63 (m, 3H) purity 96 % MS (m/e): 439 (MH+)
7.3.972	N4-(1,4-Benzoxazine-3-on-6-yl)- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R908702):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,4-benzoxazin-3-on-6-yl)phenylpyrimidineamine and 3-aminophenol were reacted to yield N4-(1,4-Benzoxazine-3-on-6-yl)- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.22 (m, 2H), 7.03 (m, 4H), 6.55 (m, 1H), 4.64 (s, 2H) purity 98 %MS (m/e): 368 (MH+)
7.3.973	5-Fluoro-N4-(3-hydroxyphenyl)- N2-(N-methyl-1,4-benzoxazine-3-on-6-yl)-2,4-pyrimidinediamine (R908703):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)]phenylpyrimidineamine and 3-(N- methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl] -N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)]pyrimidinediamine 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.23 (m, 6H), 6.55 (m, 1H), 4.64 (s, 2H), 3.18 (s, 3H) purity 96 %; MS (m/e): 382(MH+)
7.3.974	5-Fluoro-N4-(3-hydroxyphenyl)-N2-(N-methyl-1,4-benzoxazin-7-yl)-2,4-pyrimidinediamine (R908704):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)]phenylpyrimidineamine and 3-(N- methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N4-(3-hydroxyphenyl)-N2-(N-methyl-1,4-benzoxazin-7-yl)-2,4-pyrimidinediamine 1H (DMSO-d6) 8.8.13 (d, 1H, J=4 Hz), 7.13 (m, 3H), 6.72 (m, 3H), 6.59 (m, 1H), 4.24 (m, 2H), 4.27 (s, 2H), 3.28 (m, 2H), 2.83 (m, 3H) purity 93 %; MS (m/e): 367 (MH+)

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Section Number	Name of compound and reference number	Experimental
7.3.975	5-Fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy]-N4-(N-methyl-1,4-benzoxazin-7-yl)- 2,4-pyrimidinediamine (R908705):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)]phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy]- N4-(N-methyl-1,4-benzoxazin-7-yl)- 2,4-pyrimidinediamine 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.13 (m, 5H), 6.75 (m, 2H), 4.44 (s, 2H), 4.27 (m, 2H), 3.22 (m, 2H), 2.83 (s, 3H), 2.63 (m, 3H) purity 96 %; MS (m/e): 439 (MH+)
7.3.976	N2-(1,4-Benzoxazin-7-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R908706):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)]pyrimidineamine and 7-amino-1,4-benzoxazine were reacted to yield N2-(1,4-Benzoxazin-7-yl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. 1H (DMSO-d6) 7.95 (d, 1H, J=4 Hz), 7.43 (m, 1H), 7.02 (m, 4H), 6.42 (m, 2H), 4.17 (m, 2H), 3.33 (m, 2H) purity 96 %; MS (m/e): 353 (MH+)]
7.3.977	5-Fluoro-N2-(3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-7-yl)-2,4-pyrimidinediamine (R908707):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-7-yl)pyrimidineamine and 3-aminophenol were reacted to yield 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-7-yl)-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.10 (m, 5H), 6.65 (m, 1H), 4.54 (s, 2H) purity 95 % MS (m/e): 368 (MH+)
7.3.978	5-Fluoro-N4-(3-hydroxyphenyl) N2-(N-Methyl-1,4-benzoxazine-3-on-7-yl)-2,4-pyrimidinediamine (R908708):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)pyrimidineamine and 7-amino-4-N-methyl-1,4-benzoxazine-3-one were reacted to yield 5-Fluoro-N4-(3-hydroxyphenyl) N2-(N-Methyl-1,4-benzoxazine-3-on-7-yl)-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7.23 (m, 1H), 7.15 (m, 5H), 6.62 (m, 1H), 4.64 (s, 2H), 4.27 (s, 2H), 3.18 (s, 3H) purity 95 %; MS (m/e): 380 (MH+)]
7.3.979	5-Fluoro-N2-(3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)-2,4-pyrimidinediamine (R908709):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)] pyrimidineamine and 6-amino-1,4-benzoxazine were reacted to yield 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 7 43 (m, 2H), 7.19 (m, 4H), 6.55 (m, 1H), 4.64 (s, 2H), 3.25 (s, 3H) purity 95 %; MS (m/e): 382 (MH+)

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Section Number	Name of compound and reference number	Experimental
7.3.980	5-Fluoro-N2-(3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-6-yl)-2,4-pyrimidinediamine (R908710):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)pyrimidineamine and 6-amino-1,4-benzoxazine were reacted to yield 5-Fluoro-N2-(3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-6-yl)-2,4-pyrimidinediamine. 1H (MeOD-d4) 8.20 (d, 1H, J=4 Hz), 7.43 (m, 3H), 6.90 (m, 2H), 6.75 (m, 1H), 4.25 (m, 2H), 3.25 (m, 2H), 2.85 (bs, 1 H) purity 96 %, MS (m/e): 382 (MH+)
7.3.981	N4-(1,4-Benzoxazin-7-yl)-5-fluoro-N2-(3-hydroxyphenyl) -pyrimidinediamine (R908711):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-[6-(1,4-benzoxazinyl)]-N2-chloro-5-fluoropyrimidineamine and 3-ethoxyocarbonylmethyleneoxyaniline were reacted to yield N4-(1,4-Benzoxazin-7-yl)-5-fluoro-N2-(3-hydroxyphenyl) -pyrimidinediamine ^{1}H NMR (MeOD-d4): δ 8.2 (d, 1H, J=4 Hz), 7.15 (m, 4H), 6.84 (m, 2H), 6.62 (m, 1H), 4.65 (s, 2H), 4.15 (m, 4H), 3.28 (m, 2H), 1.19 (t, 3H. J=7 Hz) purity 94 %; MS (m/e): 439 (MH^+).
7.3.982	(+/-)-5-Fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy]- N4-(2-methyl-1,4-benzoxazin-6-yl)-2,4-pyrimidinediamine (R908712):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, (+/-)-2-chloro-5-fluoro-N4-(2-methyl-1,4-benzoxazin-6-yl)]phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield (+/-)-5-Fluoro-N2-[(N-methyl acetamido-2)-3-phenoxy]- N4-(2-methyl-1,4-benzoxazin-6-yl)- 2,4-pyrimidinediamine 1H (DMSO-d6) 8.20 (d, 1H, J=4 Hz), 8.13 (m, 1H), 7.1 (m, 5H), 6.96 (m, 1H), 6.63 (m, 1H), 4.62 (m, 1H), 4.40 (s, 3H), 2.63 (m, 3H), 1.25 (m, 3H) purity 93 %; MS (m/e): 453 (MH+)
7.3.983	N2-(N-Ethylcarbonylmethyleneoxy-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-hydroxyphenyl)phenyl]pyrimidinediamine (R908734):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-Chloro-5-fluoro-N4-(3-hydroxyphenyl)pyrimidineamine and 6-Amino-N-carbomethoxy-1,4-benzoxazine were reacted to yield N2-(N-Ethylcarbonylmethyleneoxy-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-hydroxyphenyl)phenyl]pyrimidinediamine 1H NMR (DMSO-d6): δ 8.23 (m, 1H), 7.20 (m, 1H), 7.14 (m, 4H), 6.95(m, 1H), 6.76 (m, 1H), 4.66 (s, 1H), 4.48 (s, 1H), 4.25 (q, 2H J=6.5 Hz), 1.28 (t, 2H, J=6.5 Hz), purity 95 % MS (m/e): 454(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.984	N4-(1,4-Benzoxazin-6-yl)-N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoropyrimidinediamine (R909255):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-[6-(1,4-benzoxazinyl)]-N2-chloro-5-fluoropyrimidineamine and 3-chloro-4-hydroxy-5-methylaniline were reacted to yield N4-(1,4-benzoxazin-6-yl)-N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoropyrimidinediamine ^{1}H NMR (DMSO-d6): δ7.89 (d, 1H, J=4 Hz), 7.25 (m, 1H), 7.14 (m, 1H), 6.80 (m, 2H), 6.82 (m, 1H), 4.29 (s, 2H), 3.35 (m, 2H), 2.20 (s, 3H) purity 99 %; MS (m/e): 402 (MH^+).
7.3.985	5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl] -N4-(N-methyl-1,4-benzoxazin-6-yl)pyrimidinediamine (R909259):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[6-(N-methyl-1,4-benzoxazinyl)]phenyl pyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]-N4-(N-methyl-1,4-benzoxazin-6-yl)pyrimidinediamine 1H (DMSO-d6) 8:01 (d, 1H, J=4 Hz), 7.33 (m, 2H), 7.22 (m, 1H), 7.02 (m, 2H), 6.65 (m, 1H), 6.42 (m, 1H), 4.37 (s, 2H), 4.22 (m, 2H), 3.18 (m, 2H), 2.78 (s, 3H) 2.63 (m, 3H) purity 98 %; MS (m/e): 439 (MH+)
7.3.986	5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy) phenyl]-N4-[6-(N-methyl-1,4-benzoxazin-3-onyl)]pyrimidinediamine (R909260):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[6-(N-methyl-1,4-benzoxazin-3-onyl)]phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl] -N4-[6-(N-methyl-1,4-benzoxazin-3-onyl)]pyrimidinediamine 1H (DMSO-d6) 8.01 (d, 1H, J=4 Hz), 7.33 (m, 2H), 7.22 (m, 1H), 7.02 (m, 2H), 6.65 (m, 1H), 6.42 (m, 1H), 4.37 (s, 2H), 4.22 (s, 2H), 3.18 (s, 3H), 2.78 (s, 3H) 2.63 (m, 3H) purity 88%; MS (m/e): 453 (MH+)
7.3.987	5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy) phenyl]-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)]-2,4-pyrimidinediamine (R909261):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)phenylpyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield 5-Fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl] -N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)pyrimidinediamine 1H (DMSO-d6) 8.08 (d, 1H, J=4 Hz), 7.43 (m, 2H), 7.19 (m, 1H), 7.09 (m, 3H), 6.55 (m, 1H), 4.64 (s, 2H), 4.27 (s, 2H), 3.18 (s, 3H), 2.63 (m, 3H) MS (m/e): 453 (MH+)

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Section Number	Name of compound and reference number	Experimental
7.3.988	(+/-)-5-Fluoro-N4-(3-hydroxyphenyl]-N2-(2-methyl-1,4-benzothiazin-3-on-6-yl)pyrimidinediamine (R909263):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(3-hydroxyphenyl)pyrimidineamine and 6-amino-2-methyl-1,4-benzothiazin-3-one were reacted to yield (+/-)-5-Fluoro-N4-(3-hydroxyphenyl]-N2-(2-methyl-1,4-benzothiazin-3-on-6-yl)pyrimidinediamine ^{1}H NMR (MeOD-d4): δ8.02 (d, 1H, J=4 Hz), 7.30 (m, 3H), 7.08 (m, 3H), 6.52 (m, 1H), 3.57 (m, 1H), 1.25 (m, 3H) purity 92 %; MS (m/e): 398 (MH^+).
7.3.989	5-Fluoro-N2-[3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)-2,4-pyrimidinediamine (R909264):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)]phenylpyrimidineamine and 3-aminophenol were reacted to yield 5-Fluoro-N2-[3-hydroxyphenyl)-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)]-2,4-pyrimidinediamine 1H (DMSO-d6) 8.08 (d, 1H, J=4 Hz), 7.53 (m, 2H), 7.09 (m, 4H), 6.42 (m, 1H), 4.64 (s, 2H), 3.27 (s, 3H) purity 95 % MS (m/e): 382 (MH+)
7.3.990	N4-(3-Ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoro -N2-[3-(N-methylaminocarbonylmethyleneoxy) phenyl]pyrimidinediamine (R909265):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-Chloro-N4-(3-ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoropyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield N4-(3-Ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoro -N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]pyrimidinediamine ^{1}H NMR (DMSO-d6): δ 8.23 (m, 2H), 8.08 (d, J=4 Hz, 1H), 7.92 (m, 1H), 7.43 (m, 1H), 7.38(m, 2H), 7.18 (m, 1H), 6.99 (t, 1H), 6.41 (m, 1H), 5.43 (s, 2H) purity 92 %; MS (m/e): 534 (MH^+).
7.3.991	N4-(1,4-Benzoxazin-7-yl)-N2-[3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (R909266):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N4-(1,4-Benzoxazin-7-yl)-2-chloro-5-fluoro- pyrimidineamine and 3-(ethoxycarbonylmethyleneoxy)aniline were reacted to yield N4-(1,4-Benzoxazin-7-yl)-N2-[3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.2 (d, 1H, J=4 Hz), 7.43 (m, 1H), 7.12 (m, 4H), 6.68 (m, 2H), 4.7 (s, 2H) 4.17 (m, 2H), 3.33 (m, 2H), 3.13 (m, 2H) 1.87 (m, 3H) purity 89 %; MS (m/e): 439 (MH+)

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Section Number	Name of compound and reference number	Experimental
7.3.992	N2-(3-Ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoro-N4-(3-hydroxyphenyl)pyrimidinediamine (R909267):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-Chloro-5-fluoro-N4-(3-hydroxyphenyl)pyrimidineamine and 3 Ethyl 6-Amino-(3-carboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazine were reacted to yield N2-(3-Ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoro-N4-(3-hydroxyphenyl)pyrimidinediamine 1H NMR (DMSO-d6): δ 8.18 (m, 1H), 8.04 (m, 1H), 7.38 (m, 1H), 7.22 (m, 1H), 7.04 (m, 2H), 6.96 (m, 1H), 6.53 (m, 1H), 5.42 (s, 2H), 4.25 (q, 2H J=6.5 Hz), 1.28 (t, 2H, J=6.5 Hz), purity 92 % MS (m/e): 409 (MH^+).
7.3.993	N2-(1,4-Benzoxazin-3-on-6-yl)- 5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R909268)	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine N4-[6-(1,4-benzoxazinyl)]-N2-chloro-5-fluoropyrimidineamine and 6-amino-1,4-benzoxazin-3-one were reacted to yield N2-(1,4-benzoxazin-3-on-6-yl)-5-fluoro-N4-(6-(1,4-benzoxazinyl)]-)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.18 (d, 1H J= 4 Hz), 7.17 (m, 2H), 6.88 (m, 2H), 6.80 (m, 1H), 6.58 (m, 1H) 4.52 (s, 2H), 4.11 (m, 2H), 3.33 (m, 2H) purity: 97 %; MS (m/e): 409 (MH^+).
7.3.994	N2-[3-(N,N-Dimethylaminocarbonylmethyleneoxy) phenyl]-N4-(1,4-benzoxazin-6-yl)-5-fluoro--2,4-pyrimidinediamine (R909290)	In like manner to N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(1,4-benzoxazin-6-yl)-N2-(3-ethoxyocarbonylmethyleneoxyphenyl)-5-fluoro-pyrimidinediamine and dimethylamine hydrochloride were reacted to yield N2-[3-(N,N-Dimethylaminocarbonylmethyleneoxy)phenyl] -N4-(1,4-benzoxazin-6-yl) -5-fluoro--2,4-pyrimidinediamine ^{1}H NMR (CD_3OD): δ 7.8 (d, 1H), 7.4 (m, 1H), 7.05 (m, 2H), 7.0 (s, 1H), 6.8 (dd, 1H), 6.66 (d, 1H), 6.56 (dd, 1H), 4.35 (s, 2H), 4.18 (m, 2H), 3.25 (m, 2H), 2.8 (s, 6H); purity: 95 %; MS (m/e): 439 (MH+)
7.3.995	N4-(4N-Carboxamidino-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl] -2,4-pyrimidinediamine (R909292)	To a solution in 2 mL THF at 0° Celsius containing 250 mg (0.59 mmol) of N4-(1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 1.4 eq, 115 uL TEA, and catalytic DMAP was added 0.4 eq,70 mg of triphosgene. After 30 min 15 mL of aqueous ammonia and stirred for 30 min at RT. The THF was evaporated and the reaction was diluted with water, and the resulting precipitate collection by suction filtration. The crude precipitate was purified by preparative TLC (5% MeOH/EtOAc) to yield N4-(4N-Carboxamidino-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.83 (m, 1H), 7.42 (m, 1H), 7.12 (m, 2H), 7.08 (s, 1H), 6.84 (m, 1H), 6.66 (m, 1H), 6.48 (m, 1H), 4.30 (s, 2H), 4.15 (m, 2H), 3.22 (m, 2H), 2.82 (s, 3H); purity: 87 %; MS (m/e): 468 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.996	N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-N2-[3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (R909308):	In like manner to N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-Chloro-N4-(3,3-dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-pyrimidineamine and 3-(ethoxycarbonylmethyleneoxy)aniline were reacted to yield N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-N2-[3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.00 (m, 1H), 7.43 (m, 2H), 7.05 (m, 1H), 6.82 (m, 2H), 6.68 (m, 1H), 6.41 (m, 1H), 4.80 (s, 2H), 4.18 (q, 2H), 3.74 (s, 2 H), 1.03 (t, 3H), 1.00 (s, 6H) purity 99 %; MS (m/e): 467 (MH+)
7.3.997	N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R909309):	In like manner to N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-N2-[3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylaminocarbonyl methyleneoxy)phenyl]-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.04 (d, 1H), 7.93 (m, 1H), 7.45 (m, 2H), 7.09 (m, 1H), 6.93 (m, 2H), 6.62 (m, 1H), 6.43 (m, 1H), 4.37 (s, 2H), 3.74 (s, 2 H), 2.62 (d, 3H), 1.07 (s, 6H) purity 99 %; MS (m/e): 453 (MH+)
7.3.998	N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R909309):	In like manner to N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-N2-[3-ethoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to yield N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-N2-[3-(N-methylaminocarbonyl methyleneoxy)phenyl]-2,4-pyrimidinediamine. 1H (DMSO-d6) 8.04 (d, 1H), 7.93 (m, 1H), 7.45 (m, 2H), 7.09 (m, 1H), 6.93 (m, 2H), 6.62 (m, 1H), 6.43 (m, 1H), 4.37 (s, 2H), 3.74 (s, 2 H), 2.62 (d, 3H), 1.07 (s, 6H) purity 99 %; MS (m/e): 453 (MH+)

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Section Number	Name of compound and reference number	Experimental
7.3.999	N4-(2,4-Diiodo-3-hydroxypheny)-5-fluoro-N2-(3-iodo-1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine (R935221)	To 5-fluoro-N2-(3-hydroxyphenyl)-N4-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine (34.4 mg, 0.098 mmole) in ethanol (2.0 mL) and aq. NH_4OH (2.0 mL), I_2 (0.126 g, 0.99 mmole atom) was added and stirred at room temperature overnight. Reaction mixture was concentrated, dissolved in EtOAc and treated with aq. hypo solution. Organic layer was separated, dried with anhydrous Na_2SO_4 and concentrated. The crude material was purified by silica gel column chromatography to provide N4-(2,4-diiodo-3-hydroxypheny)-5-fluoro-N2-[3-iodo-1-methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.86 (s, 1H), 9.51 (s, 1H), 9.12(s, 1H), 8.28 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.79 (s, 1H), 7.63 (s, 1H), 7.32 (d, 1H, J = 8.8 Hz), 7.37 (d, 1H, J = 8.8 Hz), 3.92 (s, 3H). LCMS: ret. time: 20.88 min.; purity: 91%; MS (*m/e*): 729 (MH^+).
7.3.1000	5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935222)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-(methoxycarbonyl)methylindazoline to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.17 (s, 1H), 9.13 (s, 1H), 8.10 (s, 1H), 8.03 (d, 1H, J = 4.1 Hz), 7.85 (s, 1H), 7.58 (d, 2H, J = 8.8 Hz), 7.46 (s, 2H), 6.87 (s, 2H, J = 8.8 Hz), 5.31 (s, 2H), 4.57 (sep, 1H, J = 5.8Hz), 3.65 (s, 3H), 1.25 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 21.33 min.; purity: 96%; MS (*m/e*): 451 (MH^+).
7.3.1001	N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935223)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro- 4-pyrimidineamine was reacted with 5-amino-1-(methoxycarbonyl)methyl-indazoline to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.16 (s, 1H), 9.14 (s, 1H), 8.13 (s, 1H), 8.04 (d, 1H, J = 4.1 Hz), 7.89 (s, 1H), 7.48 (s, 2H), 7.30 (d, 1H, J = 2.9 Hz), 7.20 (dd, 1H, J = 2.9 and 8.8 Hz), 6.79 (d, 1H, J = 8.8 Hz), 5.32 (s, 2H), 4.22 (s, 4H), 3.65 (s, 3H). LCMS: ret. time: 21.33 min.; purity: 96%; MS (*m/e*): 451 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1002	5-Fluoro-N2-(4-isopropoxyphenyl)-N4-[1-(*N*-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine (R935224)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N2-(4-isopropoxyphenyl)-N4-[1-(*N*-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.46 (s, 1H), 8.98 (s, 1H), 8.07 (d, 1H, J = 4.1 Hz), 8.02 (d, 1H, J = 4 7 Hz), 7.98 (s, 2H), 7.66 (d, 1H, J = 8.8 Hz), 7.50 (d, 2H, J = 8.8 Hz), 7.46 (app s, 1H), 6.74 (d, 2H, J = 8.8 Hz), 4.96 (s, 2H), 4.46 (sept, 1H, J = 5.8 Hz), 2.58 (d, 3H, J = 4.7 Hz), 1.21 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 18.22 min.; purity: 93%; MS (*m/e*): 450 (MH^+).
7.3.1003	N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-(*N*-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine (R935225)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-(3, 4-ethyelnedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-(*N*-methylaminocarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.47 (s, 1H), 8.99 (s, 1H), 8.08 (d, 1H, J = 3.5 Hz), 8.06 (s, 1H), 8.01 (d, 1H, J = 4.7 Hz), 7.98 (d, 1H, J = 1.1 Hz), 7.66 (d, 1H, J = 8.8 Hz), 7.45 (dd, 1H, J = 1.1 and 8.8 Hz), 7.31 (d, 1H, J = 2.3 Hz), 7.01 (dd, 1H, J = 2.9 and 8.8 Hz), 6.66 (d, 1H, J = 8.8 Hz), 4.95 (s, 2H), 4.14 (s, 4H), 2.57 (d, 3H, J = 4.1 Hz). LCMS: ret. time: 15.55 min.; purity: 94%; MS (*m/e*): 450 (MH^+).
7.3.1004	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935237)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-(methoxycarbonyl)methyl-indazoline to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.40 (s, 1H), 9.19 (s, 1H), 9.17 (s, 1H), 8.23 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.90 (s, 1H), 7.47 (s, 2H), 7.25 (d, 1H, J = 7.6 Hz), 7.11 (d, 1H, J = 7.6 Hz), 7.08 (d, 1H, J = 8.2 Hz), 6.53 (d, 1H, J = 8.2 Hz), 5.31 (s, 2H), 3.64 (s, 3H). LCMS: ret. time: 15.82 min.; purity: 96%; MS (*m/e*): 409 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1005	N2, N4-Bis[1-(2-hydroxyethyl)indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine (R935238)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2, N4-bis[1-(methoxycarbonyl)methyl-indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N2, N4-bis[1-(2-hydroxyethyl)indazoline-6-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.56 (s, 1H), 9.43 (s, 1H), 8.19 (d, 1H, J = 3.5 Hz), 8.06 (s, 1H), 8.03 (s, 1H), 7.98 (s, 1H), 7.86 (s, 1H), 7.66 (d, 1H, J = 8.8 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.42 (dd, 1H, J = 1.7 and 8.8 Hz), 7.23 (dd, 1H, J = 1.7 and 8.8 Hz), 4.75 (t, 1H, J = 5.3 Hz), 4.68 (t, 1H, J = 5.3 Hz), 4.09-4.02 (m, 2H), 3.81-3.74 (m, 2H), 3.63-3.60 (m, 2H), 3.56-3.52 (m, 2H). LCMS: ret. time: 13.73 min.; purity: 90%; MS (*m/e*): 449 (MH^+).
7.3.1006	5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(*N*-methylaminocarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935239)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(*N*-methylaminocarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.27 (s, 1H), 9.21 (s, 1H), 8.07 (s, 1H), 8.04 (d, 1H, J = 4.1 Hz), 7.90 (qt, 1H, J = 4.7 Hz), 7.83 (s, 1H), 7.58 (d, 2H, J = 8.8 Hz), 7.44 (s, 2H), 6.87 (d, 2H, J = 8.8 Hz), 4.98 (s, 2H), 4.57 (q, 1H, J = 5.8 Hz), 2.59 (d, 3H, J = 4.1 Hz), 1.21 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 17.74 min.; purity: 94%; MS (*m/e*): 450 (MH^+).
7.3.1007	N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(*N*-methylaminocarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935240)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(*N*-methylaminocarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.36 (br s, 2H), 8.06 (d, 1H, J = 3.5 Hz), 8.05 (s, 1H), 7.99 (qt, 1H, J = 4.7Hz), 7.87 (s, 1H), 7.46 (s, 2H), 7.30-7.28 (m, 1H), 7.20-7.17 (m, 1H), 6.79 (d, 1H, J = 8.8 Hz), 4.99 (s, 2H), 4.22 (s, 4H), 2.59 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 15.06 min.; purity: 91%; MS (*m/e*): 450 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1008	5-Fluoro-N2-(4-isopropoxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935242)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-4-pyrimidineamine was reacted with 4-isopropoxyaniline to provide 5-fluoro-N2-(4-isopropoxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.58 (s, 1H), 10.09 (s, 1H), 8.23 (d, 1H, J = 5.3 Hz), 8.04 (s, 1H), 8.02 (s, 1H, J = 5.8 Hz), 7.68 –7.63 (m 1H), 7.58-7.55 (s, 1H), 7.30 (d, 2H, J = 8.8 Hz), 6.82 (d, 2H, J = 8.8 Hz), 5.41 (s, 2H), 4.53 (sept, 1H, J = 5.8 Hz), 3.66 (s, 3H), 1.21 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 19.30 min.; purity: 93%; MS (*m/e*): 451 (MH^+).
7.3.1009	N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(2-hydroxyethyl)indazoline-6-yl]-2,4-pyrimidinediamine (R935248)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(2-hydroxyethyl)indazoline-6-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 19.42 min.; purity: 94%; MS (*m/e*): 423 (MH^+).
7.3.1010	N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935249)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-4-pyridinamine was reacted with 3, 4-ethylenedioxyaniline to provide N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.32 (s, 1H), 8.94 (s, 1H), 8.14 (d, 1H, J = 4.7 Hz), 8.03 (d, 1H, J = 4.7 Hz), 8.01 (s, 1H), 7.65-7.57 (m, 2H), 7.23 (d, 1H, J = 1.7 Hz), 7.02 (dd, 1H, J = 1.9 and 8.8 Hz), 6.63 (d, 1H, J = 8.8 Hz), 5.38 (s, 2H), 4.14 (s, 4H), 3.66 (s, 3H). LCMS: ret. time: 18.94 min.; purity: 91%; MS (*m/e*): 451 (MH^+).
7.3.1011	5-Fluoro-N2-(3-hydroxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine (R935250)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-4-pyrimidineamine was reacted with 3-aminophenol to provide 5-fluoro-N2-(3-hydroxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.34 (s, 1H), 9.16 (s, 1H), 8.25 (d, 1H, J = 4.7 Hz), 8.05 (d, 1H, J = 4.7 Hz), 8.02 (s, 1H), 7.65-7.57 (m, 2H), 7.10 (d, 2H, J = 5.8 Hz), 6.93 (d, 1H, J = 8.8 Hz), 6.90 (d, 1H, J = 8.8 Hz), 6.28 (app d, 1H, J = 8.8 Hz), 5.37 (s, 2H), 3.66 (s, 3H). LCMS: ret. time: 17.87 min.; purity: 97%; MS (*m/e*): 409 (MH^+)

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Section Number	Name of compound and reference number	Experimental
7.3.1012	5-Fluoro-N4-(4-isopropoxyphenyl)-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935251)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 1-aminopyrrole to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.93 (s, 1H), 9.21 (s, 1H), 7.97 (d, 1H, J = 4.1 Hz), 7.47 (d, 2H, J = 8.8 Hz), 6.70 (dd, 2H, J = 2.3 and 4.7 Hz), 6.67 (d, 2H, J = 8.8 Hz), 6.02 (dd, 2H, J = 2.3 and 4.7 Hz), 4.48 (sept, 1H, J = 5 8 Hz), 1.21 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 23.44 min.; purity: 90%; MS (*m/e*): 328 (MH^+)
7.3.1013	N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935252)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 1-aminopyrrole to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.95 (s, 1H), 9 16 (s, 1H), 7.95 (d, 1H, J = 3.5 Hz), 7.16-7.12 (m, 2H), 6.69 (dd, 2H, J = 2.3 and 4.7 Hz), 6.61 (d, 1H, J = 8.8 Hz), 5.99 (dd, 2H, J = 2.3 and 4.7 Hz), 4.12-4.15 (m, 4H). LCMS: ret. time: 19.86 min.; purity: 92%; MS (*m/e*): 328 (MH^+).
7.3.1014	5-Fluoro-N4-(3-hydroxyphenyl)-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935253)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 1-aminopyrrole to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.95 (s, 1H), 9.22 (s, 1H), 9.19 (s, 1H), 7.99 (d, 1H, J = 3.5 Hz), 7.22 (d, 1H, J = 8.2 Hz), 6.94 (br s, 1H), 6.89 (t, 1H, J = 8.2 Hz), 6.70 (dd, 2H, J = 2.3 and 4.7 Hz), 6.38 (d, 1H, J = 8.2 Hz), 5.99 (t, 2H, J = 2.3 and 4.7 Hz). LCMS: ret. time: 18.23 min.; purity: 94%; MS (*m/e*): 286 (MH^+).
7.3.1015	5-Fluoro-N2-[1-(2-hydroxyethyl)indazoline-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R935255)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(2-hydroxyethyl)indazoline-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.16 (s, 1H), 9.10 (s, 1H), 8.09 (s, 1H), 8.02 (s, 1H, J = 4.0 Hz), 7.79 (s, 1H), 7.59 (d, 2H, J = 8.8 Hz), 7.48 (d, 1H, J = 8.8 Hz), 7.42 (dd, 1H, J = 1.7 and 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 4.83 (t, 1H, J = 5.8 Hz), 4.57 (sept, 1H, J = 5.8 Hz), 4.35 (t, 2H, J = 5.8 Hz), 3.75 (app qt, 2H, J = 5.8 Hz), 1.26 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 20.90 min.; purity: 94%; MS (*m/e*): 423 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1016	5-Fluoro-N2-[1-(2-hydroxyethyl)indazoline-5-yl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R935256)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(2-hydroxyethyl)indazoline-5-yl]-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.39 (s, 1H), 9.18 (s, 1H), 9.14 (s, 1H), 8.19 (s, 1H), 8.07 (d, 1H, J = 4.1 Hz), 7.84 (s, 1H), 7.50-7.42 (m, 2H), 7.26 (d, 1H, J = 8.2 Hz), 7.12-7.06 (m, 2H), 6.52 (d, 1H, J = 8.2 Hz), 4.83 (t, 1H, J = 5.8 Hz), 4.35 (t, 2H, J = 5.8 Hz), 3.75 (app qt, 2H, J = 5.8 Hz). LCMS: ret. time: 15.97 min.; purity: 95%; MS (*m/e*): 381 (MH^+).
7.3.1017	N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-(2-hydroxyethyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935258)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-(2-hydroxyethyl)indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.20 (s, 1H), 8.93 (s, 1H), 8.12 (s, 1H), 8.02 (d, 1H, J = 3.5 Hz), 7.94 (s, 1H), 7.59 (s, 2H), 7.23 (d, 1H, J = 0.9 Hz), 7.02 (dd, 1H, J = 1.0 and 8.8 Hz), 6.64 (d, 1H, J = 8.8 Hz), 4.86 (t, 1H, J = 5.3 Hz), 4.40 (t, 2H, J = 5.8 Hz), 4.15 (s, 4H), 3.78 (app qt, 2H, J = 5.3 and 5.8 Hz). LCMS: ret. time: 18.07 min.; purity: 93%; MS (*m/e*): 423 (MH^+).
7.3.1018	5-Fluoro-N4-[1-(2-hydroxyethyl)indazoline-5-yl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R935259)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-(3-hydroxyphenyl)-N4-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N4-[1-(2-hydroxyethyl)indazoline-5-yl]-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.31 (s, 1H), 9.16 (s, 1H), 9.01 (s, 1H), 8.23 (s, 1H), 8.05 (d, 1H, J = 3.5 Hz), 7.96 (s, 1H), 7.60 (s, 2H), 7.10 (app s, 2H), 6.92 (t, 1H, J = 8.8 Hz), 6.31 (d, 1H, J = 8.8 Hz), 4.86 (t, 1H, J = 5.3 Hz), 4.40 (t, 2H, J = 5.8 Hz), 3.79 (app qt, 2H, J = 5.3 and 5.8 Hz). LCMS: ret. time: 16.09 min.; purity: 89%; MS (*m/e*): 381 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1019	N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-(indazoline-6-yl)-2,4-pyrimidinediamine (R935261)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-6-yl)-4-pyrimidineamine was reacted 3, 4-ethyelenedioxyaniline to produce N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-(indazoline-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 12.85 (s, 1H), 9.40 (s, 1H), 9.01 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.97 (s, 1H), 7.86 (s, 1H), 7.65 (d, 1H, J = 8.8 Hz), 7.47 (dd, 1H, J = 2.3 and 8.8 Hz), 7.27 (d, 1H, J = 2.3 Hz), 7.07 (dd, 1H, J = 2.3 and 8.8 Hz), 6.64 (dd, 1H, J = 1.7 and 8.8 Hz), 4.14 (s, 4H). LCMS: ret. time: 15.90 min.; purity: 100%; MS (*m/e*): 379 (MH^+).
7.3.1020	5-Fluoro-N2-(3-hydroxyphenyl)-N4-(indazoline-6-yl)-2,4-pyrimidinediamine (R935262)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-6-yl)-4-pyrimidineamine was reacted with 3-aminophenol to produce 5-fluoro-N2-(3-hydroxyphenyl)-N4-(indazoline-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.80 (s, 1H), 10.49 (s, 1H), 8.35 (d, 1H, J = 5.3 Hz), 8.06 (s, 1H), 7.78 (d, 1H), 7.75 (d, 1H, J = 8.8 Hz), 7.42 (dd, 1H, J = 1.7 and 8.8 Hz), 6.99-6.97 (m, 2H), 6.80 (s, 1H), 6.52-6.48 (m, 1H). LCMS: ret. time: 13.78 min.; purity: 100%; MS (*m/e*): 379 (MH^+).
7.3.1021	N2-(3-Chloro-4-hydroxy-3-methylphenyl)-5-fluoro-N4-[4H-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-2,4-pyrimidinediamine (R935263)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[4H-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-4-pyrimidineamine was reacted with 4-amino-2-chloro-6-methylphenol to produce N2-(3-chloro-4-hydroxy-3-methylphenyl)-5-fluoro-N4-[4H-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.40 (s, 1H), 9.04 (s, 1H), 8.51 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.98 (d, 1H, J = 2.3 Hz), 7.67 (s, 1H), 7.53 (s, 1H), 7.41-7.36 (m, 1H), 7.20 (s, 1H), 7.10 (d, 1H, J = 8.8 Hz), 7.07 (s, 1H), 5.24 (s, 2H), 1.98 (s, 3H). LCMS: ret. time: 13.36 min.; purity: 90%; MS (*m/e*): 439 (MH^+).
7.3.1022	N2-(3-Chloro-4-hydroxy-3-methylphenyl)-5-fluoro-N4-(indazoline-6-yl)-2,4-pyrimidinediamine (R935264)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-6-yl)-4-pyrimidineamine was reacted with 4-amino-2-chloro-6-methylphenol to produce N2-(3-chloro-4-hydroxy-3-methylphenyl)-5-fluoro-N4-(indazoline-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.62 (s, 1H), 9.19 (s, 1H), 8.61 (s, 1H,), 8.12 (s, 1H), 8.02 (s, 1H), 7.77 (s, 1H), 7.67 (d, 1H, J = 8.8 Hz), 7.50-7.45 (m, 2H), 7.26 (s, 1H), 1.98 (s, 3H). LCMS: ret. time: 13.78 min.; purity: 100%; MS (*m/e*): 385 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1023	5-Fluoro-N4-(indazoline-5-yl)-N2-(4-isopropoxyphenyl)- 2,4-pyrimidinediamine (R935266)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine was reacted with 4-isoporopoxyaniline to produce 5-fluoro-N4-(indazoline-5-yl)-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.30 (s, 1H), 9.80 (s, 1H), 8.16 (d, 1H, J = 5.3 Hz), 8.06 (s, 1H), 7.98 (s, 1H), 7.51 (s, 2H), 7.32 (d, 2H, J = 8.8 Hz), 6.79 (d, 2H, J= 8.8 Hz), 4.51 (sept, 1H, J = 5.8 Hz), 1.22 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 17.65 min.; purity: 98%; MS (*m/e*): 379 (MH^+).
7.3.1024	N2-(3, 4-Ethyelenedioxyphenyl)-5-fluoro-N4-(indazoline-5-yl)-2,4-pyrimidinediamine (R935267)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine was reacted with 3, 4-ethylenedioxyphenylaniline to produce N2-(3, 4-ethyelenedioxyphenyl)-5-fluoro-N4-(indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.20 (s, 1H), 9.61 (s, 1H), 8.13 (d, 1H, J = 5.3 Hz), 8.08 (s, 1H), 7.98 (s, 1H), 7.54-7.48 (m, 2H), 7.06 (d, 1H, J = 2.3 Hz), 6.90 (dd, 1H, J = 2.3 and 8.8 Hz), 6.72 (d, 1H, J = 8.8 Hz), 4.17 (s, 4H). LCMS: ret. time: 15.16 min.; purity: 100%; MS (*m/e*): 379 (MH^+).
7.3.1025	5-Fluoro-N2-(3-hydroxyphenyl)-N4-(indazoline-5-yl)-2,4-pyrimidinediamine (R935268)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine was reacted with 3-aminophenol to produce 5-fluoro-N2-(3-hydroxyphenyl)-N4-(indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.64 (s, 1H), 10.33 (s, 1H), 8.29 (d, 1H, J = 5.3 Hz), 8.12 (s, 1H), 8.03 (s, 1H), 7.55 (dd, 2H, J = 1.7 and 8.8 Hz), 7.00 (d, 1H, J = 8.8 Hz), 6.90 (d, 1H, J = 8.8 Hz), 6.85 (d, 1H, J = 1.7 Hz), 6.53 (d, 1H, J = 8.8 Hz). LCMS: ret. time: 12.80 min.; purity: 98%; MS (*m/e*): 337 (MH^+).
7.3.1026	5-Fluoro-N4-(indazoline-5-yl)-N2-[3-(methoxycarbonyl methyleneoxy)phenyl]-2,4-pyrimidinediamine (R935269)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine was reacted with 3-(methoxycarbonylmethyleneoxy)aniline to produce 5-fluoro-N4-(indazoline-5-yl)-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.64 (s, 1H), 9.82 (s, 1H), 8.20 (d, 1H, J = 4.6 Hz), 8.10 (s, 1H), 8.08 (s, 1H), 7.99 (s, 1H), 7.57 (m, 2H), 7.13-7.6 (m, 3H), 6.56 (d, 1H, J = 8.8 Hz), 4.60 (s, 2H), 3.65 (s, 3H). LCMS: ret. time: 15.36 min.; purity: 94%; MS (*m/e*): 409 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1027	5-Fluoro-N4-(indazoline-5-yl)-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935270)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine was reacted with 6-aminoindazoline to produce 5-fluoro-N4-(indazoline-5-yl)-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.35 (s, 1H), 9.19 (s, 1H), 8.25 (d, 1H, J = 4.1 Hz), 8.12 (s, 1H), 8.01 (s, 1H), 7.81 (s, 1H), 7.73 (s, 1H), 7.64 (d, 1H, J = 8.8 Hz), 7.60 (dd, 2H, J = 1.7 and 8.9 Hz), 7.51 (d, 1H, J = 8.9 Hz), 7.21 (dd, 1H, J = 1.7 and 8.8 Hz). LCMS: ret. time: 13.45 min.; purity: 95%; MS (*m/e*): 361 (MH^+).
7.3.1028	5-Fluoro-N4-[4H-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl] -2,4-pyrimidinediamine (R935271)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-[4H-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-4-pyrimidineamine was reacted with 3-(*N*-methylaminocarbonylmethyleneoxy)aniline to produce 5-fluoro-N4-[4H-imidazo[2,1-c][1,4]-benzoxazin-8-yl]-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.44 (s, 1H), 9.25 (s, 1H), 8.11 (d, 1H, J = 3.5 Hz), 8.03 (d, 1H, J = 2.3 Hz), 7.90 (qt, 1H, J = 4.6 Hz), 7.69 (d, 1H, J = 1.2 Hz), 7.47 –7.42 (m, 1H), 7.33 (m, 1H), 7.26 (dd, 1H, J = 1.2 and 8.2 Hz), 7.12 (s, 1H), 7.09 (d, 1H, J = 1.7 Hz), 6.97 (t, 1H, J = 8.2H), 6.40 (dd, 1H, J = 2.3 and 8.2 Hz), 5.25 (s, 2H), 4.26 (s, 2H), 2.61 (d, 3H, J = 4.6 Hz). LCMS: ret. time: 15.45 min.; purity: 97%; MS (*m/e*): 462 (MH^+).
7.3.1029	5-Fluoro-N2-(4-isopropoxyphenyl)-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine (R935276)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine was reacted with 4-isopropoxyaniline to produce 5-fluoro-N2-(4-isopropoxyphenyl)-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6)· δ 10.69 (s, 1H), 9.03 (s, 1H), 8.06 (d, 1H, J = 3.5 Hz), 7.30 (d, 2H, J = 9.3 Hz), 6.82 (t, 2H, J = 2.3 Hz), 6.58 (d, 2H, J = 9.3 Hz), 6.11 (t, 2H, J = 2.3 Hz), 4.41 (sept, 1H, J = 5.8 Hz), 1.18 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 21.21 min.; purity: 90%; MS (*m/e*): 328 (MH^+).
7.3.1030	N2-(3, 4-Ethylenedioxyphenyl)-5-Fluoro-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine (R935277)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine was reacted with 3, 4-ethylenedioxyaniline to produce N2-(3, 4-ethylenedioxyphenyl)-5-Fluoro-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 11.63 (s, 1H), 9.94 (s, 1H), 8.23 (d, 1H, J = 4.7 Hz), 6.86 (m, 4H), 6.58 (d, 1H, J = 8.8 Hz), 6.12 (t, 2H, J = 2.3 Hz), 4.15 (s, 4H). LCMS: ret. time: 17.36 min.; purity: 96%; MS (*m/e*): 328 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1031	5-Fluoro-N2-(3-hydroxyphenyl)-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine (R935278)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine was reacted with 3-aminophenol to produce 5-fluoro-N2-(3-hydroxyphenyl)-N4-(1H-pyrrol-1-yl)- 2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.68 (s, 1H), 9.04 (s, 1H), 9.00 (s, 1H), 8.08 (d, 1H, J = 4.11 Hz), 7.01 (d, 1H, J = 8.2 Hz), 6.84-6.75 (m, 4H), 6.22 (dd, 1H, J = 1.2 and 8.2 Hz), 6.08 (t, 2H, J = 2.3 Hz). LCMS: ret. time: 16.24 min.; purity: 94%; MS (*m/e*): 286 (MH^+).
7.3.1032	5-Fluoro-N4-(indazoline-5-yl)-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine (R935279)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N4-(indazoline-5-yl)-N2-[3-(-methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N4-(indazoline-5-yl)-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 12.98 (s, 1H), 9.35 (s, 1H), 9.16 (s, 1H), 8.21 (s, 1H), 8.07 (d, 1H, J = 3.5 Hz), 7.97 (s, 1H), 7.90 (qt, 1H, J = 4.7 Hz), 7.59 (dd, 1H, J = 8.8 Hz), 7.49 (d, 1H, J = 8.8 Hz), 7.32-7.28 (m, 2H), 7.03 (t, 1H, J = 8.2 Hz), 6.45 (dd, 1H, J = 1.7 and 8.2 Hz), 4.31 (s, 2H), 2.61 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 12.92 min.; purity: 90%; MS (*m/e*): 408 (MH^+).
7.3.1033	5-Fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]- N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935280)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine was reacted with 3-(methoxycarbonylmethyleneoxy)aniline to produce 5-fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]- N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 11.45(s, 1H), 9.90 (s, 1H), 8.26 (d, 1H, J = 4.7 Hz), 7.07 (d, 1H, J = 8.2 Hz), 7.68 (d, 1H, J = 8.2 Hz), 6.94 (s, 1H), 6.85 (t, 2H, J = 2.3 Hz), 6.47 (dd, 1H, J = 2.3 and 8.2 Hz), 6.12 (t, 2H, J = 2.3 Hz), 4.64 (s, 2H), 3.68 (s, 3H). LCMS: ret. time: 16.24 min.; purity: 92%; MS (*m/e*): 358 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1034	5-Fluoro-N2-[3-(*N*-methylaminocarbonylmethyleneoxy) phenyl]-N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine (R935281)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, 5-fluoro-N2-[3-(-methoxycarbonylmethyleneoxy)phenyl]-N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N2-[3-(*N*-methylaminocarbonylmethyleneoxy)phenyl]-N4-(1H-pyrrol-1-yl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 10.73 (s, 1H), 9.21 (s, 1H), 8.11 (d, 1H, J = 4.1 Hz), 7.89 (qt, 1H, J = 4.7 Hz), 7.14 (d, 1H, J = 8.2 Hz), 7.09 (s, 1H), 6.93 (t, 1H, J = 8.2 Hz), 6.84 (t, 2H, J = 2 3 Hz), 6.40 (dd, 1H, J = 2.3 and 8.2 Hz), 6.09 (t, 2H, J = 2.3 Hz), 4.29 (s, 2H), 2.63 (s, 3H, J = 4.7 Hz). LCMS: ret. time: 16.16 min.; purity: 90%; MS (*m/e*): 357 (MH^+).
7.3.1035	N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R935286)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.37 (s, 1H), 9.20 (s, 1H), 8.10 (d, 1H, J = 3.5 Hz), 8.06 (s, 1H), 7.87 (s, 1H), 7.53 (d, 1H, J = 8.8 Hz), 7.33-7.21 (m, 3H), 6.77 (d, 1H, J = 8.8 Hz), 4.34 (t, 2H, J = 6.4 Hz), 4.19 (s, 4H), 3.93 (qt, 2H, J = 7.0 Hz), 2.82 (t, 2H, J = 6.4 Hz), 1.04 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 24.70 min.; purity: 90%; MS (*m/e*): 479 (MH^+).
7.3.1036	N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-2,4-pyrimidinediamine (R935287)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.35 (s, 1H), 9.19 (s, 1H), 8.09 (d, 1H, J = 4.1 Hz), 8.01 (s, 1H), 7.85 (s, 1H), 7.53 (d, 1H, J = 8.8 Hz), 7.32-7.20 (m, 3H), 6.77 (d, 1H, J = 8.8 Hz), 4.20 (s, 4H), 3.27 (t, 2H, J = 6.4 Hz), 3.27 (t, 2H, J = 6.4 Hz), 1.84 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 24.70 min.; purity: 90%; MS (*m/e*): 479 (MH^+). LCMS: ret. time: 22.09 min.; purity: 90%; MS (*m/e*): 437 (MH^+).

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7.3.1037	N2-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine (R935288)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.35 (s, 1H), 9.19 (s, 1H), 8.10 (d, 1H, J = 3.5 Hz), 8.02 (s, 1H), 7.86 (s, 1H), 7.81 (qt, 1H, J = 4.7 Hz), 7.52 (d, 1H, J = 8.2 Hz), 7.34-7.22 (m, 3H), 6.77 (d, 1H, J = 8.8 Hz), 4.33 (t, 2H, J = 6.4 Hz), 4.19 (s, 4H), 2.57 (t, 2H, J = 6.4 Hz), 2.48 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 23.10 min.; purity: 93%; MS (*m/e*): 464 (MH^+).
7.3.1038	N4-[1-(2-Ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(isopropoxyphenyl)-2,4-pyrimidinediamine (R935289)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N4-(isopropoxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 10.74 (s, 1H), 10.55 (s, 1H), 8.35 (d, 1H, J = 5.8 Hz), 7.98 (s, 1H), 7.77 (s, 1H), 7.66 (d, 1H, J = 8.8 Hz), 7.51 (d, 2H, J = 8.8 Hz), 7.16 (dd, 1H, J = 1.2 and 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 4.55 (sept, 1H, J = 6.4 Hz), 4.31 (t, 2H, J = 6.4 Hz), 3.93 (qt, 2H, J = 7.0 Hz), 2.80 (t, 2H, J = 6.4 Hz), 1.22 (d, 6H, J = 7.0 Hz), 1.02 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 26.84 min.; purity: 96%; MS (*m/e*): 479 (MH^+).
7.3.1039	5-Fluoro-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R935290)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N4-(isopropoxyphenyl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.31 (s, 1H), 9.22 (s, 1H), 8.08 (d, 1H, J = 4.1 Hz), 7.98 (s, 1H), 7.85 (s, 1H), 7.62 (dd, 2H, J = 3.5 and 8.8 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.27 (d, 1H, J = 8.8 Hz), 6.86 (d, 2H, J = 8.8 Hz), 4.55 (sept, 1H, J = 7.0 Hz), 4.49 (t, 1H, J = 5.3 Hz), 4.14 (t, 2H, J = 6.4 Hz), 3.26 (t, 2H, J = 6.4 Hz), 1.84 (q, 2H, J = 6.4 Hz), 1.24 (d, 6H, J = 7.0 Hz). LCMS: ret. time: 24.13 min.; purity: 97%; MS (*m/e*): 437 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1040	5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2(*N*-methylamino)carbonyl]ethyl-indazoline-6-yl]-2,4-pyrimidinediamine (R935291)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N4-(isopropoxyphenyl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2(*N*-methylamino)carbonyl]ethyl-indazoline-6-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.32(s, 1H), 9.24 (s, 1H), 8.10 (d, 1H, J = 3.5 Hz), 7.99 (s, 1H), 7.85 (s, 1H), 7.80 (qt, 1H, J = 4.7 Hz), 7.63 (d, 2H, J = 8.8 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.28 (d, 1H, J = 8.8 Hz), 6.84 (d, 2H, J = 8.8 Hz), 4.54 (sept, 1H, J = 5.8 Hz), 4.30 (t, 2H, J = 6.4 Hz), 2.55 (t, 2H, 7.4 Hz), 2.48 (d, 3H, J = 4.7 Hz), 1.24 (d, 6H, J = 6H). LCMS: ret. time: 23.68 min.; purity: 95%; MS (*m/e*): 464 (MH^+).
7.3.1041	N4-[1-(2-Ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R935292)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N4-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 10.35 (s, 1H), 10.21 (s, 1H), 8.29 (d, 1H, J = 5.3 Hz), 7.96 (s, 1H), 7.90 (s, 1H), 7.63 (d, 1H, J = 8.8 Hz), 7.20-7.06 (m, 4H), 6.58 (d, 1H, J = 8.2 Hz), 4.33 (t, 2H, J = 6.4 Hz), 3.94 (qt, 2H, J = 7.0 Hz), 2.82 (t, 2H, J = 6.4 Hz), 1.03 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 22.73 min.; purity: 94%; MS (*m/e*): 437 (MH^+).
7.3.1042	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-2,4-pyrimidinediamine (R935293)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(3-hydroxypropyl)indazoline-6-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.38 (s, 1H), 9.35 (s, 1H), 9.26 (s, 1H), 8.13 (d, 1H, J = 4.1 Hz), 8.05 (s, 1H), 7.85 (s, 1H), 7.52 (d, 1H, J = 8.2 Hz), 7.28 (d, 2H, J = 8.8 Hz), 7.12 (d, 1H, J = 1.7 Hz), 7.08 (t, 1H, J = 8.2 Hz), 6.49 (d, 1H, J = 8.2 Hz), 4.15 (t, 2H, J = 7.0 Hz), 3.26 (t, 2H, J = 6.4 Hz), 1.85 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 24.70 min.; purity: 90%; MS (*m/e*): 479 (MH^+). LCMS: ret. time: 20.37 min.; purity: 98%; MS (*m/e*): 395 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1043	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine (R935294)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.36 (s, 1H), 9.33 (s, 1H), 9.25 (s, 1H), 8.14 (d, 1H, J = 3.5 Hz), 8.05 (s, 1H), 7.85 (s, 1H), 7.78 (qt, 1H, J = 4.7 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.30 (d, 2H, J = 8.8 Hz), 7.11 (d, 1H, J = 2.3 Hz), 7.07 (t, 1H, J = 8.2 Hz), 6.47 (d, 1H, J = 8.2 Hz), 4.32 (t, 2H, J = 6.4 Hz), 2.57 (t, 2H, J = 6.4 Hz), 2.48 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 20.18 min.; purity: 93%; MS (*m/e*): 422 (MH^+).
7.3.1044	N4-[1-(2-Ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R935295)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(2-methoxycarbonylbenzofur-5-yl)-4-pyrimidineamine was reacted with 6-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N4-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine Purification of the crude gave two products. N4-[1-(2-Ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R935295): ^1H NMR (DMSO-d_6): δ 9.54 (s, 1H), 9.41 (s, 1H), 8.21 (app d, 1H, J = 1.7 Hz), 8.17 (d, 1H, J = 3.5 Hz), 8.01 (s, 1H), 7.86 (s, 1H), 7.83-7.80 (m 2H), 7.68 (d, 1H, J = 8.8 Hz), 7.59 (s, 1H), 7.52 (d, 1H, J = 8.2 Hz), 7.25 (d, 1H, J = 8.2 Hz), 4.12 (t, 2H, J = 6.4 Hz), 3.91 (qt, 2H, J = 7.0 Hz), 3.88 (s, 3H), 2.72 (t, 2H, J = 6.4 Hz), 1.02 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 25.67 min.; purity: 91%; MS (*m/e*): 519 (MH^+) and N4-[1-(2-carboxyethyl)indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine (R935296) ^1H NMR (DMSO-d_6): δ 9.54 (s, 1H), 9.39 (s, 1H), 8.23 (app d, 1H, J = 1.7 Hz), 8.17 (d, 1H, J = 3.5 Hz), 8.00 (s, 1H), 7.86 (s, 1H), 7.83-7.80 (m 2H), 7.68 (d, 1H, J = 8.8 Hz), 7.58 (s, 1H), 7.52 (d, 1H, J = 8.2 Hz), 7.28 (d, 1H, J = 8.2 Hz), 4.13 (t, 2H, J = 6.4 Hz), 3.88 (s, 3H), 2.67 (t, 2H, J = 6.4 Hz). LCMS: ret. time: 23.28 min.; purity: 91%; MS (*m/e*): 491 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1045	5-Fluoro-N4-[2-(*N*-methylaminocarbonyl)benzofuran-5-yl]-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine (R935297)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N4-[2-(*N*-methylaminocarbonyl)benzofuran-5-yl]-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-6-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6). δ 10.00 (s, 1H), 9.90 (s, 1H), 8.70 (qt, 1H, J = 4.7 Hz), 8.24 (d, 1H, J = 4.1 Hz), 8.12 (d, 1H, J = 1.7 Hz), 7.911 (s, 1H), 7.86 (s, 1H), 7.81 (qt, 1H, J = 4.7 Hz), 7.71 (d, 2H, J = 1.7 and 8.8 Hz), 7.57 (dd, 1H, J = 3.5 and 8.8 Hz), 7.35 (s, 1H), 7.26 (dd, 1H, J = 3.5 and 8.8 Hz), 4.19 (t, 2H, J = 7.0 Hz), 2.53 (t, 2H, J = 7.0 Hz), 2.47 (d, 6H, J = 4.7 Hz). LCMS: ret. time: 20.18 min.; purity: 89%; MS (*m/e*): 503 (MH^+).
7.3.1046	5-Fluoro-N4-(4-isopropoxyphenyl)-N2-(2-methyl-indazoline-5-yl)-2,4-pyrimidinediamine (R935298)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine and 5-amino-2-methylindazoline were reacted to give 5-fluoro-N4-(4-isopropoxyphenyl)-N2-(2-methyl-indazoline-5-yl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.15 (s, 1H), 9.03 (s, 1H), 8.03-8.00 (m, 3H), 7.60 (dd, 2H, J = 4.1 and 8.8 Hz), 7.42 (d, 1H, J = 9.3 Hz), 7.31 (d, 1H, J = 9.3 Hz), 6.86 (d, 2H, J = 8.8 Hz), 4.57 (sept, 1H, J = 6.4 Hz), 4.08 (s, 3H), 1.26 (d, 6H, J = 6.4 Hz), LCMS: ret. time: 23.89 min.; purity: 98%; MS (*m/e*): 393 (MH^+).
7.3.1047	5-Fluoro-N4-(3-hydroxyphenyl)-N2-(2-methy-indazoline-5-yl)-2,4-pyrimidinediamine (R935299)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 5-amino-2-methylindazoline to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-(2-methy-indazoline-5-yl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 10.35 (s, 1H), 10.30 (s, 1H), 9.62 (br s, 1H), 8.22 (d, 1H, J = 5.3 Hz), 8.13 (s, 1H), 7.85 (s, 1H), 7.49 (d, 1H, J = 8.8 Hz), 7.17 (dd, 1H, J = 1.7 and 9.3 Hz), 7.08 (d, 2H, J = 5.3 Hz), 7.03 (s, 1H), 6.64-6.60 (m, 1H), 4.09 (s, 3H). LCMS: ret. time: 20.01 min.; purity: 97%; MS (*m/e*): 351 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1048	N4-(3, 4-Ethyelenedioxyphenyl)-5-fluoro-N2-(2-methy-indazoline-5-yl)-2,4-pyrimidinediamine (R935300)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5- fluoro-4-pyrimidineamine was reacted with 5-amino-2-methylindazoline to produce N4-(3, 4-ethyelenedioxyphenyl)-5-fluoro-N2-(2-methy-indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.64 (s, 1H), 10.62 (s, 1H), 8.22 (d, 1H, J = 5.3 Hz), 8.21 (s, 1H), 7.77 (s, 1H), 7.58 (d, 1H, J = 9.3 Hz), 7.23-7.19 (m, 2H), 7.10 (dd, 1H, J = 2.3 and 8.8 Hz), 6.78 (d, 1H, J = 8.8 Hz), 4.21 (s, 3H), 4.15 (s, 4H). LCMS: ret. time: 21.77 min.; purity: 92%; MS (*m/e*): 393 (MH^+).
7.3.1049	N2-[1-(2-Ethoxycarbonylethyl)indazoline-5-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R935301)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.15 (s, 1H), 9.13 (s, 1H), 8.10, (s, 1H), 8.04 (d, 1H, J = 3.5 Hz), 7.83 (s, 1H), 7.50 (s, 2H), 7.30 (d, 1H, J = 2.3 and 8.8 Hz), 6.79 (d, 1H, J = 8.8 Hz), 4.55 (t, 2H, J = 6.4 Hz), 4.22 (s, 4H), 3.97 (qt, 2H, J = 7.0 Hz), 2.88 (t, 2H, J = 6.4 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 25.19 min.; purity: 93%; MS (*m/e*): 479 (MH^+).
7.3.1050	N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935302)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.14 (s, 1H), 9.13 (s, 1H), 8.09 (s, 1H), 8.03 (d, 1H, J = 4.1 Hz), 7.82 (s, 1H), 7.48 (s, 2H), 7.30 (d, 1H, J = 2.3 Hz), 7.18 (dd, 1H, J = 2.3 and 8.8 Hz), 6.78 (d, 1H, J = 8.8 Hz), 4.59 (t, 1H, J = 6.4 Hz), 4.37 (t, 2H, J = 6.4 Hz), 4.22 (s, 4H), 3.34 (t, 2H, J = 6.4 Hz), 1.84 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 22.33 min.; purity: 100%; MS (*m/e*): 437 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1051	N4-[1-(2-Ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R935303)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N4-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.50 (s, 1H), 10.46 (s, 1H), 9 62 (br s 1H), 8.28 (d, 1H, J = 5.8 Hz), 7.96 (s, 2H), 7.65 (d, 1H, J = 8.8 Hz), 7.36 (dd, 1H, J = 1.7 and 8.8 Hz), 7.15-7.08 (m, 3H), 6.67-6.64 (m, 1H), 4.59 (t, 2H, J = 6.4 Hz), 3.97 (qt, 2H, J = 7.0 Hz), 2.89 (t, 2H, J = 6.4 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 23.68 min.; purity: 97%; MS (*m/e*): 437 (MH^+).
7.3.1052	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935304)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.39 (s, 1H), 9.18 (s, 1H), 9.15 (s, 1H), 8.20 (s, 1H), 8.07 (d, 1H, J = 4.1 Hz), 7.84 (s, 1H), 7.46 (s, 2H), 7.24 (d, 1H, J = 8.2 Hz), 7.11-7.06 (m, 2H), 6.53 (d, 1H, J = 8.8 Hz), 4.56 (t, 1H, J = 4.7 Hz), 4.37 (t, 2H, J = 6.4 Hz), 3.34 (t, 2H, J = 6.4 Hz), 1.92 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 24.70 min.; purity: 90%; MS (*m/e*): 479 (MH^+). LCMS: ret. time: 20.89 min.; purity: 98%; MS (*m/e*): 395 (MH^+).
7.3.1053	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine (R935305)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.39 (s, 1H), 9.18 (s, 1H), 9.15 (s, 1H), 8.19 (s, 1H), 8.06 (d, 1H, J = 3.5 Hz), 7.84 (s, 1H), 7.82 (qt. 1H, J = 4.7 Hz), 7.46 (t, 2H, J = 8.2 Hz), 7.25 (d, 1H, J = 8.2 Hz), 7.11 (d, 1H, J = 8.2 Hz), 7.10 (d, 1H, J = 8.2 Hz), 6.53 (t, 1H, J = 8.2 Hz), 4.51 (t, 2H, J = 7.0 Hz), 2.61 (t, 2H, J = 7.0 Hz), 2.49 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 20.66 min.; purity: 95%; MS (*m/e*): 422 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1054	N4-[1-(2-Ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N2-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R935306)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.48 (s, 1H), 10.41 (s, 1H), 8.25 (d, 1H, J = 5.8 Hz), 7.93 (s, 1H), 7.84 (s, 1H), 7.66 (d, 1H, J = 8.8 Hz), 7.49 (d, 2H, J = 8.8 Hz), 7.36 (dd, 1H, J = 2.3 and 8.8 Hz), 6.86 (d, 2H, J = 8.8 Hz), 4.59 (t, 2H, J = 6.4 Hz), 4.57 (sept, 1H, J = 7.0 Hz), 3.96 (qt, 2H, J = 7.0 Hz), 2.89 (t, 2H, J = 6.4 Hz), 1.23 (d, 6H, J = 7.0 Hz), 1.05 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 27.39 min.; purity: 98%; MS (*m/e*): 479 (MH^+).
7.3.1055	5-Fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R935307)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.16 (s, 1H), 9.10 (s, 1H), 8.09 (s, 1H), 8.03 (d, 1H, J = 4.1 Hz), 7.79 (s, 1H), 7.57 (d, 2H, J = 8.8 Hz), 7.46 (t, 2H), 6.87 (d, 2H, J = 8.8 Hz), 4.60-4.52 (m, 2H), 4.37 (t, 2H, J = 6.4 Hz), 3.34 (t, 2H, J = 6.4 Hz), 1.84 (q, 2H, J = 6.4 Hz), 1.24 (d, 6H, J = 7.0 Hz). LCMS: ret. time: 23.71 min.; purity: 98%; MS (*m/e*): 437 (MH^+).
7.3.1056	5-Fluoro-N4-(2-hydroxymethylbenzofur-5-yl)- N2-[1-(3-hydroxypropyl)indazoline-6-yl]- 2,4-pyrimidinediamine (R935308)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-[1-(2-Ethoxycarbonylethyl)indazoline-6-yl]- 5-fluoro-N2-(2-methoxycarbonylbenzofur-5-yl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N4-(2-hydroxymethylbenzofur-5-yl)- N2-[1-(3-hydroxypropyl)indazoline-6-yl]- 2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.35 (s, 1H), 9.33 (s, 1H), 8.12 (d, 1H, J = 3.5 Hz), 7.99 (d, 1H, J = 1.7 Hz), 7.95 (s, 1H), 7.84 (s, 1H), 7.55-7.49 (m, 3H), 7.28 (d, 1H, J = 8.8 Hz), 6.62 (s, 1H), 5.46 (t, 1H, J = 5.8 Hz), 4.55 (d, 2H, J = 5.8 Hz), 4.45 (t, 1H, J = 4.7 Hz), 3.96 (t, 2H, J = 6.4 Hz), 3.20 (t, 2H, J = 6.4 Hz), 1.76 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 20.86 min.; purity: 99%; MS (*m/e*): 449 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1057	N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine (R935309)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.12 (s, 1H), 9.11 (s, 1H), 8.09 (s, 1H), 8.03 (d, 1H, J = 3.5 Hz), 7.82 (s, 2H), 7.47 (s, 2H), 7.32-7.30 (m, 1H), 7.22-7.17 (m, 1H), 6.80 (d, 1H, J = 8 8 Hz), 4.51 (t, 2H, J = 7.0 Hz), 4.22 (s, 4H), 2.62 (t, 2H, J = 7.0 Hz), 2.49 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 18.67 min.; purity: 100%; MS (*m/e*): 464 (MH^+).
7.3.1058	5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]-indazoline-5-yl]-2,4-pyrimidinediamine (R935310)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.18 (s, 1H), 9.09 (s, 1H), 8.08 (s, 1H), 8.02 (d, 1H, J = 4.1 Hz), 7.82 (qt, 1H, J = 4.7 Hz), 7.79 (s, 1H), 7.57 (d, 2H, J = 8.8 Hz), 7.45 (d, 2H, J = 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 4.57 (q, 2H, J = 5.8 Hz), 4.51 (t, 2H, J = 7.0 Hz), 2.61 (t, 2H, J = 7.0 Hz), 2.47 (d, 3H, J = 4.7 Hz), 1.26 (d, 6H, J = 5.8 Hz). LCMS: ret. time: 17.14 min.; purity: 99%; MS (*m/e*): 464 (MH^+).
7.3.1059	N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine (R935320)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-1-(2-methoxy-3-carbomethoxybenzyl)indazoline to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.36 (s, 1H), 9.18 (s, 1H), 8.08 (d, 1H, J = 3.5 Hz), 8.04 (s, 1H), 7.56 (d, 1H, J = 8.2 Hz), 7.45 (d, 1H, J = 1.8 Hz), 7.43-7.38 (m, 1H), 7.36-7.34 (m, 1H), 7.30 (dd, 1H, J = 1.7 and 8.8 Hz), 7.20 (dd, 1H, J = 2.3 and 8.8 Hz), 6.75 (d, 1H, J = 8.8 Hz), 6.68 (d, 1H, J = 8.2 Hz), 6.48 (dd, 1H, J = 1.7 and 8.2 Hz), 5.39 (s, 2H), 4.16 (s, 4H), 3.83 (s, 3H), 3.79 (s, 3H). LCMS: ret. time: 29.92 min.; purity: 80%; MS (*m/e*): 557 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1060	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]- 2,4-pyrimidinediamine (R935321)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-(2-methoxy-3-carbomethoxybenzyl)indazoline to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.37 (s, 1H), 9.31(s, 1H), 9.23 (s, 1H), 8.11 (d, 1H, J = 3.5 Hz), 8.08 (s, 1H), 7.93 (s, 1H), 7.57 (d, 1H, J = 8.8 Hz), 7.45 (d, 1H, J = 1.7 Hz), 7.40 (dd, 1H, J = 1.7 and 8.8 Hz), 7.33-7.27 (, 2H), 7.13 (t, 1H, J = 1.7 HZ), 7.03 (t, 2H, J = 8.2 Hz), 6.67 (d, 1H, J = 8.2 Hz), 6.45 (dd, 1H, J = 1.7 and 8.2 Hz), 5.37 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H). LCMS: ret. time: 28.80 min.; purity: 92%; MS (*m/e*): 515 (MH^+).
7.3.1061	5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine (R935322)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.60 (s, 2H), 8.11 (d, 1H, J = 4.1 Hz), 8.00-7.92 (m, 3H), 7.61-7.53 (m, 4H), 7.47-7.24 (m, 5H), 6.81 (d, 2H, J = 8.8 Hz), 6.68 (d, 1H, J = 8.2 Hz), 5.34 (s, 2H), 4.48 (sept, 1H, J = 5.9 Hz), 3.82 (s, 3H), 2.55 (s, 3H), 1.21 (d, 6H, J = 5.9 Hz). LCMS: ret. time: 30.57 min.; purity: 95%; MS (*m/e*): 696 (MH^+).
7.3.1062	N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N4-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine (R935323)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine. . ^{1}H NMR (DMSO-d_6): δ 9.53 (s, 1H), 9.41 (s, 1H), 8.05 (d, 1H, J = 4.1 Hz), 7.96-7.90 (m, 3H), 7.55 (d, 1H, J = 8.8 Hz), 7.49 (dd, 1H, J = 7.6 Hz), 7.42-7.20 (m, 6H), 7.14-7.10 (m, 1H), 6.69 (d, 1H, J = 8.2 Hz), 6.60 (d, 1H, J = 8.8 Hz), 5.33 (s, 2H), 4.10 (s, 4H), 3.77 (s, 3H), 2.50 (s, 3H). LCMS: ret. time: 32.11 min.; purity: 93%; MS (*m/e*): 696 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1063	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine (R935324)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.64 (s, 1H), 9.56 (s, 1H), 8.15 (d, 1H, J = 4.1 Hz), 8.00 (s, 1H), 7.97 (d, 2H, J = 8.8 Hz), 7.60 (d, 1H, J = 8.8 Hz), 7.53 (d, 1H, J = 1.2 and 8.8 Hz), 7.47-7.23 (m, 6H), 7.11 (t, 1H, J = 1.7 Hz), 7.03 (t, 1H, J = 8.2 Hz), 6.62 (d, 1H, J = 8.2 Hz), 6.48 (dd, 1H, J = 1.7 and 8.2 Hz), 5.36 (s, 2H), 3.82 (s, 3H), 2.55 (s, 3H). LCMS: ret. time: 29.79 min.; purity: 92%; MS (*m/e*): 654 (MH^+).
7.3.1064	N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine (R935336)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-2-(2-methoxy-3-carbomethoxybenzyl)indazoline to provide N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.16 (s, 1H), 9.14 (s, 1H), 8.24 (s, 1H), 8.06 (s, 1h), 8.04 (d, 1H, J = 3.5 Hz), 7.51 (d, 2H, J = 7.7 Hz), 7.49 (s, 1H), 7.29-7.26 (m, 2H), 7.19 (d, 1H, J = 7.7 Hz), 6.92 (d, 1H, J = 8.8 Hz), 6.76 (d, 1H, J = 8.2 Hz), 5.58 (s, 2H), 4.22 (s, 4H), 3.92 (s, 3H), 3.82 (s, 3H). LCMS: ret. time: 10.91 min.; purity: 91%; MS (*m/e*): 557 (MH^+).
7.3.1065	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]- 2,4-pyrimidinediamine (R935337)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 6-amino-2-(2-methoxy-3-carbomethoxybenzyl)indazoline to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.31 (s, 1H), 9.17 (s, 1H), 9.15 (s, 1H), 8.26 (s, 1H), 8.09 (d, 1H, J = 5.8 Hz), 8.08 (s, 1H), 7.52 (app t, 3H, J = 7.6 Hz), 7.42 (d, 1H, J = 8.2 Hz), 7.23 (d, 1H, J = 8.2 Hz), 7.08 (app s,1H), 7.03 (d, 1H, J = 8.2 Hz), 6.93 (d, 1H, J = 7.6 Hz), 6.43 (d, 1H, J = 8.2 Hz), 5.57 (s,2H), 3.90 (s, 3H), 3.82 (s, 3H). LCMS: ret. time: 10.51 min.; purity: 93%; MS (*m/e*): 515 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1066	5-Fluoro-N4-(4-isopropoxyphenyl)-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine (R935338)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-isopropoxyphenyl)-4-pyrimidineamine was reacted with 6-amino-2-(2-methoxy-4-carbomethoxybenzyl)indazoline to provide 5-fluoro-N4-(4-isopropoxyphenyl)-N2-[2-(2-methoxy-4-carbomethoxybenzyl)indazoline-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.20 (s, 1H), 9.16 (s, 1H), 8.26 (s, 1H), 8.16 (s, 1H), 8.06 (d, 1H, J = 3.5 Hz), 7.66 (d, 2H, J = 8.8 Hz), 7.52-7.48 (m, 3H), 7.15 (d, 1H, J = 8.2 Hz), 6.86 (d, 2H, J = 8.8 Hz), 6.81 (d, 1H, J = 8.8 Hz), 5.56 (s, 2H), 4.46 (sept, 1H, J = 5.9 Hz), 3.91 (s, 3H), 3.82 (s, 3H), 1.17 (d, 6H, J = 5.9 Hz). LCMS: ret. time: 11.94 min.; purity: 90%; MS (*m/e*): 557 (MH^+).
7.3.1067	N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-5-yl]-2,4-pyrimidinediamine (R935339)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide N4-(3, 4-Ethylenedioxyphenyl)-5-fluoro-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-5-yl]-2,4-pyrimidinediamine. . ^{1}H NMR (DMSO-d_6): δ 9.57 (br s, 2H), 8.08 (d, 1H, J = 3.5 Hz), 8.01 (s, 1H), 7.99 (d, 1H, J = 1.0 Hz), 7.95 (s, 1H), 7.59-7.32 (m, 3H), 7.45-7.32 (m, 4H), 7.27-7.24 (m, 1H), 7.17-7.12 (m, 1H), 6.74 (d, 1H, J = 8.7 Hz), 6.65 (d, 1H, J = 8.7 Hz), 5.58 (s, 2H), 4.15 (s, 4H), 3.88 (s, 3H), 2.56 (s, 3H). LCMS: ret. time: 11.33 min.; purity: 98%; MS (*m/e*): 696 (MH^+).
7.3.1068	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-5-yl]-2,4-pyrimidinediamine (R935340)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-hydroxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline to provide 5-fluoro-N4-(3-hydroxyphenyl)-N2-[1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.57 (s, 1H), 9.48 (s, 1H), 8.13 (app s, 2H), 8.00 (d, 1H, J = 8.2 Hz), 7.94 (s, 1H), 7.59-7.32 (m, 7H), 7.18 (d, 1H, J = 8.2 Hz), 7.06 (app t, 3H, J = 8.8 Hz), 6.64 (d, 1H, J = 8.2 Hz), 6.55 (d, 1H, J = 8.2 Hz), 5.57 (s, 2H), 3.88 (s, 3H), 2.56 (s, 3H). LCMS: ret. time: 10.16 min.; purity: 97%; MS (*m/e*): 654 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1069	N4-(4-Chlorophenyl)-5-fluoro-N2-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine (R935351)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chlorophenyl)-5-fluoro 4-pyrimidineamine and 1-methyl-5-aminoindazoline were reacted to give N4-(4-chlorophenyl)-5-fluoro-N2-(1-methyl-indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.86 (s, 1H), 9.61 (s, 1H), 8.17 (d, 1H, J = 4.1 Hz), 8.00 (s, 1H), 7.88 (s, 1H), 7.78 (d, 2H, J = 8 8 Hz), 7.57 (d, 1H, J = 8.8 Hz), 7.43 (d, 1H, J = 8.8 Hz), 7.34 (d, 2H, J = 8.8 Hz), 4.00 (s, 3H). LCMS: ret. time: 10.64 min.; purity: 94%; MS (*m/e*): 369 (MH^+).
7.3.1070	N4-(4-Chlorophenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935352)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chlorophenyl)-5-fluoro 4-pyrimidineamime and 6-aminoindazoline were reacted to give N4-(4-chlorophenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.18 (s, 1H), 10.02 (s, 1H), 8.26 (d, 1H, J = 4.1 Hz), 7.98 (s, 1H), 7.84 (d, 1H, J = 8.8 Hz), 7.82 (d, 2H, J = 8.8 Hz), 7.65 (d, 1H, J = 8.8 Hz), 7.35 (d, 2H, J = 8.8 Hz), 7.19 (d, 1H, J = 8.8 Hz). LCMS: ret. time: 10.80 min.; purity: 90%; MS (*m/e*): 355 (MH^+).
7.3.1071	N4-(4-Chlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935353)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N4-(4-chlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.37 (s, 1H), 10.17 (s, 1H), 8.26 (d, 1H, J = 5.3 Hz), 7.96 (s, 1H), 7.88 (s, 1H), 7.33-7.66 (m, 3H), 7.40 (d, 1H, J = 8.8 Hz), 7.35 (d, 2H, J = 8.8 Hz), 4.61 (t, 2H, J = 6.4 Hz), 3.97 (qt, 2H, J = 7.0 Hz), 2.91 (t, 2H, J = 6.4 Hz), 1.05 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 11.85 min.; purity: 95%; MS (*m/e*): 455 (MH^+).
7.3.1072	N4-(3-Chloro-4-trifluoromethoxy-phenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935354)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-trifluoromethoxy-phenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N4-(3-chloro-4-trifluoromethoxy-phenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.63 (s, 1H), 9.30 (s, 1H), 8.17 (d, 1H, J = 3.5 Hz), 8.10 (t, 1H, J = 2.3 Hz), 8.01 (s, 1H), 7.87 (s, 1H), 7.86 (d, 1H, J = 8.2 Hz), 7.57 (d, 1H, J = 9.4 Hz), 7.47 (t, 2H, J = 10.0 Hz), 4.56 (t, 2H, J = 6.9 Hz), 3.97 (qt, 2H, J = 7.0 Hz), 2.88 (t, 2H, J = 6.9 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 14.4 min.; purity: 95%; MS (*m/e*): 539 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1073	N4-(3, 4-Dichlorophenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935355)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-dichlorophenyl)-5-fluoro 4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give N4-(3, 4-dichlorophenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.63 (s, 1H), 9.35 (s, 1H), 8.17 (d, 1H, J = 3.5 Hz), 8.08 (s, 1H), 8.01 (s, 1H), 7.86 (s, 1H), 7.79 (d, 1H, J = 8.8 Hz), 7.53 (d, 2H, J = 8.2 Hz), 7.47 (d, 1H, J = 8.2 Hz), 3.99 (s, 3H). LCMS: ret. time: 12.30 min.; purity: 98%; MS (*m/e*): 404 (MH^+).
7.3.1074	5-Fluoro-N2-(1-methylindazoline-5-yl)-N4-(3-trifluoromethoxypheny)-2,4-pyrimidinediamine (R935356)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-trifluoromethoxyphenyl)-4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give 5-fluoro-N2-(1-methylindazoline-5-yl)-N4-(3-trifluoromethoxypheny)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.37 (s, 1H), 10.17 (s, 1H), 8.25 (d, 1H, J = 4.1 Hz), 7.92 (s, 2H), 7.84 (d, 1H, J= 9.4 Hz), 7.75 (s, 1H), 7.59 (d, 1H, J = 8.8 Hz), 7.45 (d, 1H, J= 9.4 Hz), 7.38 (d, 1H, J = 9.4 Hz), 7.08 (d, 1H, J = 8.8 Hz), 3.99 (s, 3H). LCMS: ret. time: 12.13 min.; purity: 94%; MS (*m/e*): 419 (MH^+).
7.3.1075	N4-(3, 4-Difluoromethylendioxyphenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935357)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give N4-(3, 4-difluoromethylendioxyphenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.84 (s, 1H), 9.54 (s, 1H), 8.16 (d, 1H, J = 4.1 Hz), 8.00 (s, 2H), 7.87 (s, 1H), 7.55-7.32 (m, 4H), 3.99 (s, 3H). LCMS: ret. time: 11.26 min.; purity: 96%; MS (*m/e*): 415 (MH^+).
7.3.1076	N4-(3, 4-Difluorophenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935358)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-difluorophenyl)-5-fluoro-4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give N4-(3, 4-difluorophenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.50 (s, 1H), 9.27 (s, 1H), 8.13 (d, 1H, J = 4.1 Hz), 8.08 (app s, 2H), 7.85 (s, 1H), 7.50 (app s, 3H), 7.37 (q, 1H, J = 9.4 Hz), 3.99 (s, 3H). LCMS: ret. time: 10.42 min., purity: 90%; MS (*m/e*): 371 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1077	N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935359)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.79 (s, 1H), 9.45 (s, 1H), 8.19 (d, 1H, J = 4.1 Hz), 8.09 (t, 1H, J = 2.8 Hz), 8.00 (s, 1H), 7.85-7.81 (m, 2H), 7.51 (d, 1H, J = 8.8 Hz), 7.48-7.44 (m, 2H), 3.99 (s, 3H). LCMS: ret. time: 13.14 min.; purity: 92%; MS (*m/e*): 453 (MH^+).
7.3.1078	N2-[1-(2-Ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R935360)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-trifluoromethoxyphenyl)-4-pyrimidineamine was reacted with 5-amino-1-(2-ethoxycarbonylethyl)indazoline to provide N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.55 (s, 1H), 9.26 (s, 1H), 8.15 (d, 1H, J = 3.5 Hz), 8.05 (s, 1H), 7.95 (d, 1H, J = 8.2 Hz), 7.88 (s, 1H), 7.78 (s, 1H), 7.58 (dd, 1H, J = 8.8 and 7.4 Hz), 7.39 (t, 1H, J = 8.2 Hz), 7.01 (d, 1H, J = 8.8 Hz), 4.56 (t, 2H, J = 7.0 Hz), 3.97 (q, 4H, J = 7.0 Hz), 2.88 (t, 2H, J = 7.0 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 13.22 min.; purity: 95%; MS (*m/e*): 505 (MH^+).
7.3.1079	5-Fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-N4- (3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R935361)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide 5-fluoro-N2-[1-[2(N-methylaminocarbonyl)ethyl]indazoline-5-yl]-N4- (3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.55 (s, 1H), 9.25 (s, 1H), 8.15 (d, 1H, J = 3.5 Hz), 8.04 (s, 1H), 7.96 (d, 1H, J = 8.2 Hz), 7.87 (s, 1H), 7.83 (qt, 1H, J = 4.9 Hz), 7.70 (s, 1H), 7.49 (dd, 2H, J = 8.2 and 9.4 Hz), 7.40 (d, 1H, J = 8.8 Hz), 7.01 (d, 1H, J = 8.8 Hz), 4.52 (t, 2H, J = 7.0 Hz), 2.63 (t, 2H, J = 7.0 Hz), 2.49 (d, 3H, J = 4.7 Hz). LCMS: ret. time: 10.00 min.; purity: 100%; MS (*m/e*): 490 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1080	5-Fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R935362)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]- 5-fluoro-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine was reacted with DIBAL-H to produce 5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.55 (s, 1H), 9 24 (s, 1H), 8.15 (d, 1H, J = 2.9 Hz), 8.05 (s, 1H), 7.92 (d, 1H, J = 7.6 Hz), 7.87 (s, 1H), 7.78 (s, 1H), 7.50 (s, 2H), 7.39 (t, 1H, J = 8.2 Hz), 7.01 (d, 1H, J = 7.6 Hz), 4.56 (t, 1H, J = 5.2 Hz), 4.38 (t, 2H, J = 7.0 Hz), 3.35 (dd, 2H, J = 5.2 and 7.0 Hz), 1.84 (qt, 2H, J = 7.0 Hz). LCMS: ret. time: 10.42 min.; purity: 97%; MS (*m/e*): 463 (MH^+).
7.3.1081	5-Fluoro-N2-(indazoline-6-yl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R935363)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-trifluoromethoxyphenyl)-4-pyrimidineamine and 6-aminoindazoline were reacted to give 5-fluoro-N2-(indazoline-6-yl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 12.72(s, 1H), 9.60 (s, 1H), 9.42 (s, 1H), 8.21 (d, 1H, J = 3.5 Hz), 8.06 (br s, 2H), 7.89 (s, 1H), 7.83 (s, 1H), 7.57 (d, 1H, J = 8.8 Hz), 7.42 (t, 1H, J = 8.2 Hz), 7.27 (d, 1H, J = 8.8 Hz), 7.00 (d, 1H, J = 8.2 Hz). LCMS: ret. time: 12.17 min.; purity: 97%; MS (*m/e*): 405 (MH^+).
7.3.1082	5-Fluoro-N2-(indazoline-5-yl)-N4-(3-trifluoro methoxyphenyl)-2,4-pyrimidinediamine (R935364)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(3-trifluoromethoxyphenyl)-4-pyrimidineamime and 5-aminoindazoline were reacted to give 5-fluoro-N2-(indazoline-5-yl)-N4-(3-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 12.85 (s, 1H), 9.54 (s, 1H), 9.23 (s, 1H), 8.15 (d, 1H, J = 3.5 Hz), 8.05 (s, 1H), 7.93 (d, 1H, J = 8.2 Hz), 7.89 (s, 1H), 7.78 (s, 1H), 7.48-7.35 (m, 3H), 7.01 (d, 1H, J = 8.2 Hz). LCMS: ret. time: 10.44 min.; purity: 98%; MS (*m/e*): 405 (MH^+).
7.3.1083	N4-(4-Chlorophenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935365)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chlorophenyl)-5-fluoro 4-pyrimidineamime and 5-aminoindazoline were reacted to give N4-(4-chlorophenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 12.85 (s, 1H), 9.43 (s, 1H), 9.19 (s, 1H), 8.11 (d, 1H, J = 3.5 Hz), 8.08 (s, 1H), 7.87 (s, 1H), 7.82 (dd, 2H, J = 3.0 and 8.8 Hz), 7.42 (dd, 2H, J = 3.0 and 8.8 Hz), 7.31 (d, 2H, J = 8.8 Hz). LCMS: ret. time: 9.07 min.; purity: 91%; MS (*m/e*): 355 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1084	N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935366)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamime and 5-aminoindazoline were reacted to give N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 12.90 (s, 1H), 9.45 (s, 1H), 9.27 (s, 1H), 8.15 (d, 1H, J = 3.5 Hz), 8.11 (t, 1H, J = 3.0 Hz), 8.02 (s, 1H), 7.87 (s, 1H), 7.84 (d, 1H, J = 8.8 Hz), 7.47 (d, 2H, J = 8.8 Hz), 7.44 (d, 1H, J = 8.8 Hz). LCMS: ret. time: 11.65 min.; purity: 98%; MS (*m/e*): 439 (MH^+).
7.3.1085	5-Fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-N2-(3, 4,5-trimethoxyphenyl)-2,4-pyrimidinediamine (R935367)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine and 3, 4,5-trimethoxyaniline were reacted by microwave heating at 180 °C. Upon concentration of the ethanol and addition of 2N HCl provided 5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-N2-(3, 4,5-trimethoxyphenyl)-2,4-pyrimidinediamine as fine flakes of the solid. ^{1}H NMR (DMSO-d_6): δ 9.59 (s, 1H), 9.25 (s, 1H), 8.09 (d, 1H, J = 3.5 Hz), 8.01 (dd, 2H, J = 5.3 and 1.2 Hz), 7.39 (dd, 2H, J = 3.1 and 8.8 Hz), 7.60-7.54 (m, 3H), 7.03 (d, 2H, J = 8.8 Hz), 6 94 (d, 2H, J = 3.1 Hz), 5.57 (s, 2H), 3.59 (s, 6H), 3.57 (s, 3H). LCMS: ret. time: 13.00 min.; purity: 97%; MS (*m/e*): 547 (MH^+).
7.3.1086	N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935368)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamime and 6-aminoindazoline were reacted to give N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 12.73 (s, 1H), 9.67 (s, 1H), 9.46 (s, 1H), 8.21 (d, 1H, J = 3.5 Hz), 8.17 (app d, 1H, J = 8.8 Hz), 8.04 (br s, 1H), 7.97 (dt, 1H, J = 2.4 and 9.3 Hz), 7.89 (s, 1H), 7.58 (d, 1H, J = 8.8 Hz), 7.47 (d, 1H, J = 9.3 Hz), 7.27 (dd, 1H, J = 1.7 and 8.8 Hz). LCMS: ret. time: 13.08 min.; purity: 96%; MS (*m/e*): 439 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1087	N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine (R935369)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-trifluoromethoxyphenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.62 (s, 1H), 9.29 (s, 1H), 8.17 (d, 1H, J = 3.5 Hz), 8.11 (t, 1H, J = 2 4 Hz), 8.02 (app s, 1H), 7.88-7.82 (m, 3H), 7.53 (d, 1H, J = 9.3 Hz), 7.47 (d, 2H, J = 8.8 Hz), 4.52 (t, 2H, J = 7.0 Hz), 2.48 (t, 2H, J = 7.0 Hz), 2.48 (d, 3H, *J* = 4.7 Hz). LCMS: ret time: 10.51 min.; purity: 99%; MS (*m/e*): 524 (MH^+).
7.3.1088	N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935370)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-trifluoromethoxyphenyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.62 (s, 1H), 9.28 (s, 1H), 8.17 (d, 1H, J = 3.5 Hz), 8.11 (s, 1H), 8.02 (s, 1H), 7.85 (s, 2H), 7.53 (t, 2H, J = 8.8 Hz), 7.46 (t, 1H, J = 8.8 Hz), 4.56 (t, 1H, J = 5.8 Hz), 4.38 (t, 2H, J = 6.4 Hz), 3.35 (dd, 2H, J = 5.8 and 6.4 Hz), 1.93 (q, 2H, J = 6.4 Hz). LCMS: ret. time: 11.33 min.; purity: 99%; MS (*m/e*): 497 (MH^+).
7.3.1089	N4-(3, 4-Dichlorophenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935371)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-dichlorophenyl)-5-fluoro 4-pyrimidineamime and 5-aminoindazoline were reacted to give N4-(3, 4-dichlorophenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.90 (s, 1H), 9.60 (s, 1H), 8.20 (d, 1H, J = 4.2 Hz), 8.06 (t, 1H, J = 2.3 Hz), 7.92 (s, 2H), 7.73 (d, 1H, J = 8.8 Hz), 7.51-7.40 (m, 3H). LCMS: ret. time: 9.83 min.; purity: 98%; MS (*m/e*): 390 (MH^+).
7.3.1090	N4-(3, 4-Dichlorophenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935372)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-dichlorophenyl)-5-fluoro 4-pyrimidineamine and 6-aminoindazoline were reacted to give N4-(3, 4-dichlorophenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 12.82 (s, 1H), 9.63 (s, 1H), 9.48 (s, 1H), 8.22 (d, 1H, J = 4.3 Hz), 8.15 (t, 1H, J = 2.3 Hz), 8.02 (s, 1H), 7.92-7.90 (m, 2H), 7.59 (d, 1H, J = 8.8 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.26 (dd, 1H, J = 1.7 and 8.8 Hz). LCMS: ret. time: 11.73 min.; purity: 99%; MS (*m/e*): 390 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1091	N4-(3, 4-Difluoromethylendioxyphenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935373)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 5-aminoindazoline were reacted to give N4-(3, 4-difluoromethylendioxyphenyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.40 (s, 1H), 10.11 (s, 1H), 8.25 (d, 1H, J = 4.5 Hz), 7.95 (s, 1H), 7.89 (app s, 2H), 7.49 (d, 1H, J = 8.8 Hz), 7.37 (app d, 3H, J = 8.2 Hz). LCMS: ret. time: 8.56 min.; purity: 99%; MS (*m/e*): 401 (MH^+).
7.3.1092	N4-(3, 4-Difluoromethylendioxyphenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine (R935374)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 6-aminoindazoline were reacted to give N4-(3, 4-difluoromethylendioxyphenyl)-5-fluoro-N2-(indazoline-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.53 (s, 1H), 9.52 (s, 1H), 8.21 (d, 1H, J = 4.5 Hz), 8.10 (s, 1H), 8.01 (s, 1H), 7.92 (s, 1H), 7.59 (d, 1H, J = 8.8 Hz), 7.48 (dt, 1H, J = 2.3 and 8.8 Hz), 7.34 (d, 1H, J = 8.2 Hz), 7.21 (dd, 1H, J = 2.3 and 8.8 Hz). LCMS: ret. time: 11.29 min.; purity: 90%; MS (*m/e*): 401 (MH^+).
7.3.1093	N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine (R935375)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(6-chloro-3-pyridyl)-5-fluoro-4-pyrimidineamine and 5-amino-1-methylindazoline were reacted to give N4-(6-chloro-3-pyridyl)-5-fluoro-N2-(1-methylindazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.96 (s, 1H), 9.58 (s, 1H), 8.86 (s, 1H), 8.25 (dt, 1H, J = 3.9 and 8.8 Hz), 8 20 (d, 1H, J = 4.1 Hz), 8.04 (s, 1H), 7.55 (d, 1H, J = 8.8 Hz), 7.44 (d, 2H, J = 8.8 Hz), 4.00 (s, 3H). LCMS: ret. time: 8.95 min.; purity: 100%; MS (*m/e*): 370 (MH^+).
7.3.1094	N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine (R935376)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(6-chloro-3-pyridyl)-5-fluoro-4-pyrimidineamine and 5-aminoindazoline were reacted to give N4-(6-chloro-3-pyridyl)-5-fluoro-N2-(indazoline-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.78 (s, 1H), 9.41 (s, 1H), 8.88 (s, 1H), 8.24 (d, 1H, J = 8.2 Hz), 8.18 (d, 1H, J = 3.5 Hz), 8.06 (s, 1H), 7.92 (s, 1H), 7.42 (app s, 3H). LCMS: ret. time: 7.87 min.; purity: 90%; MS (*m/e*): 356 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1095	N4-(6-Chloro-3-pyridyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935377)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(6-chloro-3-pyridyl)-5-fluoro-4-pyrimidineamine and 5-amino-1-(2-ethoxycarbonylethyl)indazoline were reacted to give N4-(6-chloro-3-pyridyl-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.37 (s, 1H), 10.04 (s, 1H), 8.78 (s, 1H), 8.28 (d, 1H, J = 4.8 Hz), 8.20 (dt, 1H, J = 2.8 and 8.8 Hz), 7.96 (s, 1H), 7.92 (s, 1H), 7.65 (d, 1H, J = 8.8 Hz), 7.45 (d, 1H, J = 8.8 Hz), 7.41 (d, 1H, J = 8.8 Hz), 4.59 (t, 2H, J = 6.0 Hz), 3 97 (qt, 2H, J = 7.0 Hz), 2.90 (t, 2H, J = 6.4 Hz), 1.06 (t, 3H, J = 7.0 Hz). LCMS: ret. time: 10.87 min.; purity: 94%; MS (*m/e*): 456 (MH^+).
7.3.1096	N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine (R935378)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(6-chloro-3-pyridyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-[1-[2(*N*-methylaminocarbonyl)ethyl]indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.67 (s, 1H), 9.31 (s, 1H), 8.88 (s, 1H), 8.27 (dt, 1H, J = 3.0 and 8.8 Hz), 8.17 (d, 1H, J = 3.5 Hz), 8.08 (s, 1H), 7.88 (s, 1H), 7.83 (q, 1H, J = 5.3 Hz), 7.53 (d, 1H, J = 8.8 Hz), 7.45 (d, 1H, J = 8.8 Hz), 4.53 (t, 2H, J = 7.0 Hz), 2.63 (t, 2H, J = 7.0 Hz), 2.49 (d, 3H, J = 5.3 Hz). LCMS: ret. time: 7.62 min.; purity: 89%; MS (*m/e*): 441 (MH^+).
7.3.1097	N4-(6-Chloro-3-pyridyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine (R935379)	In like manner to the preparation of N2-(3, 4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(6-chloro-3-pyridyl)-N2-[1-(2-ethoxycarbonylethyl)indazoline-5-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with DIBAL-H to produce N4-(6-chloro-3-pyridyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6):. LCMS: ret. time: 8.02 min.; purity: 98%; MS (*m/e*): 414 (MH^+).
7.3.1098	N4-(2,6-Dimethoxy-3-pyridyl)-5-fluoro-N2-[1-methylindazoline-5-yl]-2,4-pyrimidinediamine (R935380)	In like manner to the preparation of N4-(3, 4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(2,6-dimethoxy-3-pyridyl)-6-5-fluoro-4-pyrimidineamine and 1-methyl-5-aminoindazoline were reacted to give N4-(2,6-dimethoxy-3-pyridyl)-5-fluoro-N2-[1-methylindazoline-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.08 (s, 1H), 8.68 (s, 1H), 8.01 (d, 1H, J = 4.1 Hz), 7.96 (s, 1H), 7.76 (dd, 1H, J = 4.1 and 8.8 Hz), 7.65 (s, 1H), 7.37 (d, 1H, J = 8.8 Hz), 7.34 (d, 1H, J = 8.2 Hz), 6.46 (d, 1H, J = 8 2 Hz), 3.94 (s, 3H), 3.91 (s, 3H), 3.83 (s, 3H). LCMS: ret. time: 9.57 min.; purity: 92%; MS (*m/e*): 396 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1099	Additional 2,4-Pyrimidinediamine	Compounds R008951, R008952, R008953, R008955, R008956, R008958, R070153 and R070790 (structures provided below) were purchased from Contact Services. Additional compounds whose structures are provided below were synthesized using methods similar to those described in the previous examples.
7.3.1100	Synthesis of Intermediates, 2,4-Pyrimidinediamines and 2,4,6-Pyrimidinetriamines According to Schemes VIII and IX	A variety of intermediates and 2,4-pyrimidinediamine compounds were synthesized according to Schemes VIII and IX. Scheme VIII is exemplified by the reaction of 2,4,6-trichloropyrimidine with 3-hydroxyaniline to form a mixture of three compounds, which were separated and purified by chromotography. Scheme IX is exemplified by the reaction of 2,4,5,6-tetrachloridepyrimidine with 3,4-ethylenedioxyaniline to form a mixture of three compounds, which were separated and purified by chromotography.
7.3.1101	Reaction of 2,4,6-trichloropyrimidine with 3-hydroxyaniline 4,6-Dichloro-N2-(3-hydroxyphenyl)-2-pyrimidineamine (R926407) N2,N4-Bis(3-hydroxyphenyl)-6-chloro-2,4-pyrimidinediamine (R926408) and N2,N4,N6-Tris(3-hydroxyphenyl)-2,4,6-pyrimidinetriamine (R926409)	A mixture of 2,4,6-trichloroaniline (0.183g, 1 mmol) and 3-hydroxyaniline (0.327g, 3 mmol) in 5 mL MeOH was heated at 100 °C in a sealed vial for 24h. The reaction mixture was diluted with H_2O, acidified with 2N HCl and extracted with EtOAc (3 x 50 mL). Upon removal of solvent the residue was purified by chromatography (as well as preparative TLC) to afford three products, mainly the mono-SNAr, 4,6-dichloro-N2-(3-hydroxyphenyl)-2-pyrimidineamine (**R926407**),: ^{1}H NMR ($CDCl_3$): δ 7.16 (t, 1H, J= 8.1 Hz), 6.78 (m, 2H), 6.64 (dd, 1H, J= 1.2 and 8.1 Hz), 6.58 (s, 1H); LCMS: ret. time: 25.08 min.; purity: 99%; MS (m/e): 256 (M^+); bis-SNAr product, N2,N4-bis(3-hydroxyphenyl)-6-chloro-2,4-pyrimidinediamine (**R926408**), ^{1}H NMR (CD_3OD): δ 7.21 (m, 1H), 7.14-7.03 (m, 5H), 6.50 (m, 1H), 6.44 (m, 1H), 6.16 (s, 1H); LCMS: ret. time: 25.14 min.; purity: 99%; MS (m/e): 329 (M^+); and tris-SNAr product, N2,N4,N6-tris(3-hydroxyphenyl)-2,4,6-pyrimidinetriamine (**R926409**), ^{1}H NMR (CD_3OD): δ 7.29 (m, 1H), 7.12-7.05 (m, 5H), 7.02 (m, 2H), 6.88 (dd, 2H, J= 1.2 and 8.1 Hz), 6.46 (dd, 1H, J= 1.5 and 8.1 Hz), 6.41 (dt, 1H); LCMS: ret. time: 20.49 min.; purity: 94%; MS (m/e): 402 (MH^+).
7.3.1102	N2,N4-Bis(4-methoxycarbonylmethyleneoxyphenyl)-6-chloro-2,4-pyrimidinediamine (R926411)	In like manner to the reaction of 2,4,6-trichloropyrimidine with 3-hydroxyaniline, the reaction of 2,4,6-trichloropyrimidine with methyl 4-aminophenoxyacetate gave N2,N4-bis(4-methoxycarbonylmethyleneoxyphenyl)-6-chloro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.65 (bs, 1H), 7.40 (bd, 4H), 6.82 (bd, 4H), 6.00 (s, 1H), 6.62 (bs, 4H), 3.78 (bs, 6H); LCMS: ret. time: 29.87 min.; purity: 98%; MS (m/e): 473 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1103	Reaction of 2,4,6-trichloropyrimidine with 3,4-ethylenedioxyaniline 4,6-Dichloro-N2-(3,4-ethylenedioxyphenyl)-2-pyrimidineamine (R926515) N2,N4-Bis(3,4-ethylenedioxyphenyl)-6-chloro-2,4-pyrimidinediamine (R926245) N2,N4,N6 -Tris(3,4-ethylenedioxyphenyl)-2,4,6-pyrimidinetriamine (R926516)	A mixture of 2,4,6-trichloroaniline (1 mmol) and 3,4-ethylenedioxyaniline (3 mmol) in 5 mL MeOH was heated at 100 °C in a sealed vial for 24h. The reaction mixture was diluted with H_2O, acidified with 2N HCl and extracted with EtOAc (3 x 50 mL). Upon removal of solvent the residue was purified by chromatography (as well as preparative TLC) to afford three products, mainly the Mono-SNAr product, 4,6-dichloro-N2-(3,4-ethylenedioxyphenyl)-2-pyrimidineamine (**R926515**). ^{1}H NMR (CD_3OD): δ 7.05 (s, 1H), 6.83 (m, 2H), 6.45 (bs, 1H), 4.20 (bs, 4H); LCMS: ret. time: 29.75 min.; purity: 96%; MS (m/e): 298 (M^+); Bis-SNAr product, N2,N4-bis(3,4-ethylenedioxyphenyl)-6-chloro-2,4-pyrimidinediamine (**R926245**): ^{1}H NMR ($CDCl_3$): δ 7.23 (d, 1H, J= 3 Hz), 6.90-6.70 (m, 6H), 6.02 (s, 1H), 4.26 (bs, 4H), 4.23 (m, 4H); LCMS: ret. time: 31.34 min.; purity: 95%; MS (m/e): 413 (MH^+) and Tris-SNAr product, N2,N4,N6 -tris(3,4-ethylenedioxyphenyl)-2,4,6-pyrimidinetriamine (**R926516**) ^{1}H NMR (CD_3OD): δ 7.16 (d, 1H, J= 3Hz), 7.05 (bd, 1H), 6.99-6.90 (m, 3H), 6.80-6.70 (m, 4H), 6.03 (s, 1H), 4.22 (s, 4H), 4.20 (s, 8H); LCMS: ret. time: 27.72 min.; purity: 61%; MS (m/e): 528 (M^+).
7.3.1104	Reaction of 2,4,6-trichloropyrimidine with ethyl-4-aminophenoxyacetate 4,6-Dichloro-N2-(4-ethoxycarbonylmethyl)-4,6-dichloro-2-pyrimidineamine (R926549) 2,6-Dichloro-N4-(ethoxycarbonylmethyl)-4-pyrimidineamine (R926550)	A mixture of 2,4,6-trichloroaniline (1 mmol) and ethyl 2-aminoacetate (3 mmol) in 5 mL MeOH was heated at 100 °C in a sealed vial for 24h. The reaction mixture was diluted with H_2O, acidified with 2N HCl and extracted with EtOAc (3 x 50 mL). Upon removal of solvent the residue was purified by chromatography (as well as preparative TLC) to afford three products, mainly the mono-SNAr product, 4,6-dichloro-N2-(4-ethoxycarbonylmethyl)-4,6-dichloro-2-pyrimidineamine (**R926549**). ^{1}H NMR ($CDCl_3$): δ 6.67 (s, 1H), 5.85 (bs, 1H), 4.23 (q, 2H, J= 7.2 Hz), 4.19 (s, 2H), 1.29 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 26.18 min.; purity: 100%; MS (m/e): 250 (MH^+); and Mono-SNAr product, 2,6-dichloro-N4-(ethoxycarbonylmethyl)-4-pyrimidineamine (**R926550**): ^{1}H NMR ($CDCl_3$): d 6.37 (bs, 1H), 4.28 (q, 2H, J= 6.9 Hz), 4.19 (bs, 2H), 1.31 (t, 3H, J= 7.2 Hz)
7.3.1105	6-Chloro-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(methoxycarbonylmethyl)-2,4-pyrimidinediamine (R926555)	In like manner to the preparation of 4-[N-(L)-phenylalanine ethyl ester]-N2-(3-hydroxyphenyl)-5-ethoxycarbonyl-2-pyrimidineamine, the reaction of ethyl 4-aminophenoxyacetate with methyl 2-aminoacetate gave 6-chloro-N2-(4-ethoxycarbonylmethyleneoxyphenyl)-N4-(methoxycarbonylmethyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.40 (d, 2H, J= 8.7 Hz), 6.86 (d, 2H, J= 9.3 Hz), 5.97 (s, 1H), 4.64 (s, 2H), 4.26 (q, 2H, J= 7.2 Hz), 4.14 (q, 2H, J= 6.9 Hz), 4.05 9s, 2H), 1.25 (m, 6H); LCMS: ret. time: 26.21 min.; purity: 93%; MS (m/e): 409 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1106	Reaction of 3,4-ethylenedioxyaniline with 2,4,5,6-tetrachloropyrimidine. N4-(3,4-Ethylenedioxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (R926466) N2,N4-Bis(3,4-ethylenedioxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (R926467) and N4,N6-Bis(3,4-ethylenedioxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (R926468)	A mixture of 3,4-ethylenedioxyaniline (0.775 g, 5 mmol) and 2,4,5,6-tetrachloropyrimidine (0.434 g, 2 mmol) in the presence of DIPEA (1.043 mL, 6 mmol) in EtOAc (10 mL) was heated at 80 °C for 3 days. The reaction was diluted with water (50 mL), acidified (2N HCl) and extracted with EtOAc (3 x 50 mL). The residue obtained after removal of solvent was chromatographed using 5-30% EtOAc/hexanes to obtain three products viz. N4-(3,4-Ethylenedioxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (**R926466**): ^{1}H NMR ($CDCl_3$): δ 7.18 (d, 1H, J= 2.7 Hz), 6.92 (dd, 1H, J= 2.1 and 8.7 Hz), 6.87 (d, 1H, J= 9 Hz); LCMS: ret. time: 33 53 min.; purity: 100%; MS(m/e): 292 (MH^+); N2,N4-Bis(3,4-ethylenedioxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (**R926467**): ^{1}H NMR ($CDCl_3$): δ 7.11 (d, 1H, J= 2.4 Hz), 7.06 (d, 1H, J= 2.1 Hz), 7.04 (s, 1H0, 6.94 (m, 2H), 6.84 (d, 1H, J= 8.1 Hz), 6.76 (bd, 2H, J= 8.7 Hz), 4 27 (bs, 4H), 4.24 (bs, 1H); LCMS: ret. time: 26.54 min.; purity: 87%; MS(m/e): 364 (MH^+); and N4,N6-Bis(3,4-ethylenedioxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (**R926468**): ^{1}H NMR ($CDCl_3$): δ 7.07 (t, 1H, J= 2.4 Hz), 6.99 (s, 2H), 6.83 (dd, 2H, J= 2.4 and 8.7 Hz), 6.75 (dd, 2H, J= 1.8 and 9 Hz), 4.19 (bs, 4H); LCMS: ret. time: 34.70 min.; purity: 99%; MS(m/e): 365 (MH^+).
7.3.1107	Reaction of 2,4,5,6-tetrachloropyrimidine with ethyl-4-aminophenoxyacetate N4-(4-Ethoxycarbonylmethyleneoxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (R926568) N2,N4-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (R926569) N2,N5-Bis(4-ethoxycarbonylmethyleneoxyphenyl)-2,5-pyrimidinediamine (R926570)	In like manner to the reaction of 2,4,6-trichloropyrimidine with 3,4-ethylenedioxyaniline, the reaction of 2,4,5,6-tetrachloropyrimidine with ethyl 4-aminophenoxyacetate gave a mixture of mono-SNAr product, N4-(4-ethoxycarbonyl methyleneoxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (**R926568**): ^{1}H NMR ($CDCl_3$): δ 7.46 (dd, 2H, J= 2.4 and 6.9 Hz), 7.3 (s, 1H), 6.95 (dd, 2H, J= 2.4 and 6.9 Hz), 4.63 (s, 2H), 4.28 (q, 2H, J= 7.2 Hz), 1.30 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 30.62 min.; purity: 99%; MS (m/e): 378 (MH^+); Bis-SNAr product, N2,N4-bis((4-ethoxycarbonylmethylene oxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (**R926569**): ^{1}H NMR ($CDCl_3$): δ 7.42 (d, 2H, J= 9 Hz), 7.35 (d, 2H, J= 8.7 Hz), 6.90 (d, 2H, J= 9Hz), 6.83 (d, 2H, J= 8.7 Hz), 4.67 (s, 2H), 4.60 (s, 2H), 4.28 (2q, 4H, J= 4.8 Hz), 1.31 (2t, 6H, J= 6.3 Hz); LCMS: ret. time: 33.09 min.; purity: 85%; MS (m/e): 537 (MH^+) and Bis-SNAr product, N2,N5-bis((4-ethoxycarbonylmethyleneoxyphenyl)-2,5-pyrimidinediamine (**R926570**): ^{1}H NMR ($CDCl_3$): δ 7.45 (d, 4H, J= 8.7 Hz), 6.92 (d, 4H, J= 9Hz), 6.85 (s, 1H), 4.61 (s, 4H), 4.26 (q, 4H, J= 6.9 Hz), 1.30 (t, 6H, J= 7.2 Hz); LCMS: ret. time: 31.66 min.; purity: 97%; MS (m/e): 535 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1108	Reaction of 2,4,5,6-tetrachloropyrimidine with tert-Butyl-4-aminophenoxyacetate, N4-(4-tert-Butoxyoxycarbonylmethyleneoxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (R926575), N2,N4-Bis(4-tert-butoxyoxycarbonylmethyleneoxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (R926576) and N4,N6-Bis(4-tert-butoxyoxycarbonylmethyleneoxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (R926577)	In like manner to the reaction of 2,4,6-trichloropyrimidine with 3,4-ethylenedioxyaniline, the reaction of 2,4,5,6-tetrachloropyrimidine with tert-butyl-4-aminophenoxyacetate gave a mixture of mono-SNAr product, N4-(4-tert-butoxyoxycarbonyl methyleneoxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (**R926575**): ^{1}H NMR ($CDCl_3$): δ 7.45 (dd, 2H, J= 2.4 and 7.2 Hz), 6.93 (dd, 2H, J= 2.4 and 7.2 Hz), 4.52 (s, 2H); LCMS: ret. time: 32.56 min.; purity: 100%; MS (m/e): 402 (MH^+); Bis-SNAr product, N2,N4-bis(4-tert-butoxyoxycarbonylmethyleneoxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (**R926576**): ^{1}H NMR ($CDCl_3$): δ 7.42 (d, 2H, J= 9 Hz), 7.35 (d, 2H, 9.3 Hz), 7.08 (s, 1H), 6.90 (d, 2H, J= 9 3 Hz), 6 82 (d, 2H, J= 8.7 Hz), 4.53 (s, 2H), 4.49 (s, 2H), 1.50 (s, 9H), 1.49 (s, 9H); LCMS: ret. time: 36.04 min.; purity: 92%; MS (m/e): 591 (MH^+) and Bis-SNAr product, N4,N6-bis(4-tert-butoxyoxycarbonylmethyleneoxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (**R926577**): ^{1}H NMR ($CDCl_3$): δ 7.43 (d, 4H, J= 8.7 Hz), 6.90 (dd, 4H, J= 9.3 Hz), 4.50 (s, 2H), 1.49 (s, 18H); LCMS: ret. time: 35.31 min.; purity: 100%; MS (m/e): 591 (MH^+).
7.3.1109	Reaction of 2,4,5,6-tetrachloropyrimidine with 3-hydroxyaniline, N4-(3-Hydroxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (R926590), N2,N4-Bis(3-hydroxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (R926591) and N4,N6-Bis(3-hydroxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (R926592)	In like manner to the reaction of 2,4,6-trichloropyrimidine with 3,4-ethylenedioxyaniline, the reaction of 2,4,5,6-tetrachloropyrimidine with tert-butyl-4-aminophenoxyacetate gave a mixture of mono-SNAr product, N4-(3-hydroxyphenyl)-2,5,6-trichloro-4-pyrimidineamine (**R926590**): ^{1}H NMR ($CDCl_3$): δ 7.38 (bs, 1H), 7.32 (t, 1H, J= 2.4 Hz), 7.22 (s, 1H), 7.01 (dd, 1H, J= 1.2 and 8.1 Hz), 6.68 (dd, 1H, J= 1.8 and 8.1 Hz); LCMS: ret. time: 26.09 min.; purity: 99%; MS (m/e): 292 (MH^+); Bis-SNAr product, N2,N4-bis(3-hydroxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (**R926591**): ^{1}H NMR ($CDCl_3$): δ 7.45 (s, 1H), 7.30 (t, 1H, J= 2.4 Hz), 7.18 (t, 1H, J= 2.4 Hz), 7.07 (t, 1H, j= 6.6 Hz), 6.98 (t, 1H, J= 8.1 Hz), 6.75 (m, 2H), 6.54 (dd, 1H, J= 2.4 and 8.1 Hz); LCMS: ret. time: 26.54 min.; purity: 87%; MS (m/e): 364 (MH^+); and Bis-SNAr product, N4,N6-bis(3-hydroxyphenyl)-2,5-dichloro-4,6-pyrimidinediamine (**R926592**): ^{1}H NMR ($CDCl_3$): δ 7.34 (t, 2H, j= 2.4 Hz), 7.21 (t, 2H, J= 7.5 Hz), 6.98 (m, 4H), 6.60 (m, 2H); LCMS: ret. time: 25.38 min.; purity: 73%; MS (m/e): 364 (MH^+).
7.3.1110	N2,N4-Bis(3-hydroxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine (R926595)	The reaction of N2 N4-bis(3-hydroxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine (18 mg, 0.05 mmol) with sodium thiomethoxide (10 mg, 0.15 mmol) in absolute EtOH (1 mL) was heated at 80 °C for 3 days, diluted with H_2O, extracted with EtOAc (3 x 10 mL), and solvent was evaporated to obtain the N2 N4-bis(3-hydroxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine (**R926595**). ^{1}H NMR (CD_3OD): δ 7.40-7.2 (m, 2H), 7.20-6.80 (m, 3H), 6.67 (m, 1H), 6.45-6.30 (m, 2H), 2.4 (s, 3H); LCMS: ret. time: 27.78 min.; purity: 80%; MS (m/e): 376 (MH^+).

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7.3.1111	N2,N4-Bis(3,4-ethyelenedioxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine (R926475)	In like manner to the preparation of N2 N4-bis(3-hydroxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine (**R926595**), the reaction of N2,N4-bis(3,4-ethyelenedioxyphenyl)-5,6-dichloro-2,4-pyrimidinediamine gave N2,N4-bis(3,4-ethyelenedioxyphenyl)-5-chloro-6-thiomethyl-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.10 (bd, 2H), 7.00-6.00 (m, 4H), 4.23 (s, 4H), 4.10 (s, 4H), 2.60 (s, 3H); LCMS: ret. time: 36.14 min; purity: 100%; MS (m/e): 459 (MH^+).
7.3.1112	6-Chloro N4-(3-hydroxyphenyl)-4-pyrimidineamine (R926530)	The reaction of 4,6-dichloropyrimidine with excess 3-hydroxyaniline in MeOH at 80 0 °C for 24 h followed by dilution with water and acidification gave the crude product which was purified by silica gel column chromatography to obtain 6-chloro N4-(3-hydroxyphenyl)-4-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 8.36 (d, 1H, J= 1.2 Hz), 7.15 (t, 1H, J= 8.4 Hz), 6.93 (dd, 1.2 and 8.1 Hz), 6.74 (d, 1H, J= 1.2 Hz), 6.55 (dd, 1.8 and 8.1 Hz); LCMS (m/e): ret. time: 19.75 min.; purity: 99%; MS (m/e): 222 (MH^+).
7.3.1113	N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine (R925784)	A mixture of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine (20 mg, 0.044 mmol) and phenylboronic acid (6.9 mg, 0.057 mmol) in DME (1 mL) was prepared in a sealed tube and purged with N_2. Tetrakis(triphenylphosphine) palladium(0) (0.002 mmol) was added, and the reaction tube sealed and heated at 80 °C overnight. After cooling, the reaction mixture was diluted with EtOAc, washed with 1N NaOH and brine, dried ($MgSO_4$), and concentrated. The residue was purified by preparative TLC (40% EtOAc/hexanes) to afford N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.77 (s, 1H), 7.52-7.36 (m, 5H), 7.10 (d, 1H, J= 2.4 Hz), 7.05 (d, 1H, J= 2.4 Hz), 6.93 (dd, 1H, J= 2.4 and 8.7 Hz), 6.87 (dd, 1H, J= 2.4 and 8.7 Hz), 6.73 (d, 1H, J= 8.7 Hz), 6.69 (d, 1H, J= 8.7 Hz), 4.23-4.20 (m, 8H); LCMS: ret. time: 25.38 min.; purity: 100 %; MS (m/e): 455 (MH^+).
7.3.1114	N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(2-furanyl)-2,4-pyrimidinediamine (R925785)	In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and furan-2-boronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(2-furanyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.13 (s, 1H), 7.61 (d, 1H, J=1.8 Hz), 7.12 (d, 1H, J= 2.4 Hz), 7.08 (d, 1H, J= 2.4 Hz), 6.93 (td, 2H, J= 2.4 and 8.7 Hz), 6.78 (d, 1H, J= 8.7 Hz), 6.68 (d, 1H, J= 8.7 Hz), 6.58 (d, 1H, J= 2.4 Hz), 6.54 (dd, 1H, J= 1.8 and 3.6), 4.24 (s, 4H), 4.20 (bs, 4H); LCMS: ret. time: 15.03 min.; purity: 88 %; MS (m/e): 445 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1115	N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(4-chlorophenyl)-2,4-pyrimidinediamine (R925786)	In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and 4-chlorophenylboronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(4-chlorophenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.99 (bs, 1H), 8.05 (bs, 1H), 7.85 (s, 1H), 7.50-7.42 (m, 4H), 7.23 (bs, 1H), 7.10 (dd, 1H, J= 2.4 and 8.7 Hz), 7.06 (t, 1H, J= 2.4 Hz), 7.00-6.94 (m, 1H), 6.73 (d, 1H, J= 8.7 Hz), 6.63 (d, 1H, J= 8.7 Hz); LCMS: ret. time: 16.12 min.; purity: 86 %; MS (m/e): 490 (MH^+).
7.3.1116	N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(3-chlorophenyl)-2,4-pyrimidinediamine (R925787)	In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and 3-chlorophenylboronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(3-chlorophenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.77 (s, 1H), 7.45-7.41 (m, 2H), 7.38-7.33 (m, 2H), 7.09 (d, 1H, J= 2.4 Hz), 7.01 (d, 1H, J= 2.4 Hz), 6.92 (dd, 1H, J= 2.4 and 9.0 Hz), 6.86 (dd, 1H, J= 2.4 and 8.7 Hz), 6.74 (d, 1H, J= 8.7 Hz), 6.67 (d, 1H, J= 8.7 Hz), 4.21 (s, 4H), 4.19 (s, 4H); LCMS: ret. time: 27.18 min.; purity: 95 %; MS (m/e): 490 (MH^+).
7.3.1117	N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(4-methoxycarbonylphenyl)-2,4-pyrimidinediamine (R925813)	In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and (4-methoxycarbonylphenyl)boronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(4-methoxycarbonylphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 26.35 min.; purity: 90 %; MS (m/e): 514 (MH^+).
7.3.1118	N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-(4-hydroxyphenyl)-2,4-pyrimidinediamine (R925816)	In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-5-bromo-2,4-pyrimidinediamine and 4-hydroxyphenylboronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-(4-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.53 (s, 1H), 8.92 (s, 1H), 7.78 (s, 1H), 7.74 (bs, 1H), 7.24 (bs, 1H), 7.22 (d, 2H, J= 8.7 Hz), 7.12-7.09 (m, 2H), 6.97 (dt, 1H, J= 2.4 and 8.7 Hz), 6.83 (d, 2H, J= 8.4 Hz), 6.72 (d, 1H, J= 8.1 Hz), 6.62 (d, 1H, J= 9.0 Hz), 4.19 (s, 4H), 4.17 (s, 4H); LCMS: ret. time: 23.51 min.; purity: 95 %; MS (m/e): 471 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1119	N2,N4-Bis(3-hydroxyphenyl)-5-phenyl-2,4-pyrimidinediamine (R925783)	In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3-hydroxyphenyl)-5-bromo-2,4-pyrimidinediamine and phenylboronic acid were reacted to yield N2,N4-bis(3-hydroxyphenyl)-5-phenyl-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.85 (bs, 1H), 7.54-7.38 (m, 5H), 7.13-7.11 (m, 2H). 7.10-7.04 (m, 3H), 6.97 (dt, 1H, J= 1.8 and 8.1 Hz), 6.54 (ddd, 1H, J= 1.9, 2.4, and 7.2 Hz), 6.44 (dt, 1H, J= 1.8 and 6.0 Hz); LCMS: ret. time: 20.66 min.; purity: 96 %; MS (m/e): 371 (MH^+).
7.3.1120	N2,N4-Bis(3-hydroxyphenyl)-5-(3,4-methylenedioxyphenyl)-2,4-pyrimidinediamine (R925788)	In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3-hydroxyphenyl)-5-bromo-2,4-pyrimidinediamine and 3,4-methylenedioxyphenylboronic acid were reacted to yield N2,N4-bis(3-hydroxyphenyl)-5-(3,4-methylenedioxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.82 (s, 1H), 7.13-7.06 (m, 3H), 7.04-7.01 (m, 2H), 6.97 (dt, 1H, J= 1.2 and 8.7 Hz), 6.94-6.88 (m, 3H), 6.52 (ddd, 1H, J= 1.2, 2.4, and 6.9 Hz), 6.42 (dt, 1H, J= 2.1 and 7.5 Hz), 6.01 (s, 2H); LCMS: ret. time: 21.11 min.; purity: 99 %; MS (m/e): 415 (MH^+).
7.3.1121	N2,N4-Bis(3,4-ethylenedioxyphenyl)-6-phenyl-2,4-pyrimidinediamine (R925811)	In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3,4-ethylenedioxyphenyl)-6-chloro-2,4-pyrimidinediamine and phenylboronic acid were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-6-phenyl-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.97-7.92 (m, 2H), 7.46-7.43 (m, 3H), 7.35 (d, 1H, J= 2.7 Hz), 7.19 (d, 1H, J= 2.4 Hz), 7.07-7.00 (m, 2H), 6.75 (t, 2H, J= 8.7 Hz), 6.50 (s, 1H), 4.24-4.19 (m, 8H); LCMS: ret. time: 26.68 min.; purity: 97 %; MS (m/e): 455 (MH^+).
7.3.1122	N2,N4-Bis(3-hydroxyphenyl)-6-phenyl-2,4-pyrimidinediamine (R925812)	In a manner similar to the preparation of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-phenyl-2,4-pyrimidinediamine, N2,N4-bis(3-hydroxyphenyl)-6-chloro-2,4-pyrimidinediamine and phenylboronic acid were reacted to yield N2,N4-bis(3-hydroxyphenyl)-6-phenyl-2,4-pyrimidinediamine. LCMS: ret. time: 22.13 min.; purity: 90 %; MS (m/e): 371 (MH^+).
7.3.1123	N2-(3-Aminocarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926747)	The hydrolysis of N2-(3-cyanomethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine gave N2-(3-aminocarbonylmethyleneoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: ret. time: 16.76 min.; purity: 93 %; MS (m/e): 412 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1124	N2,N4-Bis(3-sodiumphenoxy)-5-fluoro-2,4-pyrimidinediamine (R926461)	The reaction of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine with 2 equivalents of sodium methoxide in methanol gave the requisite compound, N2,N4-bis(3-sodiumphenoxy)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (D_2O): δ 7.65 (bd, 1H), 7.00-6.90 (m, 2H), 6.71 (m, 2H), 6.55 (dd, 1H, J= 1.2 and 6.3 Hz), 6.31 (bd, 1H, J= 8.1 Hz), 6.23 (bd, 1H, J= 8.7 Hz); ^{19}F NMR (D_2O): - 47016; LCMS: ret. time: 15.68 min.; purity: 99%; MS (m/e): 313 (MH^+).
7.3.1125	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1,4,5,6-tetrahydro-2-pyrimidyl)methyleneoxyphenyl]-2,4-pyrimidinediamine (R945169)	The reaction of N2-(4-cyanomethyleneoxyphenyl)-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and HCl in ethanol, followed by 1;3-diaminopropane in methanol at 100 °C gave 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(1,4,5,6-tetrahydro-2-pyrimidyl)methyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 2.05 (p, J= 5.7 Hz, 2H), 3.49 (t, J= 5.7 Hz, 4H), 4.84 (s, 2H), 6.56 (ddd, J= 2.1, 3.6 and 5.4 Hz, 1H), 6.93 (d, J= 9.0 Hz, 2H), 7.11-7.13 (m, 2H), 7.21 (m, 1H), 7.55 (d, J= 9.0 Hz, 2H), 7.87 (d, J= 3.9 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD): δ - 168.66; LCMS: ret. time: 12.77 min.; purity: 97.61%; MS (m/e): 409.08 (MH^+).
7.3.1126	5-Fluoro-N4-(3-hydroxyphenyl)-N2-[4-[(4,4-dimethyl-3-oxazolin-2-yl)methyleneoxy]phenyl]-2,4-pyrimidinediamine (R926702)	N2-[4-(cyanomethyleneoxy)phenyl]-5-fluoro-N4-(3-hydroxyphenyl)-2,4-pyrimidinediamine and 2-amino-2-methylpropanol were reacted to yield 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-[(4,4-dimethyl-3-oxazolin-2-yl)methyleneoxy]phenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 1H, J= 3.6 Hz), 7.37 (t, 1H, J= 2.4 Hz), 7.34 (d, 2H, J= 9.0 Hz), 7.14 (t, 1H, J= 8.1 Hz), 6.94 (bs, 1H), 6.90 (d, 2H, J= 9.0 Hz), 6.78 (dd, 1H, J= 2.4 and 8.4 Hz), 6.74 (d, 1H, J= 3.0 Hz), 6.62 (ddd, 1H, J= 1.2, 2.4, and 8.4 Hz), 4.67 (s, 2H), 4.02 (s, 2H), 1.25 (s, 6H); ^{19}F NMR ($CDCl_3$): -47399; LCMS: ret. time: 13.82 min.; purity: 98%; MS (m/e): 425 (M+2H).
7.3.1127	N4-(3-Carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950290)	A mixture of equimolar amounts of 2-chloro-N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 97.8%; MS (m/e): 443.20 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1128	N4-(3-Carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-carboxymethyleneoxyphenyl]-2,4-pyrimidinediamine (R950291)	The reaction of N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (0.1 g) and LiOH (10 equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatment with aqueous HCl gave the solid. The resulting solid was filtered, washed with water and dried to give N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-carboxymethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 91.5%; MS (m/e): 415.16 (MH^+).
7.3.1129	N4-(3-Methoxycarbonyl-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine (R950293)	A solution of N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a 4 M solution of HCl in dioxane. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(3-methoxycarbonyl-4-hydroxyphenyl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 10.30 (s, 1H), 10.13 (s, 1H), 8.22 (d, 1H, J= 5.3 Hz), 7.96 (d, 1H, J= 2.4 Hz), 7.71 (dd, J = 2.4, 9.0 Hz, 1H), 6.95-7.11 (m, 4H), 6.51 (m, 1H), 4.56 (s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.72 (s, 3H), 1.14 (j, J = 7.2 Hz, 3H); LCMS: purity: 96.8%; MS (m/e): 457.25 (MH^+).
7.3.1130	N4-(4-Methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950294)	A mixture of equimolar amounts of 2-chloro-N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 92.1%; MS (m/e): 469.26 (MH^+).
7.3.1131	N4-(4-Methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950295)	A mixture of equimolar amounts of 2-chloro-N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-4-aminopyridine and 3-ethoxycarbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h followed by aqueous work up gave N4-(4-methoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 87.6%; MS (m/e): 455.26 (MH^+).
7.3.1132	N4-(4-Ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino) carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950296)	A solution of N4-(4-ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-ethoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in EtOH was treated with the HCl salt of methylamine. The mixture was stirred for 4 hours at 100°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-ethoxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 87.4%; MS (m/e): 468.29 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1133	N4-(4-Carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine (R950344)	A mixture of equimolar amounts of 2-chloro-N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 97.8%; MS (m/e): 456.32 (MH^+).
7.3.1134	N4-(2,3-Dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine (R950345)	A solution of N4-(4-Methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in TfOH was heated for 2 hours at 100°C. Aqueous work up followed by flash chromatography on silica gel gave N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.2%; MS (m/e): 435.95 (MH^+).
7.3.1135	N4-(4-Methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950346)	A solution of N4-(4-carboxyethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a 4 M solution of HCl in dioxane. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 85.2%; MS (m/e): 468.01 (MH^+).
7.3.1136	N4-(4-Hydroxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950347)	The reaction of N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and LiOH (10 equivalents) in MeOH:water (1:1, v/v) for 1h at room temperature followed by treatment with aqueous HCl gave a pale yellow solid. The resulting solid was filtered, washed with water and dried to give N4-(4-hydroxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 94.7%; MS (m/e): 382.03 (MH^+).
7.3.1137	N4-(2,3-Dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950348)	A mixture N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 89.5%; MS (m/e): 451.00 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1138	N4-(4-Hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine (R950349)	A solution of N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeOH was treated with a sodiumcyanoborohydride. The mixture was stirred for 1 hour at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-Hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 9.19 (s, 1H), 9.09 (s, 1H), 8.03 (d, 1H, J= 2.4 Hz), 7.28-7.93 (m, 5H), 7.07 (t, 1H, J = 7.2 Hz), 6.71 (d, 1H, J = 7.2 Hz), 6.44 (dd, 1H, J = 2.6, 7.2 Hz), 5.31 (d, 1H, J = 5.1 Hz), 4.14-4.59 (m, 3H), 4.30 (s, 2H), 2.63 (d, 3H, J = 4.8 Hz), 1.82-2.03 (m, 2H); LCMS: purity: 93.3%; MS (m/e): 440.15 (MH^+).
7.3.1139	N4-(2,3-Dihydro-4-O-methyloxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine (R950356)	A mixture N4-(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and methoxyamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 85.5%; MS (m/e): 465.10 (MH^+).
7.3.1140	N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine (R950368)	A mixture N4-(4-azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and Pd/C (10%) in MeOH was hydrogenated at 22°C for 6 hours (40psi). The mixture was filtered and concentrated to dryness to give N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 9.60 (s, 1H), 9.46 (s, 1H), 8.73 (bs, 3H), 8.00-8.10 (m, 3H), 7.47 (s, 1H), 7 42 (m, 1H), 7.29 (d, 1H, J = 7.2 Hz), 7.11 (t, 1H, J = 7.2 Hz), 6.82 (d, 1H, J 7.0 Hz), 6.46 (m, 1H), 4.23-4.46 (m, 3H), 4.31 (s, 3H), 2.63 (d, 3H, J = 4.8 Hz), 2.09-2.29 (m, 2H); LCMS: purity: 97.6%; MS (m/e): 438.98 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1141	N4-(3-Methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine (R950371)	A mixture of equimolar amounts of 2-chloro-N4-(3-methylcarbonylphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 10.16 (s, 1H), 9.82 (s, 1H), 8.24 (d, 1H, J= 2.4 Hz), 8.15 (s, 1H), 7.91-8.07 (m, 2H), 7.70 (d, 1H, J= 7.0 Hz), 7.49 (t, 1H, J = 7.2 Hz), 7.08-7.21 (m, 3H), 6.56 (d, 1H, J = 7.2 Hz), 4.30 (s, 3H), 2.62 (d, 3H, J = 4.8 Hz), 2.48 (s, 3H); LCMS: purity: 93.8%; MS (m/e): 410.50 (MH^+).
7.3.1142	N4-(3-Phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine (R950372)	A mixture of equimolar amounts of 2-chloro-N4-(3-phenylcarbonylphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 86.0%; MS (m/e): 472.50 (MH^+).
7.3.1143	N4-(3-Methylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950373)	A mixture N4-(3-methylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(3-methylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 11.21 (s, 1H), 10.11 (s, 1H), 9.85 (s, 1H), 6.54-8.23 (m, 9H), 4.32 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H), 2.47 (s, 3H); LCMS: purity: 92.4%; MS (m/e): 425.28 (MH^+).
7.3.1144	N4-(3-Phenylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950374)	A mixture N4-(3-phenylcarbonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N4-(3-phenylcarbonyloximephenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 11.63 (s, 1H), 10.30 (s, 1H), 9.85 (s, 1H), 6.44-8.43 (m, 14H), 4.42 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H); LCMS: purity: 92.4%; MS (m/e): 487.31 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1145	N2,N4-Bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950376)	A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-acetophenone in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N2,N4-bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.1%; MS (m/e): 365.19 (MH^+).
7.3.1146	N2,N4-Bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine (R950377)	A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-benzophenone in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N2,N4-bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.7%; MS (m/e). 489.29 (MH^+).
7.3.1147	N2,N4-Bis(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950378)	A solution of N2,N4-bis(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine in TfOH was heated for 2 hours at 100°C. Aqueous work up followed by flash chromatography on silica gel gave N2,N4-bis(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 9.36 (s, 1H), 9.14 (s, 1H), 8.06 (d, 1H, J= 2.4 Hz), 7.72-7.99 (m, 3H), 6.97 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 4.42-4.52 (m, 4H), 2.70-2.78 (m, 4H); LCMS: purity: 94.3%; MS (m/e): 484.50 (MH^+).
7.3.1148	N2,N4-Bis(3-methylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine (R950379)	A mixture of N2,N4-bis(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(3-methylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 11.21 (s, 1H), 10.11 (s, 1H), 9.85 (s, 1H), 6.54-8.23 (m, 9H), 4.32 (s, 2H), 2.63 (d, J = 7.0 Hz, 3H), 2.47 (s, 3H); LCMS: purity: 92.1%; MS (m/e): 393.06 ($M-H^-$).
7.3.1149	N2,N4-Bis(3-phenylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine (R950380)	A mixture of N2,N4-bis(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(3-phenylcarbonyloximephenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.3%; MS (m/e): 486.05 ($M-H^-$).
7.3.1150	N2,N4-Bis(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950381)	A mixture of N2,N4-bis(2,3-dihydro-4-benzypyranon-6-yl)-5-fluoro-2,4-pyrimidinediamine and hydroxylamine (20 equivalents) in pyridine at 22°C for 16 hours followed by aqueous work up gave N2,N4-bis(2,3-dihydro-4-oxime-benzypyran-6-yl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98.1%; MS (m/e): 449.03 ($M-H^-$).

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Section Number	Name of compound and reference number	Experimental
7.3.1151	N4-(4-Acetyloxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine (R950382)	A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in pyridine was treated with acetic anhydride at 22°C for 16 hours. Aqueous work up gave N4-(4-acetyloxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 10.43 (bs, 1H), 9.62 (bs, 1H), 8.03 (d, 1H, J = 2.4 Hz), 7.10-7.83 (m, 7H), 6.83 (d, 1H, J = 7.4 Hz), 6.52 (d, 1H, J = 7.2 Hz), 5.01 (m, 1H), 4.75 (s, 2H), 4.03-4.32 (m, 2H), 2.62 (s, 3H), 2.23 (s, 3H), 1.93-2.13 (m, 2H); LCMS: purity: 92.1%; MS (m/e): 393.06 ($M-H^-$).
7.3.1152	N4-(4-Azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine (R950383)	A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry THF was treated with 2 equivalents of DPPA and DBU. The mixture was stirred for 3 hours at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-azido-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 10.09 (bs, 1H), 9.83 (bs, 1H), 8.18 (d, 1H, J = 2.4 Hz), 7.97 (m, 1H), 7.11-7.61 (m, 6H), 6.82 (d, 1H, J = 7.8 Hz), 6.62 (d, 1H, J = 7.2 Hz), 4.78 (s, 2H), 4.03-4.33 (m, 3H), 2.62 (s, 3H), 1.93-2.13 (m, 2H); LCMS: purity: 97.9%; MS (m/e): 463.07 (MH^+).
7.3.1153	N4-(4-Benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950385)	A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in THF was treated with bortrifluoride etherate at 80°C for 8 hours. Aqueous work up gave N4-(4-benzypyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 9.18 (s, 1H), 9.14 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.93 (bs, 1H), 5.86-7.48 (m, 9H) 4.73-4.74 (m, 2H), 4.33 (s, 2H), 2.62 (s, 3H); LCMS: purity: 96.5%; MS (m/e): 420.07 ($M-H^-$).
7.3.1154	N4-(3-Hydroxymethylen-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950386)	A mixture of equimolar amounts of 2-chloro-N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethylene oxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 89.2%; MS (m/e): 410.5 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1155	N4-(3-Amino-4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine (R950388)	A mixture of 2-chloro-N4-(3-amino-4-ethoxyphenyl)-5-fluoro-4-aminopyridine and 3 equivalents of 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-amino-4-ethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.1%; MS (m/e): 427.18 (MH^+).
7.3.1156	N4-(4-Ethoxy-3-hydroxysulfonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine (R950389)	A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in HOAc was treated with sodium nitrate followed by addition of concentrated aqueous HCl and copper dichloride. The mixture was stirred for 2 hours at 22°C for 8 hours and purified by aqueous work up followed by column chromatography on silica gel to give N4-(4-ethoxy-3-hydroxysulfonylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 82.3%; MS (m/e): 474.09 ($M-H^-$).
7.3.1157	N2,N4-Bis(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950391)	A mixture of 2,4-dichloro-5-fluoropyridine and three equivalents of 3-methoxycarbonyl-4-trifluoromethoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up N2,N4-bis(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ^1H NMR (DMSO): δ 9.96 (s, 1H), 9.82 (s, 1H), 8.16-8.26 (m, 4H), 7.91 (dd, 1H, J = 3.0, 7.2 Hz), 7.42 (d, 1H, J= 7.2 Hz), 7.31 (d, 1H, J= 7.2 Hz), 3.77 (s, 3H), 3.75 (s, 3H); LCMS: purity: 93.0%; MS (m/e): 565.37 (MH^+).
7.3.1158	N4-(3-Methoxycarbonyl-4-trifluoro methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950392)	A mixture of equimolar amounts of 2-chloro-N4-(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-4-aminopyridine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH in a pressure tube at 110°C for 24h or in EtOH using microwave at 175°C for 10-20 min followed by aqueous work up gave N4-(3-methoxycarbonyl-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.8%; MS (m/e): 510.41 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1159	N4-(4-Acetylamino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine (R950393)	A solution of N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in dry MeCN was treated with concentrated sulfuric acid. The mixture was stirred for 3 hours at 22°C, concentrated to dryness and purified by flash chromatography on silica gel to give N4-(4-acetylamino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO): δ 10.46 (bs, 1H), 9.52 (bs, 1H), 7.98 (d, 1H, J = 2.4 Hz), 7.12-7.73 (m, 7H), 6.66 (d, 1H, J = 7.2 Hz), 6.49 (d, 1H, J = 7.2 Hz), 4.75 (s, 2H), 4.03-4.32 (m, 2H), 3.80 (m, 1H), 2.64 (s, 3H), 2.143 (s, 3H), 1.90-2.11 (m, 2H); LCMS: purity: 92.1%; MS (m/e): 393.06 ($M-H^-$). LCMS: purity: 96.2%; MS (m/e): 479.13 ($M-H^-$).
7.3.1160	N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine HCl salt (R950399)	A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of 1 N aqueous HCl. The clear solution was concentrated to dryness and the remaining solid was washed with dry acetone to give the HCl salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98.2%, MS (m/e): 438.98 (MH^+).
7.3.1161	N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine succinic acid salt (R950400)	A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of succinic acid. The clear solution was concentrated to dryness and the remaining solid was crystallized from dry acetone to give the succinic acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98.1%; MS (m/e): 438.98 (MH^+).
7.3.1162	N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine maleic acid salt (R950401)	A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of maleic acid. The clear solution was concentrated to dryness and the remaining solid was crystallized from dry acetone to give the maleic acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 97.9%; MS (m/e): 438.98 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.3.1163	N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine fumaric acid salt (R950402)	A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of fumaric acid. The clear solution was concentrated to dryness and the remaining solid was crystallized from dry acetone to give the fumaric acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 97.9%; MS (m/e): 438.98 (MH^+).
7.3.1164	N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine citric acid salt (R950403)	A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of citric acid. The clear solution was concentrated to dryness and the remaining solid was crystallized from dry acetone to give the citric acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 97.9%; MS (m/e): 438.98 (MH^+).
7.3.1165	N4-(4-Amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylene oxyphenyl]-2,4-pyrimidinediamine HNO_3 salt (R950404)	A solution of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in MeOH was treated with 1 equivalent of 1 N aqueous HNO_3. The clear solution was concentrated to dryness and the remaining solid was washed with dry acetone to give the nitric acid salt of N4-(4-amino-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonyl methyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 98 2%; MS (m/e): 438.98 (MH^+).
7.4	Synthesis of Prodrugs	Exemplary prodrugs according to structural formula (II) were synthesized as described below.
7.4.1	N-2(4)-Acetyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926233)	A mixture of N2,N4-bis(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine, acetyl chloride (4 equivalents), pyridine (4 equivalents) in CH_2Cl_2 was stirred at room temperature for 48h. After an aqueous work up the residue was chromatographed on silica gel to give N-2(4)-acetyl-N2,N4-bis(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 8.23 (d, 1H, J= 5.4 Hz), 7.03 (d, 1H, J= 2.4 Hz), 7.90-7.80 (m, 3H), 6.76 (m, 2H), 4.28 (bs, 4H), 2.10 (s, 3H); ^{19}F NMR ($CDCl_3$): -42125; LCMS: ret. time: 27.94 min.; purity: 99%; MS (m/e): 439 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.2	N2,N4-Bis(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950244)	N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 2:1) to give N2,N4-bis(3-N-acetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine. LCMS: ret. time: 17.03 min.; purity: 87.0%; MS (m/e): 478.89 (MH^+).
7.4.3	N4-(3-N,N-Diacetylaminophenyl)-N2-(3-N-acetylaminopheny)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950245)	N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 2:1) to give N4-(3-N,N-diacetylaminophenyl)-N2-(3-N-acetylaminopheny)-5-fluoro-N2,N4-pyrimidinediacetylamine. LCMS: ret. time: 19.27 min.; purity: 92.6%; MS (m/e): 521.01 (MH^+).
7.4.4	N4-(3-N-Acetylaminophenyl)-N2-(3-N,N-diacetylaminopheny)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950246)	N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 2:1) to give N4-[3-N-acetylaminophenyl]-N2-(3-N,N-diacetylaminopheny)-5-fluoro-N2,N4-pyrimidinediacetylamine. LCMS: ret. time: 18.89 min.; purity: 83.0%; MS (m/e): 520.97 (MH^+).
7.4.5	N2,N4-Bis(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine (R950247)	N2,N4-Bis(3-aminophenyl)-5-fluoro-2,4-pyrimidinediamine, dimethylaminopyridine (DMAP) and acetic anhydride were refluxed in pyridine for 1 hour. The mixture was cooled to room temperature, concentrated, and the residue was subjected to column chromatography on silica gel ($CHCl_3$:Acetone, 2:1) to give N2,N4-bis(3-N,N-diacetylaminophenyl)-5-fluoro-N2,N4-pyrimidinediacetylamine. LCMS: ret. time: 21.51 min.; purity: 91.8%; MS (m/e): 563.00 (MH^+).
	Synthesis of Anilines	

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Section Number	Name of compound and reference number	Experimental
7.4.6	3-Chloro-4-(methoxycarbonylmethyleneoxy)nitrobenzene	A dry reaction flask equipped with a magnetic stirring bar, reflux condenser and N2 inlet was charged with a commercially available 2-chloro-4-nitrophenol (3.48 g, 20 mmol), K_2CO_3 (3.03 g, 21.81 mmol) and dry acetone (100 mL) under N_2 atmosphere. To this was added methyl bromoacetate (1.72 mL, 18.18 mmol) and refluxed for 6 hours. Upon cooling, the reaction mixture was diluted with ice-water (1 liter), solid obtained was filtered, washed with water (2 x 50 mL), and dried to give 3-chloro-4-(methoxycarbonylmethyleneoxy)nitrobenzene. ^{1}H NMR ($CDCl_3$): δ 8.33 (d, 1H, J= 3 Hz), 8.13 (dd, 1H, J= 2.7 and 9.3 Hz), 6.87 (d, 1H, J= 9.3 Hz), 4.84 (s, 2H), 3.83 (s, 3H); LCMS: purity: 87%; MS (m/e): 287 (M+ acetonitrile).
7.4.7	3-Chloro-4-(methoxycarbonylmethyleneoxy)aniline	To a solution of 3-chloro-4-(methoxycarbonylmethyleneoxy)nitrobenzene (1.00 g) in MeOH (50 mL) was added 0.050 g of 10% Pd/C, degassed and hydrogenated with a balloon filled with hydrogen (ca. 1 atmosphere) for 2 hours. The reaction mixture was filtered through a pad of celite, concentrated and the resulting residue was then sonicated with ethyl acetate and filtered. The filtrate upon concentration and drying under a high vacuum gave the 3-chloro-4-(methoxycarbonylmethyleneoxy)aniline. ^{1}H NMR ($CDCl_3$): δ 6.79 (d, 1H, J= 9 Hz), 6.73 (d, 1H, J= 2.1 Hz), 6.50 (dd, 1H, J= 2.7 and 9.3 Hz), 4.60 (s, 2H), 3.80 (s, 3H); LCMS: purity: 87%; MS (m/e): 216 (MH^+).
7.4.8	3-Chloro-4-(2-hydroxyethyleneoxy)nitrobenzene	A dry reaction flask equipped with a magnetic stirring bar, N_2 inlet and a rubber septum was charged with 3-chloro-4-(methoxycarbonylmethyleneoxy)nitrobenzene (1.23 g, 5 mmol) and CH_2Cl_2 (50 mL) under N_2 atmosphere. The reaction solution was cooled to –78 °C and to it was added diisobutyllithiumaluminum hydride diisobutyl lithiumaluminum hydride (1.0 M in toluene, 15 mL, 15 mmol) over a period of 15 minutes. The reaction mixture was stirred at –78 °C for 2 hours and at room temperature for 1 hour, quenched with saturated solution of Rochelle's salt and again stirred for 2 hours. Upon extraction with CH_2Cl_2, drying over anhydrous Na_2SO_4 and evaporation of solvent gave 3-chloro-4-(2-hydroxyethyleneoxy)nitrobenzene. ^{1}H NMR ($CDCl_3$): δ 8.30 (d, 1H, J= 3 Hz). 8.15 (dd, 1H, J= 2.4 and 9 Hz), 7.02 (d, 1H, J= 8.7 Hz), 4.25 (t, 2H, J= 4.8 Hz), 4.07 (m, 2H); LCMS: purity: 92%.
7.4.9	3-Chloro-4-(2-hydroxyethyleneoxy)aniline	In like manner to the preparation of 3-chloro-4-(methoxycarbonylmethyleneoxy)aniline, the hydrogenation of 3-chloro-4(2-hydroxyethyleneoxy)nitrobenzene with balloon filled with hydrogen (ca. 1 atmosphere) in the presence of10% Pd/C as a catalyst gave 3-chloro-4-[2-hydroxyethyleneoxy)aniline. LCMS: MS (m/e): 187 (M^+)

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Section Number	Name of compound and reference number	Experimental
7.4.10	2-(N-Methylaminocarbonyl)-5-nitrobenzofuran	A dry reaction flask equipped with a magnetic stirring bar, a rubber septum and N_2 inlet was charged with 2-carboxy-5-nitrobenzofuran (2.07 g, 10 mmol), N,N-dimethylformamide (DMF) (0.100 mL) and CH_2Cl_2 (50 mL) under N_2 atmosphere. The reaction mixture was cooled to 0 °C and to it was added oxalyl chloride [$(COCl)_2$] (2.65 mL, 30 mmol) over a period of 10 minutes. The resulting mixture was stirred for 2 hours by the time the 0 °C became room temperature and also the reaction became as a clear solution. It was concentrated and dried under high vacuum to yield the intermediate acid chloride. The resulting acid chloride was cooled to 0 °C and to it were added CH_2Cl_2 (50 mL), pyridine (2.96 mL, 30 mmol) followed by methylamine hydrogen chloride salt (1.34 g, 20 mmol). Upon stirring for 24 hours at room temperature, the solvent was removed under a reduced pressure and residue was suspended in water (200 mL). The solid formed was filtered, washed well with water and dried to give 2-(N-methylaminocarbonyl)-5-nitrobenzofuran. ^{1}H NMR ($CDCl_3$): δ 8.63 (d, 1H, J= 2.4 Hz), 8.33 (dd, 1H, J= 2.4 and 9 3 Hz), 7.60 (d, 1H, J= 7.8 Hz), 7.59 (s, 1H), 3.07 (d, 3H, J= 4.8 Hz); LCMS: purity: 98%; MS (m/e): 221 (MH^+).
7.4.11	(±)-5-Amino-[2-(N-methylaminocarbonyl)-2,3-dihydro]benzofuran	A suspension of 2-(N-methylaminocarbonyl)-5-nitrobenzofuran (1.5 g), 10% Pd/C (1.5 g), Na_2SO_4 (1.5 g) in MeOH (200 mL) was hydrogenated at 55 PSI for 3 days. The resulting solution was filtered through a pad of celite, concentrated to give (±)-5-amino-[2-(N-methylaminocarbonyl)-2,3-dihydro]benzofuran. ^{1}H NMR ($CDCl_3$): δ 6.65 (m, 2H), 6.53 (m, 1H), 5.01 (dd, 1H, J= 6.0 and 6.6 Hz), 3.46 (dd, 1H, J= 9.9 and 10.2 Hz), 3.18 (dd, 1H, J= 6.0 and 4.2 Hz), 2.75 (d, 3H).
7.4.12	2-(N,N-Dimethylaminocarbonyl)-5-nitrobenzofuran	In like manner to the preparation of 2-(N-methylaminocarbonyl)-5-nitrobenzofuran, the reaction of 2-carboxy-5-nitrobenzofuran with oxalyl chloride followed by dimethylamine hydrogen chloride salt afforded 2-(N,N-dimethylaminocarbonyl)-5-nitrobenzofuran. ^{1}H NMR ($CDCl_3$): δ 8.61 (d, 1H, J= 2.4 Hz), 8.31 (dd, 1H, J= 2.4 and 9.3 Hz), 7.63 (d, 1H, J= 9.3 Hz), 7.40 9s, 1H), 3.35 (s, 3H), 3.17 (s, 3H); LCMS: purity: 97%; MS (m/e): 235 (MH^+).
7.4.13	(±)-5-Amino-[2-(N,N-dimethylaminocarbonyl)-2,3-dihydro]benzofuran	In like manner to the preparation of (±)-5-amino-[2-(N-methylaminocarbonyl)-2,3-dihydro]benzofuran, the hydrogenation of 2-(N,N-dimethylaminocarbonyl)-5-nitrobenzofuran yielded (±)-5-amino-[2-(N,N-dimethylaminocarbonyl)-2,3-dihydro]benzofuran. ^{1}H NMR (DMSO-d6): δ 6.44 (m, 2H), 6.27 (dd, 1H, J= 2.1 and 8.7 Hz), 5.42 (dd, 1H, J= 6.5 and 7.5 Hz), 4.54 (bd, J= 5.4 Hz), 3.23 (m, 2H), 2.83 (s, 3H), 2.82 (s, 3H); LCMS: purity: 70%; MS (m/e): 207 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.14	2-[(1R, 2S, 5R)-Menthyloxycarbonyl)-5-nitrobenzofuran	In like manner to the preparation of 2-(N-methylaminocarbonyl)-5-nitrobenzofuran, the reaction of 2-carboxy-5-nitrobenzofuran with oxalyl chloride followed by treatment with (1R, 2S, 5R)-(-)-menthol afforded 2-[(1R, 2S, 5R)-menthyloxycarbonyl)-5-nitrobenzofuran. ^{1}H NMR ($CDCl_3$): δ 8.63 (d, 1H, J= 2.4 Hz), 8.35 (dd, J= 2.4 and 8.7 Hz), 7.69 (d, 1H, J= 9.3 Hz), 7.62 (s, 1H), 5.00 (dt, 1H, J= 4.8 and 10.5 Hz), 2.14 (bd, 1H, J= 9.3 Hz), 1.95 (m, 1H), 1.76 (m, 2H), 1.56 (m, 3H), 1.11 (m, 2H), 0.94 (d, 3H), 0.93 (d, 3H), 0.82 (d, 3H, J= 7.2 Hz); LCMS: purity: 99.67%.
7.4.15	5-Amino-[2(R)-(1R, 2S, 5R)-menthyloxycarbonyl-2,3-dihydro]benzofuran	In like manner to the preparation of (±)-5-amino-[2-(N-methylamino)carbonyl]-2,3-dihydrobenzofuran, the hydrogenation of 2-[(1R, 2S, 5R)-menthyloxycarbonyl)-5-nitrobenzofuran yielded a diastereomeric mixture of 5-amino-[2-(1R, 2S, 5R)-menthyloxycarbonyl-2,3-dihydro]benzofuran, from which the 5-amino-[2(R)-(1R, 2S, 5R)-menthyloxycarbonyl-2,3-dihydro]benzofuran was isolated as a crystalline diastereoisomer using solvent diffusion method* (CH_2Cl_2:n-n-hexanes) of crystallization. ^{1}H NMR ($CDCl_3$): δ 6.77 (bd, (1H), 6.73 (bs, 1H), 6.68 (dd, 1H, J= 2.4 and 8.7 Hz), 5.11 (dd, 1H, J= 6.9 and 7.5 Hz), 4.76 (dt, 4.5 and 11.1 Hz), 3.49 (dd, 1H, J= 9.9 and 10.5 Hz), 3.25 (dd, 1H, J= 7.2 and 7.8 Hz), 1.99 (bd, 1H), 1.86 (dpent, 1H, J= 3.0 and 6.9 Hz), 1.70 (m, 1H), 1.66 (m, 1H), 1.46 (m, 2H), 1.02 (m, 1H). 0.90 (d, 3H, 7.2 Hz), 0.89 (d, 3H, J= 6.6 Hz), 0.75 (d, 3H, J= 6.9 Hz); MS (m/e): 318 (MH^+). *Solvent Diffusion Method: The organic molecule was dissolved in a minimum amount of CH_2Cl_2 and the container was placed in a jar containing anti-solvent (n-hexanes), the lid was placed to avoid a loss of solvent and allowed to equilibrate them till the crysatallıztion was seen. The resulting crystals were isolated by decantation of the solvent.
7.4.16	3,5-Dichloro-4-methoxyaniline	To a solution of commercially available 3,5-dichloro-4-methoxynitrobenzene (1.00 g, 4.5 mmol) in MeOH (100 mL) was added 10% Pd/C (0.100 g), degassed and hydrogenated using balloon filled with hydrogen (ca. 1 atmosphere) for 2 hours. Upon filtration through celite and concentration afforded 3,5-dichloro-4-methoxyaniline, which was isolated as 3,5-dichloro-4-methoxyaniline hydrogen chloride salt by acidification with equivalent amount of HCl (4M, dioxane). Alternatively, this transformation was also achieved by stirring 3,5-dichloro-4-methoxynitrobenzene (1.00 g, 4.5 mmol) with $Na_2S_2O_4$ (3.91 g, 22.5 mmol) and K_2CO_3 (3.12 g, 22.5 mmol) in MeOH:H_2O (50 mL, each) at room temperature for 24 hours. The extraction with ethyl acetate followed by removal of solvent gave 3,5-dichloro-4-methoxyanilıne. LCMS: purity: 87%; MS (m/e): 233 (M+ acetonitrile).

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Section Number	Name of compound and reference number	Experimental
7.4.17	4-Chloro-3-methoxyaniline	To a solution of commercially available 3,5-dichloro-4-methoxynitrobenzene (1.00 g, 4.5 mmol) in MeOH (100 mL) was added 10% Pd/C (0.100 g), degassed and hydrogenated using balloon filled with hydrogen (ca. 1 atmosphere) for 2 hours. Upon filtration through celite and concentration afforded 3,5-dichloro-4-methoxyaniline, which was isolated as 3,5-dichloro-4-methoxyaniline hydrogen chloride salt by acidification with equivalent amount of HCl (4M, dioxane). Alternatively, this transformation was also achieved by stirring 3,5-dichloro-4-methoxynitrobenzene (1.00 g, 4.5 mmol) with $Na_2S_2O_4$ (3.91 g, 22.5 mmol) and K_2CO_3 (3.12 g, 22.5 mmol) in MeOH:H_2O (50 mL, each) at room temperature for 24 hours. The extraction with ethyl acetate followed by removal of solvent gave 3,5-dichloro-4-methoxyaniline. LCMS: purity: 87%; MS (m/e): 233 (M+ acetonitrile).
7.4.18	4-Chloro-3,5-dimethylaniline	To a suspension of commercially available 4-chloro-3,5-dimethylnitrobenzene (0.185 g, 1 mmol) in EtOH: H_2O (5 mL, each) at room temperature was added ammonium chloride (0.265 g, 5 mmol) and iron powder (0.280 g, 5 mmol), stirred for 5 minutes at room temperature followed by 10 minutes at 60 °C. Upon cooling to room temperature, the reaction mixture was filtered through a pad of celite, washed with ethanol and the filtrate was concentrated. The resulting residue was diluted with water, saturated with sodium chloride and extracted with ethyl acetate. The organic solvent was removed under a reduced pressure to afford the desired 4-chloro-3,5-dimethylaniline. ^{1}H NMR ($CDCl_3$): δ 6.34 (s, 2H), 3.42 (bs, 2H), 2.20 (s, 6H); LCMS: purity: 82%; MS: 156 (MH^+).
7.4.19	3,4,5-Trimethylaniline	In like manner to the hydrogenation of 3-(methoxycarbonylmethyleneoxy)aniline, the hydrogenation of commercially available 3,4,5-trimethylnitrobenzene gave 3,4,5-trimethylaniline. LCMS: purity: 91%; MS (m/e): 136 (MH^+).
	Synthesis of Mono-SNAr Products	
7.4.20	N2-Chloro-N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine	A mixture of 2,4-dichloro-5-fluoropyrimidine (0.305 g, 1.8 mmol) and 3-chloro-4-(methoxycarbonylmethyleneoxy)aniline (0.332 g, 1.2 mmol) was stirred in MeOH:H_2O (4 ml, each) at room temperature for 24 hours. The reaction mixture was diluted with water (200 mL), sonicated for few minutes, allowed to stand at room temperature for 30 minutes in order to sublime the residual 2,4-dichloro-5-fluoropyrimidine and the solid formed was filtered to obtain N2-chloro-N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.07 (d, 1H, J= 3 Hz), 7.66 (d, 1H, J= 2.4 Hz), 7.53 (dd, 1H, J= 2.1 and 9.3 Hz), 6.90 (m, 2H), 4.72 (s, 2H), 3.82 (s, 3H); LCMS: purity: 80%; MS (m/e): 346 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.21	N2-Chloro-N4-[3-chloro-4-(2-hydroxyethyleneoxy)phenyl]-5-fluoro-4-pyrimidineamine	In like manner to the preparation of N2-chloro-N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-chloro-4(2-hydroxyethyleneoxy)aniline gave N2-chloro-N4-[3-chloro-4-(2-hydroxyethyleneoxy)phenyl]-5-fluoro-4-pyrimidineamine. LCMS: purity: 84%; MS (m/e): 318 (MH^+).
7.4.22	2-Chloro-N4-(4-chloro-3-methoxyphenyl)-5-fluoro-4-pyrimidineamine	A mixture of 2,4-dichloro-5-fluoropyrimidine (0.305 g, 1.8 mmol) and 3-chloro-4-(methoxycarbonylmethyleneoxy)aniline (0.332 g, 1.2 mmol) was stirred in MeOH:H_2O (4 ml, each) at room temperature for 24 hours. The reaction mixture was diluted with water (200 mL), sonicated for few minutes, allowed to stand at room temperature for 30 minutes in order to sublime the residual 2,4-dichloro-5-fluoropyrimidine and the solid formed was filtered to obtain N2-chloro-N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine. ^1H NMR ($CDCl_3$): δ 8.07 (d, 1H, J= 3 Hz), 7.66 (d, 1H, J= 2.4 Hz), 7.53 (dd, 1H, J= 2.1 and 9.3 Hz), 6.90 (m, 2H), 4.72 (s, 2H), 3.82 (s, 3H); LCMS: purity: 80%; MS (m/e): 346 (MH^+).
7.4.23	N2-Chloro-N4-[3-chloro-4-(2-hydroxyethyleneoxy)phenyl]-5-fluoro-4-pyrimidineamine	In like manner to the preparation of N2-chloro-N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-chloro-4(2-hydroxyethyleneoxy)aniline gave N2-chloro-N4-[3-chloro-4-(2-hydroxyethyleneoxy)phenyl]-5-fluoro-4-pyrimidineamine. LCMS: purity: 84%; MS (m/e): 318 (MH^+).
7.4.24	2-Chloro-N4-(4-chloro-3-methoxyphenyl)-5-fluoro-4-pyrimidineamine	In like manner to the preparation of N2-chloro-N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-chloro-4(2-hydroxyethyleneoxy)aniline gave N2-chloro-N4-[3-chloro-4-(2-hydroxyethyleneoxy)phenyl]-5-fluoro-4-pyrimidineamine. LCMS: purity: 84%; MS (m/e): 318 (MH^+).
7.4.25	2-Chloro-N4-(4-chloro-3-methoxyphenyl)-5-fluoro-4-pyrimidineamine	In like manner to the preparation of N2-chloro-N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-chloro-3-methoxyaniline gave 2-chloro-N4-(4-chloro-3-methoxyphenyl)-5-fluoro-4-aminopyrimidine. LCMS: purity: 88%; MS (m/e): 288 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.26	2-Chloro-N4-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine	In like manner to the preparation of N2-chloro-N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3,5-dichloro-4-methoxyaniline hydrogen chloride salt gave 2-chloro-N4-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.15 (s, 1H), 8.38 (d, 1H, J= 3.4 Hz), 7.86 (d, 2H, J= 3.0 Hz); LCMS: purity: 94%; MS (m/e): 321 (MH^+).
7.4.27	N4-(2-Aminopyrid-6-yl)-2-chloro-5-fluoro-4-pyrimidineamine	A mixture of 2,6-diaminopyridine (0.109 g, 1 mmol) and 2,4-dichloro-5-fluoropyrimidine (0.167 g, 1 mmol) in MeOH (2 mL) was shaken in a sealed tube at 60 °C for 48 hours. Upon concentration, the residue was absorbed on silica gel and chromatographed (silica gel; CH_2Cl_2 then 1% of 2N NH_3/MeOH in CH_2Cl_2) gave N4-(2-aminopyrid-6-yl)-2-chloro-5-fluoro-4-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 8.16 (d, 1H, J= 3.6 Hz), 7.46 (m, 2H), 6.32 (dd, 1H, J= 3.9 and 5.1 Hz); LCMS: purity: 80%; MS (m/e): 240 (MH^+).
7.4.28	N4-[2-(N-Acetylamino)pyrid-6-yl]-2-chloro-5-fluoro-4-pyrimidineamine	A dry reaction flask equipped with a magnetic stirring bar, rubber septum and a N_2 inlet was charged with N4-(2-aminopyrid-6-yl)-2-chloro-5-fluoro-4-pyrimidineamine (0.120 g, 0.5 mmol) and CH_2Cl_2. It was cooled to 0 °C and to it were added pyridine (0.100 mL, 1.0 mmol) followed by acetyl chloride (0.042 mL, 0.6 mmol) and stirred at room temperature for 2 hours. The reaction was quenched with water, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and solvent was evaporated to yield N4-[2-(N-acetylamino)pyrid-6-yl]-2-chloro-5-fluoro-4-pyrimidineamine. LCMS: purity: 80%; MS (m/e): 282 (MH^+).
7.4.29	2-Chloro-5-fluoro-N4-[2-(N-methylaminocarbonyl)aminopyrid-6-yl]-2,4-pyrimidineamine	To a suspension of N4-(2-aminopyrid-6-yl)-2-chloro-5-fluoro-4-pyrimidineamine (0.06 g, 0.25 mmol) in THF (1 mL) at 0 °C were added triethylamine (0 050 mL, 0.35 mmol), 4-N,N-dimethylaminopyridine (0.5 mg) followed by triphosgene (0.037 g, 0.125 mmol). The resulting reaction mixture was then stirred at room temperature for 1 hour, quenched with an aqueous solution of methylamine (40%, 2 mL), shaken for 5 minutes and diluted with water. The aqueous solution was extracted with ethyl acetate, solvent was evaporated and the residue was chromatographed (silica gel; CH_2Cl_2 then 2-5% of 2M NH_3/MeOH in CH_2Cl_2) to yield 2-chloro-5-fluoro-N4-[2-(N-methylaminocarbonyl)aminopyrid-6-yl]-2,4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.34 (s, 1H), 9.34 (s, 1H), 8.72 (m, 1H), 8.45 (d, 1H, J= 3.6 Hz), 7.68 (t, 1H, J= 8.1 Hz), 7.52 (d, 1H, J= 7.8 Hz), 6.89 (d, 1H, J= 8.1 Hz), 2.77 (d, 3H, J= 3.3 Hz); LCMS: purity: 88%; MS (m/e): 297 (MH^+).
	Synthesis of Bis-SNAr Products	

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Section Number	Name of compound and reference number	Experimental
7.4.30	N4-(4-Chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R927042)	A sealed tube was charged with 2-chloro-N4-(4-chloro-3-methoxyphenyl)-5-fluoro-4-pyrimidineamine (0.109 g, 0.38 mmol), 3-[N-(methylamino)carbonylmethyleneoxy]aniline (0.068 g, 0.38 mmol) and MeOH (2 mL) and then heated at 100 °C for 24 hours. Upon cooling to the room temperature, it was diluted with water, acidified and the solid obtained was filtered dried and purified by column chromatography (silica gel, CH_2Cl_2 then 2N NH_3/MeOH upto 2-5% in CH_2Cl_2) to give N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. Alternatively, the resulting reaction was diluted with ethyl acetate, the solid was isolated by using centrifuge technique and subjected for the purification as above. By doing this, the most of the unreacted mono-SNAr product and second aniline go into ethyl acetate keeping the desired bis-SNAr product as a solid. ^{1}H NMR (DMSO-d6): δ 9.89 (bs, 1H), 9.66 (bs, 1H), 8.20 (d, 1H, J= 4.8 Hz), 7.95 (bd, 1H), 7.48 (m, 2H), 7.33 (d, 1H, J= 9.3 Hz), 7.26 (bs, 1H), 7.17 (m, 2H), 6.57 (bd, 1H, J= 7.8 Hz), 4.34 (s, 2H), 3.72 (s, 3H), 2.66 (s, 3H); LCMS: purity: 97%; MS (m/e): 432 (MH^+).
7.4.31	N4-(3-Chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine	In like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-chloro-N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine with 3-[N-(methylamino)carbonylmethyleneoxy]aniline gave N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: purity: 81%; MS (m/e): 490 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.32	N4-[3-Chloro-4-(N-methylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R927043)	A sealed tube charged with N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (0.123 g, 0.25 mmol), methylamine hydrogen chloride salt (0.084 g, 1.25 mmol), diisopropylethyl amine (0.217 mL, 1.25 mmol) and MeOH (4 mL) and heated at 100 °C for 24 hours. Upon cooling to the room temperature, it was diluted with water (50 mL), extracted with ethyl acetate (3 x 25 mL) and the organic solvent was evaporated. The resulting residue was purified by column chromatography (silica gel, CH_2Cl_2 then 2N NH_3/MeOH upto 2% in CH_2Cl_2) to give N4-[3-chloro-4-(N-methylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.35 (bs, 1H), 9.24 (bs, 1H), 8.09 (d, 1H, J= 3.6 Hz), 7.94 (bd, 1H), 7.87 (bd, 1H, J= 4.2 Hz), 7.83 (t, 1H, J= 2.4 Hz). 7.72 (m, 1H), 7.29 (m, 2H), 7.11 (t, 1H, J= 8.4 Hz), 6.99 (d, 1H, J= 8.7 Hz), 6.47 (dd, 1H, J= 1.8 and 10.5 Hz), 4.53 (s, 2H), 4.33 (s, 2H), 2.66 (d, 3H, J= 4.8 Hz), 2 63 (d, 3H, J= 4.8 Hz); LCMS: purity: 92%; MS (m/e): 489 (MH^+).
7.4.33	N4-[3-Chloro-4-(2-hydroxyethyleneoxy)phenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R927047)	In like manner to the preparartion of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N2-chloro-N4-[3-chloro-4-(2-hydroxyethyleneoxy)phenyl]-5-fluoro-4-pyrimidineamine with 3-[N-(methylamino)carbonylmethyleneoxy]aniline gave N4-[3-chloro-4-(2-hydroxyethyleneoxy)phenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.31 (s, 1H), 9.22 (s, 1H), 8.08 (d, 1H, J= 3.6 Hz), 7.94 (m, 1H), 7.80 (d, 1H, J= 2.4 Hz), 7.68 (dd, 1H, J= 2.4 and 8.7 Hz), 7.31 (bs, 1H), 7.29 (d, 1H, J= 1.2 Hz), 7.10 (m, 2H), 6.46 (m, 1H), 4.34 (s, 2H), 4.04 (t, 2H, J= 5.4 Hz), 3.71 (t, 2H, J= 5.1 Hz), 2.62 (d, 3H, J= 4.8 Hz); LCMS: purity: 89%; MS (m/e): 462 (MH^+)
7.4.34	N4-(3,5-Dichloro-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R927057)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine with 3-[N-(methylamino)carbonylmethyleneoxy]aniline gave N4-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.80 (s, 1H), 9.60 (bs, 1H), 8.21 (d, 1H, J= 3.6 Hz), 7.98 (bd, 1H), 7.90 (m, 2H), 7.20 (m, 3H), 6.56 (bd, 1H), 4.36 (s, 1H), 3.78 (s, 3H), 2.63 (d, 3H, J= 3.3 Hz); LCMS: purity: 96%; MS (m/e): 394 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.35	N4-(2-Aminopyrid-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R927080)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(2-aminopyrid-6-yl)-2-chloro-5-fluoro-4-pyrimidineamine with 3-[N-(methylamino)carbonylmethyleneoxy]aniline gave N4-(2-aminopyrid-6-yl)-5-fluoro-N2-[3-(N-36methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.96 (d, 1H, J= 3.0 Hz), 7.58 (d, 1H, J= 7.8 Hz), 7.40 (m, 2H), 7.17 (m, 2H), 6.60 (m, 1H), 6.27 (bd, 1H, J= 7.8 Hz), 4.47 (s, 2H), 2.82 (s, 3H); LCMS: purity: 100%; MS (m/e): 384 (MH^+).
7.4.36	N4-[2-(N-Acetylamino)pyrid-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R927093)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-[2-(N-acetylamino)pyrid-6-yl]-2-chloro-5-fluoro-4-pyrimidineamine with 3-[N-(methylamino)carbonylmethyleneoxy]aniline gave N4-[2-(N-acetylamino)pyrid-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine ^{1}H NMR (DMSO-d6): δ 10.22 (s, 1H), 9.35 (s, 1H), 9.05 (s, 1H), 8.18 (d, 1H, J= 3.3 Hz), 7.96 (m, 1H), 7.75 (s, 2H), 7.38 (bs, 1H), 7.29 (bd, 1H, J= 8.4 Hz), 7.11 (t, 1H, J= 8.4 Hz), 6.49 (bdd, 1H, J= 8.4 Hz), 4.37 (s, 2H), 2.65 (d, 3H), 2.18 (s, 3H); LCMS: purity: 80%; MS (m/e): 426 (MH^+)
7.4.37	N4-(3-Chloro-4-methoxyphenyl)-N2-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927044)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine with 3,5-dichloro-4-hydroxyaniline gave N4-(3-chloro-4-methoxyphenyl)-N2-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): □ 9.46 (s, 1H), 9.34 (s, 1), 9.22 (s, 1H), 8.09 (d, 1H, J= 3.6 Hz), 7.66 (m, 1H), 7.63 (m, 2H), 7.10 (d, 1H, J= 9.3 Hz), 3.82 (s, 3H); LCMS: purity: 100%; MS (m/e): 430 (MH^+).
7.4.38	N4-(3-Chloro-4-trifluoromethoxyphenyl)-N2-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927046)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine with 3,5-dichloro-4-hydroxyaniline gave N4-(3-chloro-4-trifluoromethoxyphenyl)-N2-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.70 (s, 1H), 9.54 (s, 1H), 9.35 (s, 1H), 8.20 (d, 1H, J= 3.6 Hz), 8.01 (t, 1H, J= 3 Hz), 7.85 (m, 1H), 7 65 (s, 1H), 7.64 (s, 1H), 7.46 (bdd, 1H, J= 8.1 Hz); LCMS: purity: 97%; MS (m/e): 484 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.39	N2-(3,5-Dichloro-4-hydroxyphenyl)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R927048)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine with 3,5-dichloro-4-hydroxyaniline gave N2-(3,5-dichloro-4-hydroxyphenyl)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine ^{1}H NMR (DMSO-d6): δ 11.96 (s, 1H), 9.58 (s, 1H), 9.47 (s, 1H), 9.27 (s, 1H), 8.13 (d, 1H, J= 3 6 Hz), 7.65 (s, 2H), 7.38 (m, 2H), 7.25 (d, 1H, J= 9 Hz); LCMS: purity: 92%; MS (m/e)· 472 (MH^+).
7.4.40	N2-(3,5-Dichloro-4-hydroxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R927051)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-3-oxo-6-yl)-5-fluoro-4-pyrimidineamine with 3,5-dichloro-4-hydroxyaniline gave N2-(3,5-dichloro-4-hydroxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.61 (s, 1H), 9.45 (s, 1H), 9.34 (s, 1H), 9.18 (s, 1H), 8.07 (bs, 1H), 7.66 (bs, 2H), 7.23 (bd, 1H, J= 8.1 Hz), 7.12 (s, 1H), 6.88 (d, 1H, J= 8.4 Hz), 1.39 (s, 6H); LCMS: purity: 100%; MS (m/e): 464 (MH^+).
7.4.41	N4-(3-Chloro-4-methoxyphenyl)-N2-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927054)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidineamine with 3,5-dichloro-4-methoxyaniline hydrogen chloride salt gave N4-(3-chloro-4-methoxyphenyl)-N2-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.46 (s, 1H), 9.42 (s, 1H), 8.12 (d, 1H, J= 3 Hz), 7.73 (s, 2H), 7.65 (d, 1H, J= 2.4 Hz), 7.60 (dd, 1H, J= 2.1 and 8.7 Hz), 7.12 (d, 1H, J= 8.7 Hz), 3.84 (s, 3H), 3.73 (s, 3H); LCMS: purity: 97%; MS (m/e): 443 (MH^+).
7.4.42	N4-(3-Chloro-4-trifluoromethoxyphenyl)-N2-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927055)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidineamine with 3,5-dichloro-4-methoxyaniline hydrogen chloride salt gave N4-(3-chloro-4-trifluoromethoxyphenyl)-N2-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.77 (s, 1H), 9.59 (s, 1H), 8.23 (d, 1H, J= 3.9 Hz), 8.00 (d, 1H, J= 2.1 Hz), 7.84 (dd, 1H, J= 2.7 and 9.0 Hz), 7.75 (d, 2H, J= 1.5 Hz), 7.50 (bd, 1H, J= 9.3 Hz), 3.74 (s, 3H); LCMS: purity: 75%; MS (m/e): 499 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.43	N4-(3,4-Dichlorophenyl)-N2-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927058)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidineamine with 3,5-dichloro-4-methoxyaniline hydrogen chloride salt gave N4-(3,4-dichlorophenyl)-N2-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 93%; MS (m/e): 449 (MH^+).
7.4.44	N2-(3,5-Dichloro-4-methoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R927056)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine with 3,5-dichloro-4-methoxyaniline hydrogen chloride salt gave N2-(3,5-dichloro-4-methoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 92%; MS (m/e): 478 (MH^+).
7.4.45	N2-(3,5-Dichloro-4-methoxyphenyl)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R927061)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine with 3,5-dichloro-4-methoxyaniline hydrogen chloride salt gave N2-(3,5-dichloro-4-methoxyphenyl)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-3-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 11.95 (s, 1H), 9.64 (s, 1H), 9.50 (s, 1H), 8.16 (d, 1H, J= 3.6 Hz), 7.74 (s, 2H), 7.38 (m, 2H), 7.26 (m, 1H), 3.71 (s, 3H); LCMS: purity: 92%; MS (m/e): 486 (MH^+).
7.4.46	N2-(3,5-Dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-3-6-yl)-5-fluoro-2,4-pyrimidinediamine (R927050)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-3-6-yl)-5-fluoro-4-pyrimidineamine with 3,5-dimethoxyaniline gave N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 10.53 (s, 1H), 9.31 (s, 1H), 8.99 (s, 1H), 8.06 (d, 1H, J= 3.9 Hz), 7.26 (m, 2H0, 6.93 (s, 1H), 6.92 (s, 1H), 6.85 (d, 1H, J= 8.7 Hz), 6.03 (t, 1H, J= 2.4 Hz), 3.61 (s, 6H), 1.39 (s, 6H); LCMS: purity: 92%; MS (m/e): 440 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.47	N4-(3,4-Dichlorophenyl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927060)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine with 3,5-dimethoxyaniline gave N4-(3,4-dichlorophenyl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.60 (s, 1H), 9.26 (s, 1H), 8.16 (d, 1H, J= 3.6 Hz), 8.08 (t, 1H, J= 3.0 Hz), 7.85 (m, 1H), 7.51 (d, 1H, J= 9.0 Hz), 6.89 (t, 2H, J= 2.4 Hz), 6.08 (t, 1H, J= 2.4 Hz), 3.64 (s, 6H); LCMS: purity: 96%; MS (m/e): 409 (MH^+).
7.4.48	N4-(3-Chloro-4-methoxyphenyl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927066)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine with 3,5-dimethoxyaniline gave N4-(3-chloro-4-methoxyphenyl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.31 (s, 1H), 9.14 (s, 1H), 8.08 (d, 1H, J= 3.3 Hz), 7.74 (m, 2H), 7.08 (d, 1H, J= 8.7 Hz), 6.90 (d, 2H, J= 2.1 Hz) 6.05 (t, 1H, J= 2.4 Hz), 3.84 (s, 3H), 3.63 (s, 6H); LCMS: purity: 100%; MS (m/e): 405 (MH^+).
7.4.49	N4-(3-Chloro-4-trifluoromethoxyphenyl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927067)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine with 3,5-dimethoxyaniline gave N4-(3-chloro-4-trifluoromethoxyphenyl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.67 (s, 1H), 9.28 (s, 1H), 8.18 (d, 1H, J= 3.6 Hz), 8.09 (t, 1H, J= 1.2 Hz), 7.91 (dd, 1H, J= 2.7 and 9.0 Hz), 7.45 (bd, 1H, J= 9.0 Hz), 6.89 (d, 2H, J= 1.8 Hz), 6.08 (s, 1H), 3.64 (s, 6H); LCMS: purity: 97%; MS (m/e): 459 (MH^+).
7.4.50	N4-[2-Aminopyrid-6-yl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927077)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(2-aminopyrid-6-yl)-2-chloro-5-fluoro-4-pyrimidineamine with 3,5-dimethoxyaniline gave N4-[2-aminopyrid-6-yl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.00 (bs, 1H), 7.75 (bd, 1H), 7.45 (t, 1H), 7.30 (bs, 1H), 7.25 (bs, 1H), 7.05 (bs, 1H), 6.80 (bs, 2H), 6.20 (m, 2H), 4.35 (bs, 2H), 3.75 (s, 6H); LCMS: purity: 91%; MS (m/e): 357 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.51	N2-(3,5-Dimethoxyphenyl)-5-fluoro-N4-(indol-6-yl)-2,4-pyrimidinediamine (R927089)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(indol-6-yl)-4-pyrimidineamine with 3,5-dimethoxyaniline gave N2-(3,5-dimethoxyphenyl)-5-fluoro-N4-(indol-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.60 (bs, 1H), 8.43 (s, 1H), 7.90 (d, 1H, J= 3.3 Hz), 7.56 (d, 1H, J= 8.4 Hz), 7.22 (m, 2H), 6.95 (bd, 1H), 6.88 (dd, 1H, J= 1.8 and 8.4 Hz), 6.82 (s, 1H), 6.81 (s, 1H), 6.52 (bt, 1H), 6.25 (t, 1H, J= 1.8 Hz), 3.74 (s, 6H); LCMS: purity: 97%; MS (m/e): 380 (MH^+).
7.4.52	N4-[2-(N-Acetylamino)pyrid-6-yl]-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927096)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-[2-(N-acetylamino)pyrid-6-yl]-2-chloro-5-fluoro-4-pyrimidineamine with 3,5-dimethoxyaniline gave N4-[2-(N-acetylamino)pyrid-6-yl]-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 82%; MS (m/e): 399 (MH^+).
7.4.53	N2-(3,5-Dichlorophenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R927064)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine with 3,5-dichloroaniline gave N2-(3,5-dichlorophenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.61 (s, 1H), 9.55 (s, 1H), 9.42 (s, 1H), 8.13 (d, 1H, J= 3.6 Hz), 7.74 (s, 1H), 7.73 (s, 1H), 7.21 (m, 1H), 7.11 (s, 1H), 6.98 (s, 1H), 6.90 (d, 1H, J= 8.7 Hz), 1.38 (s, 6H); LCMS: purity: 91%; MS (m/e): 448 (MH^+).
7.4.54	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(3-methoxy-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R927065)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine with 3-methoxy-5-trifluoromethylaniline gave N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(3-methoxy-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.57 (s, 1H), 9.41 (s, 1H), 9.38 (s, 1H), 8.11 (d, 1H, J= 3.6 Hz), 7.65 (s, 1H), 7.59 (s, 1H), 7.30 (m, 1H), 7.18 (s, 1H), 6.85 (d, 1H, J= 8.7 Hz), 6.69 (s, 1H), 3.70 (s, 3H), 1.39 (s, 6H); LCMS: purity: 98%; MS (m/e): 478 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.55	N2-(2,6-Dimethoxypyrid-3-yl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R927068)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine with 3-amino-2,6-dimethoxypyridine gave N2-(2,6-dimethoxypyrid-3-yl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.56 (s, 1H), 9.28 (s, 1H), 7.87 (m, 2H), 7.67 (s, 1H), 7.34 (s, 1H), 7.16 (dd, 1H, J= 2.1 and 8.4 Hz), 6.79 (d, 1H, J= 8.7 Hz), 6.26 (d, 1H, J= 8.4 Hz), 3.87 (s, 3H), 3 82 (s, 3H), 1.39 (s, 6H); LCMS: purity: 97%; MS (m/e): 441 (MH^+).
7.4.56	N2-(2,6-Dimethylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R927069)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine with 3,5-dimethylaniline gave N2-(2,6-dimethylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.74 (s, 1H), 10.40 (bs, 1H), 10.10 (bs, 1H), 8.25 (bd, 1H), 7.24 9dd, 1H, J= 2.4 and 8.1 Hz), 7.14 (s, 1H), 7.09 (bs, 2H), 6.92 (d, 1H, J= 9.0 Hz), 6.68 (bs, 1H), 2.16 (s, 6H), 1.40 (s, 6H); LCMS· purity: 95%; MS (m/e): 408 (MH^+).
7.4.57	N4-(2-Aminopyrid-6-yl)-N2-(2,6-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R927078)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(2-aminopyrid-6-yl)-2-chloro-5-fluoro-4-pyrimidineamine with 3,5-dimethylaniline gave N4-(2-aminopyrid-6-yl)-N2-(2,6-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.33 (bs, 1H), 7.78 (t, 1H, J= 8.7 Hz), 7.29 (bs, 2H), 6.77 (bd, 1H, J= 5.4 Hz), 6.61 (bs, 1H), 6.47 (d, 1H, J= 8.7 Hz), 2.22 (s, 6H); LCMS: purity: 100%; MS (m/e): 325 (MH^+).
7.4.58	N4-(3,4-Dichlorophenyl)-N2-(2,6-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R927079)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine with 3,5-dimethylaniline gave N4-(3,4-dichlorophenyl)-N2-(2,6-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.57 (s, 1H), 9.18 (s, 1H), 8.16 (d, 1H, J= 3.6 Hz), 8.04 (d, 1H, J= 2.7 Hz), 7.81 (dd, 1H, J= 2.7 and 9.3 Hz), 7.52 (d, 1H, J= 9.0 Hz), 7.22 (s, 2H), 6.54 (d, 1H, J= 1.2 Hz), 2.17 (s, 6H); LCMS: purity: 92%; MS (m/e): 377 (M^+).

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Section Number	Name of compound and reference number	Experimental
7.4.59	N2-(2,6-Dimethylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927086)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 3,5-dimethylaniline gave N2-(2,6-dimethylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.11 (s, 1H), 9.01 (s, 1H), 8.02 (d, 1H, J= 3.9 Hz), 7.26 (m, 3H), 7.18 (m, 1H), 6.78 (d, 1H, J= 8.7 Hz), 6.49 (bs, 1H), 4.21 (s, 4H), 2.16 (s, 6H); LCMS: purity: 97%; MS (m/e): 367 (MH^+).
7.4.60	N2-(2,6-Dimethylphenyl)-5-fluoro-N4-(indol-6-yl)-2,4-pyrimidinediamine (R927088)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(indol-6-yl)-4-pyrimidineamine with 3,5-dimethylaniline gave N2-(2,6-dimethylphenyl)-5-fluoro-N4-(indol-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.12 (bs, 1H), 7.95 (bs, 1H), 7.92 (d, 1H, J= 3.3 Hz), 7.60 (d, 1H, J= 8.7 Hz), 7.19 (t, 1H, J= 2.7 Hz), 7.15 (s, 2H), 7.07 (dd, 1H. J= 1.5 and 8.1 Hz), 6.93 (s, 1H), 6.86 (bs, 1H), 6.65 (s, 1H), 6.54 (m, 1H), 2.19 (s, 6H); LCMS: purity: 100%; MS (m/e): 348 (MH^+).
7.4.61	N4-[2-(N-Acetylamino)pyrid-6-yl]-N2-(3,5-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R927092)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-[2-(N-acetylamino)pyrid-6-yl]-2-chloro-5-fluoro-2,4-pyrimidineamine with 3,5-dimethylaniline gave N4-[2-(N-acetylamino)pyrid-6-yl]-N2-(3,5-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.23 (s, 1H), 9.18 (s, 1H), 8.99 (bs, 1H), 8.17 (m, 1H), 7.73 (m, 2H), 7.28 (s, 1H), 7.25 (s, 2H), 6.55 (m, 1H), 2.20 (s, 3H), 2.17 (s, 3H); LCMS: purity: 80%; MS (m/e): 367 (MH^+).
7.4.62	N2-(3,5-Dimethylphenyl)-5-fluoro-N4-[2-(N-methylamino)carbonylaminopyrid-6-yl]-2,4-pyrimidinediamine (R927098)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-[2-(N-methylamino)carbonylaminopyrid-6-yl]-2,4-pyrimidineamine with 3,5-dimethylaniline gave N2-(3,5-dimethylphenyl)-5-fluoro-N4-[2-(N-methylamino)carbonylaminopyrid-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.73 (s, 1H), 9.26 (s, 1H), 9.21 (s, 1H), 8.77 (bs, 1H0, 8.21 (d, 1H, J= 3.3 Hz), 7.79 (d, 1H, J= 7.5 Hz), 7.57 (t, 1H, J= 7.8 Hz), 7.27 (s, 2H), 6.62 (d, 1H, J= 8.4 Hz), 6.55 (s, 1H), 2,74 (d, 3H, J= 4.2 Hz), 2.20 (s, 6H); LCMS: purity: 100%; MS (m/e): 382 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.63	N2-(3,5-Dimethylphenyl)-5-fluoro-N4-[1-(N-methylamino)carbonylindol-6-yl]-2,4-pyrimidinediamine (R927099)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[2-(N-methylamino)carbonylaminopyrid-6-yl]-2,4-pyrimidineamine, the reaction of N2-(3,5-dimethylphenyl)-5-fluoro-N4-(indol-6-yl)-2,4-pyrimidinediamine with triphosgene gave N2-(3,5-dimethylphenyl)-5-fluoro-N4-[1-(N-methylaminocarbonyl)indol-6-yl)-2,4-pyrimidinediamine. LCMS: purity: 92%; MS (m/e): 405 (MH^+).
7.4.64	N4-(2-Aminopyrid-6-yl)-N2-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927081)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(2-aminopyrid-6-yl)-2-chloro-5-fluoro-4-pyrimidineamine with 3-chloro-4-trifluoromethoxyaniline gave N4-(2-aminopyrid-6-yl)-N2-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 9.66 (s, 1H), 8.94 (s, 1H), 8.16 (d, 1H, J= 3.0 Hz), 8.12 (bd, 1H), 7.65 (bd, 1H, J= 9.0 Hz), 7.39 (m, 2H), 7.22 (m. 1H), 6.20 (d, 1H, J= 7.8 Hz), 5.84 (bs, 2H); LCMS: purity: 95%; MS (m/e): 415 (MH^+).
7.4.65	N2-(3-Chloro-4-trifluoromethoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927085)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 3-chloro-4-trifluoromethoxyaniline gave N2-(3-chloro-4-trifluoromethoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. 1H NMR (DMSO-d6): d 9.56 (s, 1H), 9.28 (s, 1H0, 8.10 (d, 1H, J= 3.9 Hz), 8.05 (d, 1H, J= 2.4 Hz), 7.60 (dd, 1H, J= 2.7 and 9.0 Hz), 7.34 (dd, 1H, J= 1.2 and 9.0 Hz), 7.24 (d, 1H, J= 2.4 Hz), 7.12 (dd, 1H, J= 2.4 and 8.7 Hz), 6.81 (d, 1H, J= 8.4 Hz), 4.22 (s, 4H); LCMS: purity: 90%; MS (m/e): 457 (MH^+).
7.4.66	N4-(2-Aminopyrid-6-yl)-N2-(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927082)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(2-aminopyrid-6-yl)-2-chloro-5-fluoro-4-pyrimidineamine with 3-chloro-4-methoxyaniline gave N4-(2-aminopyrid-6-yl)-N2-(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 9.23 (s, 1H), 8.68 (s, 1H), 8.09 (d, 1H, J= 3.3 Hz), 7.86 (d, 1H, J= 2.4 Hz), 7.46 (bd, 1H, J= 9.6 Hz), 7.34 (m, 2H), 7.02 (d, 1H, J= 9.0 Hz), 6.17 9d, 1H, J= 7.2 Hz), 5.80 (m, 2H), 3.78 (s, 3H); LCMS: purity: 100%; MS (m/e): 361 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.67	N2-(3-Chloro-4-methoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927084)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 3-chloro-4-methoxyaniline gave N2-(3-chloro-4-methoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.15 (s, 1H), 9.12 (s, 1H), 8.02 (d, 1H, J= 3.9 Hz), 7.80 (d, 1H, J= 2.4 Hz), 7.48 (dd, 1H, J= 2.4 and 6 3 Hz), 7.26 (d, 1H, J= 2.4 Hz), 7.16 (dd, 1H, J= 2.7 and 9.3 Hz), 7.00 (d, 1H, J= 8.7 Hz), 6.79 (d, 1H, J= 8.7 Hz), 4.22 (bs, 4H), 3.78 (s, 3H); LCMS: purity: 96%; MS (m/e): 403 (MH^+).
7.4.68	N2-(3-Chloro-4-methoxyphenyl)-5-fluoro-N4-(indol-6-yl)-2,4-pyrimidinediamine (R927091)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(indol-6-yl)-4-pyrimidineamine with 3-chloro-4-methoxyaniline gave N2-(3-chloro-4-methoxyphenyl)-5-fluoro-N4-(indol-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.25 (bs, 1H), 8.03 (bs, 1H), 7.89 (d, 1H, J= 3.3 Hz), 7.82 (d, 1H, J= 2.7 Hz), 7.59 (d, 1H, J= 8.4 Hz), 7.20 (m, 1H), 7.15 (d, 1H, J= 2.4 Hz), 7.02 (bs, 1H), 6.96 (dd, 1H, J= 2.1 and 8.4 Hz), 6.92 (m, 1H), 6.84 (d, 1H, J= 8.7 Hz), 6.52 (m, 1H), 3 89 (s, 3H); LCMS: purity: 97%; MS (m/e): 380 (MH^+).
7.4.69	N2-(3-Chloro-4-methoxyphenyl)-5-fluoro-N4-[1-(N-methylaminocarbonyl)indol-6-yl]-2,4-pyrimidinediamine (R927100)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[2-(N-methylaminocarbonyl)aminopyrid-6-yl]-2,4-pyrimidineamine, the reaction of N2-(3-chloro-4-methoxyphenyl)-5-fluoro-N4-(indol-6-yl)-2,4-pyrimidinediamine with triphosgene followed by methylamine quench gave N2-(3-chloro-4-methoxyphenyl)-5-fluoro-N4-[N1-(N-methylaminocarbonyl)indol-6-yl]-2,4-pyrimidinediamine. LCMS: purity: 88%; MS (m/e): 441 (MH^+).
7.4.70	N4-(2-Aminopyrid-6-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R927083)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(2-aminopyrid-6-yl)-2-chloro-5-fluoro-4-pyrimidineamine with 3-hydroxyaniline gave N4-(2-aminopyrid-6-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine ^{1}H NMR (DMSO-d6): δ 9.17 (s, 1H), 9.13 (s, 1H), 8.62 (s, 1H), 8.08 (d, 1H, J= 3.0 Hz), 7.42 (m, 1H), 7.35 (t, 1H, J= 7.8 Hz), 7.18 (bs, 1H), 7.14 (bd, 1H, J= 7.2 Hz), 6.98 (t, 1H, J= 7.8 Hz), 6.31 (dd, 1H, J= 1.2 and 6.9 Hz), 6.17 (d, 1H, J= 7.5 Hz), 5.77 (m. 1H); LCMS: purity: 100%; MS (m/e): 313 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.71	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2[1-(N-methylaminocarbonyl)indol-6-yl]-2,4-pyrimidinediamine (R927094)	In like manner to the preparation of 2-chloro-5-fluoro-N4-[2-(N-methylaminocarbonyl)aminopyrid-6-yl]-2,4-pyrimidineamine, the reaction of N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(indol-6-yl)-2,4-pyrimidinediamine with triphosgene followed by methylamine quench gave N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2[1-(N-methylaminocarbonyl)indol-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): d 11.09 (s, 1H), 9.70 (d, 1H, 4.2 Hz), 9.49 (s, 1H), 8.18 (d, 1H, J= 3.3 Hz), 7.54 (d, 1H, J= 8.4 Hz), 7.41 (t, 1H, J= 2.7 Hz), 7.30 (d, 1H, J= 2.7 Hz), 7.15 (s, 1H), 6 81 (dd, 1H, J= 2.7 and 9.0 Hz), 6.72 (dd, 1H), J= 1.8 and 8.1 Hz), 6.54 (s, 1H), 5.74 (d, 1H, J= 9.6 Hz), 3.62 (s, 3H), 2.77 (d, 3H, J= 4.5 Hz); LCMS: purity: 99%; MS (m/e): 441 (MH^+).
7.4.72	N2-(3-Chloro-4-methoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R927097)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine with 3-chloro-4-methoxyaniline gave N2-(3-chloro-4-methoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-3-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.60 (s, 1H), 9.31 (s, 1H0, 9.08 (s, 1H), 8.04 (d, 1H, J= 3.6 Hz), 7.81 (d, 1H, J= 3.3 Hz), 7.45 (dd, 1H, J= 2.7 and 9.3 Hz), 7.23 (dd, 1H, J= 2.1 and 8.7 Hz), 7.16 (d, 1H, J= 2.4 Hz), 6.93 (d, 1H, J= 9.0 Hz), 6.89 (d, 1H, J= 8.4 Hz), 3.76 (s, 3H), 1.40 (s, 9H); LCMS: purity: 97%; MS (m/e): 444 (MH^+).
7.4.73	N4-(3,4-Dichlorophenyl)-N2-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R927059)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4pyrimidineamine with 6-amino-2,2-dimethyl-3-oxo-4H-benz[1,4]oxazine gave N4-(3,4-dichlorophenyl)-N2-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.64 (s, 1H), 10.10 (s, 1H), 9.72 (s, 1H), 8.22 (d, 1H, J= 3.9 Hz), 8.10 (bs, 1H), 7.74 (bd, 1H, J= 9.0 Hz), 7.52 (d, 1H, J= 9 Hz); LCMS: purity: 89%; MS (m/e): 448 (MH^+).
7.4.74	N2-(4-Chloro-3,5-dimethylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R927117)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine with 4-chloro-3,5-dimethylaniline gave N2-(4-chloro-3,5-dimethylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6). δ 9.16 (bs, 2H), 8.04 (d, 1H, J= 3.6 Hz), 7.45 (s, 2H), 7.25 (m, 1H), 6.80 (d, 1H, J= 8.7 Hz), 4.21 (bs, 4H), 2.22 (s, 6H); LCMS: purity: 91%; MS (m/e): 401 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.75	N2-(4-Chloro-3,5-dimethylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R927118)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine with 4-chloro-3,5-dimethylaniline gave N2-(4-chloro-3,5-dimethylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.62 (s, 1H), 9.32 (s, 1H), 9.11 (s, 1H), 8.06 (d, 1H, J= 3.9 Hz), 7.46 (s, 2H), 7.26 (dd, 1H, J= 2.4 and 8.7 Hz), 7.18 (m, 1H), 6.89 (d, 1H, J= 8.7 Hz), 2.20 (s, 6H), 1 40 (s, 6H); LCMS: purity: 99%; MS (m/e): 441 (M^+).
7.4.76	(±)-N4-(2,2-Difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[2-(N-methylaminocarbonyl)-2,3-dihydrobenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927049)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine with (±)-5-amino-2-(N-methylaminocarbonyl)-2,3-dihydrobenzofuran gave (±)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[2-(N-methylaminocarbonyl)-2,3-dihydrobenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.96 (s, 1H), 9.48 (s, 1H), 8.92 (s, 1H), 8.06 (d, 1H, J= 3.6 Hz), 8.01 (d, 1H, J= 4.5 Hz), 7.56 (m, 1H), 7.49 (bs, 1H), 7.40 (s, 1H), 7.23 (m, 2H), 6.67 (d, 1H, J= 8.7 Hz), 5.04 (dd, 1H, J= 5.7 and 6.6 Hz), 3.58 (dd, 1H), 3.11 (dd, 1H, J= 5.7 and 6.6 Hz), 2.59 (d, 3H, J= 4.5 Hz); LCMS: purity: 98%; MS (m/e): 487 (MH^+).
7.4.77	(±)-N4-(3-Chloro-4-methoxyphenyl)-N2-[2-(N,N-dimethylaminocarbonyl)-2,3-dihydrobenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927052)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine with (±)-5-amino-2-(N,N-dimethylaminocarbonyl)-2,3-dihydrobenzofuran gave (±)-N4-(3-chloro-4-methoxyphenyl)-N2-[2-(N,N-dimethylaminocarbonyl)-2,3-dihydrobenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.24 (s, 1H), 8.98 (s, 1H), 8.01 (d, 1H, J= 3.3 Hz), 7.74 (d, 1H, J= 2.4 Hz), 7.64 (dd, 1H, J= 2.1 and 9.0 Hz), 7.49 (s, 1H), 7.19 (d, 1H, 8.7 Hz), 7.10 (d, 1H, J= 8.7 Hz), 6.64 (d, 1H, J= 8.7 Hz), 5.54 (dd, 1H, J= 8.7 and 7.8 Hz), 3.84 (s, 3H), 3.30 (m, 2H), 3.08 (s, 3H), 2.86 (s, 3H); LCMS: purity: 93%; MS (m/e): 458 (MH+).

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Section Number	Name of compound and reference number	Experimental
7.4.78	(±)-N4-(3-Chloro-4-trifluoromethoxyphenyl)-N2-[2-(N,N-dimethylaminocarbonyl)-2,3-dihydrobenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927053)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine with (±)-5-amino-2-(N,N-dimethylaminocarbonyl)-2,3-dihydrobenzofuran gave (±)-N4-(3-chloro-4-trifluoromethoxyphenyl)-N2-[2-(N,N-dimethylaminocarbonyl)-2,3-dihydrobenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.59 (s, 1H), 9.10 (s, 1H), 8.12 (d, 1H, J= 3.6 Hz), 8.09 (s, 1H), 7.83 (bd, 1H, J= 8.7 Hz), 7.48 (m, 2H), 7.20 (bd, 1H, J= J= 8.4 Hz), 6.67 (d, 1H, J= 8.4 Hz), 5.58 (d, 1H, J= 8.1 Hz), 3.30 (m, 2H), 3.08 (s, 3H), 3.86 (s, 3H); LCMS: purity: 96%; MS (m/e): 512 (MH^+).
7.4.79	(±)-N4-(3-Chloro-4-methoxyphenyl)-N2-[2-(N-methylaminomethylene)-2,3-dihydrobenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927045)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-[2-(N-morpholino)ethyleneoxy]phenyl]-2,4-pyrimidinediamine, the reduction of (±)-N4-(3-chloro-4-methoxyphenyl)-N2-[2-(N-methylaminocarbonyl)-2,3-dihydrobenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine with borane:methyl sulfide gave (±)-N4-(3-chloro-4-methoxyphenyl)-N2-[2-(N-methylaminomethylene)-2,3-dihydrobenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.22 (s, 1H), 8.92 (s, 1H), 8.01 (d, 1H, J= 3.6 Hz), 7.78 (t, 1H, J= 3.0 Hz), 7.64 (m, 1H), 7.43 (bs, 1H), 7.16 (dd, 1H, J= 2.4 and 10.5 Hz), 7.08 (d, 1H, J= 8.7 Hz), 6.57 (d, 1H, J= 8.1 Hz), 4.77 (m, 1H), 3.82 (s, 3H), 3.11 (dd, 1H, J= 9.3 and 8.7 Hz), 2.85 (dd, 1H, J= 7.5 Hz), 2.66 m, 2H), 2.30 (d, 3H); LCMS: purity: 95%; MS (m/e): 429 (M^+); 430 (MH^+).
7.4.80	5-Fluoro-N2-[2(R)-{(1R, 2S, 5R)-menthyloxycarbonyl}-2,3-dihydrobenzofuran-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine (R927062)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(4-isopropoxyphenyl)-4-pyrimidineamine with 5-amino-[2(R)-{(1R, 2S, 5R)-menthyloxycarbonyl}]-2,3-dihydrobenzofuran gave 5-fluoro-N2-[2(R)-{(1R, 2S, 5R)-menthyloxycarbonyl}-2,3-dihydrobenzofuran-5-yl]-N4-(4-isopropoxyphenyl)-2,4-pyrimidinediamine. LCMS: purity: 93%; MS (m/e): 563 (MH^+).
7.4.81	N4-(2,2-Difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[2(R)-{(1R, 2S, 5R)-menthyloxycarbonyl}-2,3-dihydrobenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R927063)	In like manner to the preparation of N4-(3-chloro-4-methoxycarbonylmethyleneoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidineamine with 5-amino-[2(R)-{(1R, 2S, 5R)-menthyloxycarbonyl}-2,3-dihydro]benzofuran gave N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[2(R)-{(1R, 2S, 5R)-menthyloxycarbonyl}-2,3-dihydrobenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 93%; MS (m/e): 612 (MH^+).

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Section Number	Name of compound and reference number	Experimental
	Formulation of Salts from Bis-SNAr Products	
7.4.82	N2-(3,5-Dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine p-Toluenesulfonic Acid Salt (R927070)	A dry reaction flask equipped with a magnetic stirring bar, rubber septum and a N_2 inlet was charged with N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (0.220 g, 0.5 mmol) and MeOH (15 mL). To this suspension was added p-toluenesulfonic acid monohydrate (0.095 g, 0.5 mmol) at 0 °C over a period of 2-3 minutes. As soon as the addition of p-toluenesulfonic acid monohydrate was completed, the suspension turned into a clear solution. It was further stirred for 5 minutes, concentrated using a rotary evaporator and the residue was recrystallized from EtOH:EtOAc:n-hexanes (1:1:5 mL; v/v) to afford N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine p-toluenesulfonic acid salt. Alternatively, the residue was taken into EtOH and precipitated with either n-hexanes or ethyl ether to get N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine p-toluenesulfonic acid salt as a amorphous solid. ^{1}H NMR (DMSO-d6): δ 10.60 (s, 1H), 10.07 (bs, 1H), 9.60 (bs, 1H), 8.15 (d, 1H, J= 5.1 Hz), 7.44 (dd, 2H, J= 1.2 and 6.0 Hz), 7.28 (m, 1H), 7.16 (m, 1H), 7.10 (dd, 2H, J= 1.2 and 6.0 Hz), 6.85 (, d, 1H, J= 8.4 Hz), 6.74 (t, 2H, 2.8 Hz), 6.19 (t, 1H, J= 2.8 Hz), 3.64 (s, 6H), 2.28 (s, 3H), 1.41 (s, 6H); LCMS: purity: 100%; MS (m/e): 440 (MH^+ for parent base).
7.4.83	N2-(3,5-Dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine Methanesulfonic Acid Salt (R927071)	In like manner to the preparation of N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine p-toluenesulfonic acid salt, the reaction of N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine with methanesulfonic acid gave N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine methanesulfonic acid salt. LCMS: purity: 98%; MS (m/e): 440 (MH^+; for parent base).
7.4.84	N2-(3,5-Dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine Benzenesulfonic Acid Salt (R927072)	In like manner to the preparation of N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine p-toluenesulfonic acid salt, the reaction of N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine with benzenesulfonic acid gave N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine benzenesulfonic acid salt. ^{1}H NMR (DMSO-d6): δ 10.61 (s, 1H), 10.00 (bs, 1H), 9.57 (bs, 1H), 8.15 (d, 1H, J= 4.5 Hz), 7.57 (m, 2H), 7.28 (m, 3H), 7.16 (bs, 1H), 6.86 (d, 1H, J= 8.4 Hz), 7.76 (bs, 1H), 6.17 (d, 1H, J= 2.1 Hz), 3.64 (s, 6H), 1.41 (s, 6H); LCMS: purity: 100%; MS (m/e): 440 (MH^+; for parent base).

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Section Number	Name of compound and reference number	Experimental
7.4.85	N2-(3,5-Dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine Hydrogen Chloride Salt (R927073)	In like manner to the preparation of N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine p-toluenesulfonic acid salt, the reaction of N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine with hydrogen chloride (4M, dioxane) gave N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine hydrogen chloride salt. LCMS: purity: 100%; MS (m/e): 440 (MH^+; for parent base).
7.4.86	N2-(3,5-Dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine DL-Camphoursulfonic Acid Salt (R927074)	In like manner to the preparation of N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine p-toluenesulfonic acid salt, the reaction of N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine with DL-camphoursulfonic acid gave N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine DL-camphoursulfonic acid salt. ^{1}H NMR (DMSO-d6): δ 10.59 (s, 1H), 10.10 (bs, 1H), 9.65 (bs, 1H), 8.17 (d, 1H, J= 4.5 Hz), 7.27 (m, 1H), 7.15 (bs, 1H), 6.86 (d, 1H, J= 8.4 H), 6.74 (d, 1H, J= 2.1 Hz), 6.19 (m, 1H), 3.64 (s, 6H), 2.89 (d, 1H, J= 11.7 Hz), 2.66 (m, 1H), 2.48 (m, 2H), 2.40 (d, 1H, J= 14.7 Hz), 2.23 (dt, 1H, J= 3.3 and 18.3 Hz), 1.94 (m, 1H), 1.85 (m, 2H), 1.41 (s, 6H), 1.25 (m, 2H), 1.05 (s, 3H), 0.75 (s, 3H); LCMS: purity: 100%; MS (m/e): 440 (MH^+; for parent base).
7.4.87	N2-(3,5-Dimethylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine p-Tolunesulfonic Acid Salt (R927075)	In like manner to the preparation of N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine p-toluenesulfonic acid salt, the reaction of N2-(3,5-dimethylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine with p-toluenesulfonic acid gave N2-(3,5-dimethylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine p-toluenesulfonic acid salt. ^{1}H NMR (DMSO-d6): δ 10.65 (s, 1H), 9.95 (bs, 1H), 9.40 (bs, 1H), 8.13 (d, 1H, J= 4.8 Hz), 7.45 (d, 2H, J= 7.8 Hz), 7.26 (m, 1H), 7.14 (bs, 1H), 7.09 (d, 2H, J= 7.8 Hz), 6.89 (d, 1H, J= 8.7 Hz), 6.63 (bs, 1H), 2.28 (s, 3H), 2.16 (s, 6H), 1.40 (s, 6H); LCMS: purity: 100%; MS (m/e): 408 (MH^+; for parent base).

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Section Number	Name of compound and reference number	Experimental
7.4.88	N2-(3,5-Dimethylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine Benzenesulfonic Acid Salt (R927076)	In like manner to the preparation of N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine p-toluenesulfonic acid salt, the reaction of N2-(3,5-dimethylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine with benzenesulfonic acid gave N2-(3,5-dimethylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine benzenesulfonic acid salt. ^{1}H NMR (DMSO-d6): δ 10.67 (s, 1H), 10.12 (bs, 1H), 9.55 (s, 1H), 8.15 (d, 1H, J= 4.8 Hz), 7.57 (m, 2H), 7.28 (m, 4H), 7.11 (bs, 3H), 6.90 (d, 1H, J= 8.4 Hz), 6.66 (bs, 1H), 1.40 (s, 6H); LCMS: purity: 100%; MS (m/e): 408 (MH^+; for parent base).
7.4.89	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-(indol-6-yl)-2,4-pyrimidinediamine p-Toluenesulfonic Acid Salt (R927087)	In like manner to the preparation of N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-4H-benz[1,4-oxazin-3-oxo-6-yl)-5-fluoro-2,4-pyrimidinediamine p-toluenesulfonic acid salt, the reaction of N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(indol-6-yl)-2,4-pyrimidinediamine with p-toluenesulfonic acid gave N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(indol-6-yl)-2,4-pyrimidinediamine p-toluenesulfonic acid salt. LCMS: purity: 100%; MS (m/e): 384 (MH^+; for parent base).
7.4.90	N4-(3,4-Ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine p-Toluenesulfonic Acid Salt (R927090)	In like manner to the preparation of N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-4H-benz[1,4-oxazin-3-oxo-6-yl)-5-fluoro-2,4-pyrimidinediamine p-toluenesulfonic acid salt, the reaction of N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine with p-toluenesulfonic acid gave N4-(3,4-ethylendioxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine p-toluenesulfonic acid salt. ^{1}H NMR (DMSO-d6): δ 9.99 (bs, 1H), 9.79 (bs, 1H), 8.14 (d, 1H, J= 4.8 Hz), 7.97 (bd, 1H, J= 5.1 Hz), 7.44 (dd, 2H, J= 2.4 and 9.0 Hz), 7.25 (m, 1H), 7.14 (m, 5H), 6.80 (d, 1H, J= 8.4 Hz), 6.64 (m, 1H), 4.36 (s, 2H), 4.22 (s, 4H), 2.64 (d, 3H, J= 4.8 Hz), 2.28 (s, 3H); LCMS: purity: 100%; MS (m/e): 426 (MH^+; for parent base).
	Synthesis of Anilines and mono SNAr Products	
7.4.91	2-Isopropoxy-5-nitropyridine	A solution of 2-bromo-5-nitropyridine (1.0g, 4.9 mmol), potassium t-butoxide (6.9 ml, 6.9 mmol, 1N solution in THF), and isopropyl alcohol (75 mL) was heated at 75°C for 2 days. The reaction mixture was concentrated in vacuo and the residue suspended in water and sonicated at room temperature for several minutes. The product was collected as a tan solid by filtration. ^{1}H NMR ($CDCl_3$): δ 9.06 (d, J= 3.0 Hz, 1H), 8.31 (dd, J= 3.0 and 9.3 Hz, 1H), 6.73 (d, J= 9.3 Hz, 1H), 5.43 (quintet, J= 5.7 Hz, 1H), and 1.37 (d, J= 6.3 Hz, 1H).

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Section Number	Name of compound and reference number	Experimental
7.4.92	5-Amino-2-isopropoxypyridine	In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of 2-isopropoxy-5-nitropyridine was carried out to prepare 5-amino-2-isopropoxypyridine. ^{1}H NMR ($CDCl_3$): δ 7.65 (d, J= 2.7 Hz, 1H), 7.01 (dd, J= 3.0 and 8.7 Hz, 1H), 6.54 (d, J= 9.0 Hz, 1H), 5.13 (quintet, J= 6.6 Hz, 1H), 3.20 (bs, 2H), and 1.32 (d, J= 6.6 Hz, 6H).
7.4.93	2-Chloro-5-fluoro-N4-(2-isopropoxypyridin-5-yl)-4-pyrimidineamine	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-amino-2-isopropoxypyridine were reacted to provide 2-chloro-5-fluoro-N4-(2-isopropoxypyridin-5-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.30 (d, J= 3.0 Hz, 1H), 8.06 (d, J= 2.1 Hz, 1H), 6.81 (bs, 1H), 6.75 (d, J= 9.0 Hz, 1H), 5.27 (quintet, J= 6.6 Hz, 1H), and 1.35 (d, J= 6.6 Hz, 6H).
7.4.94	3-Chloro-4-(N-morpholino)nitrobenzene	A mixture of 2-chloro-4-fluoronitrobenzene (1.36g, 7.72 mmol) and morpholine (8.0 mL, 90 mmol) was heated at 80°C for 3 hours. The reaction mixture was poured into water (150 mL) and the product collected as a yellow solid after filtration. ^{1}H NMR ($CDCl_3$): δ 8.26 (d, J= 3.0 Hz, 1H), 8.11 (dd, J= 3.0 ad 9.3 Hz, 1H), 7.05 (d, J= 8.7 Hz, 1H), 3.91-3.87 (m, 4H), and 3.23-3.19 (m, 4H).
7.4.95	3-Chloro-4-(N-morpholino)aniline	To a solution of 3-chloro-4-(N-morpholino)nitrobenzene (1.0g, 4.1 mmol) in ethanol/water (70 mL, 2:1) was added iron powder (1.4g, 25 mmol) followed by NH_4Cl (0.46g, 8.6 mmol). The reaction mixture was stirred at room temperature for 10 minutes and then heated at 70°C for 1.5h. After cooling to room temperature, the reaction mixture was filtered through celite and the filter cake was washed with methanol. Concentration of the filtrate in vacuo gave a white solid, which was dissolved in ethyl acetate and washed with $NaHCO_3$ (aq) and brine. The organic layer was then dried ($MgSO_4$), filtered, and concentrated in vacuo to give the product as a white solid. ^{1}H NMR ($CDCl_3$): δ 6.98-6.91 (m, H), 6.82 (bs, 1H), 6.67-6.61 (m, 1H), 3.90-3.82 (m, 4H), and 3.02-2.90 (m, 4H).
7.4.96	2-Chloro-N4-[3-chloro-4-(N-morpholino)phenyl]-5-fluoro-4-pyrimidineamine	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloro-4-(N-morpholino)aniline were reacted to provide 2-chloro-N4-[3-chloro-4-(N-morpholino)phenyl]-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.09 (d, J= 2.4 Hz, 1H), 7.75 (d, J= 3.0 Hz, 1H), 7.55 (dd, J= 2.7 and 8.7 Hz, 1H), 7.32 (d, J= 8.7 Hz, 1H), 6.92 (bs, 1H), 3.99-3.92 (m, 4H), and 3.21-3.14 (m, 4H).

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Section Number	Name of compound and reference number	Experimental
7.4.97	3-Chloro-4-isopropoxynitrobenzene	In a like manner to the preparation of 2-isopropoxy-5-nitropyridine, 3-chloro-4-fluoronitrobenzene was reacted with isopropanol and potassium t-butoxide to provide 3-chloro-4-isopropoxynitrobenzene. ^{1}H NMR ($CDCl_3$): δ 8.26 (d, J= 3.0 Hz, 1H), 8.11 (dd, J= 3.0 and 8.7 Hz, 1H), 6.97 (d, J= 8.7 Hz, 1H), 4.71 (quintet, J= 6.0 Hz, 1H), and 1.43 (d, J= 6.0 Hz, 6H).
7.4.98	3-Chloro-4-isopropoxyaniline	In a like manner to the preparation of 3-chloro-4-(N-morpholino)aniline, 3-chloro-4-isopropoxynitrobenzene was reduced to provide 3-chloro-4-isopropoxyaniline. ^{1}H NMR (DMSO-d_6): δ 6.80 (d, J= 8.7 Hz, 1H), 6.59 (d, J= 2.4 Hz, 1H), 6.43 (dd, J= 3.0, 8.7 Hz, 1H), 4.92 (bs, 2H), 4.24 (quintet, J= 5.7 Hz, 1H), and 1.18 (d, J= 5.7 Hz, 6H).
7.4.99	2-Chloro-N4-(3-chloro-4-isopropoxyphenyl)-5-fluoro-4-pyrimidineamine	In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloro-4-isopropoxyaniline were reacted to provide 2-chloro-N4-(3-chloro-4-isopropoxyphenyl)-5-fluoro-4-pyrimidineamine ^{1}H NMR ($CDCl_3$): δ 8.04 (d, J= 3.0 Hz, 1H), 7.61 (d, J= 2.7 Hz, 1H), 7.48 (dd, J= 3.0 and 8.7 Hz, 1H), 6.99-6.93 (m, 2H), 4.52 (quintet, J= 6.0 Hz, 1H), 1.37 (d, J= 6.0 Hz, 6H); ^{19}F NMR (282 MHz, $CDCl_3$): -158.12; LCMS: purity: 94%; MS (m/e): 317 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.100	5-Amino-2-(N,N-dimethylaminomethyl)benzofuran	Borane-methyl sulfide complex (4.0 mL, 43 mmole) was added to a suspension of 2-[(N,N-dimethylamino)carbonyl]-5-nitrobenzofuran (1.0 g, 43 mmole) in anhydrous THF (10 mL). The reaction mixture was heated at reflux for 3h. Upon cooling, the solvent was removed in vacuo to give a gel-like solid. Cold (0 °C) methanol (50 mL) was cautiously added dropwise and the resulting mixture was heated at 80 °C for 30 min providing a clear yellow solution. The solvent was removed in vacuo and the resulting solid was suspended in methanol (50 mL) and HCl (1.5 mL, 4N in dioxane) was added. After heating at 80 °C for 30 min the solvent was removed under reduced pressure to give an amorphous solid. The solid was dissolved in methanol (20 mL) and ammonia (2N in methanol) was added until basic. A precipitate formed after dilution with dichloromethane (50 mL). Filtration and concentration gave crude 2-(N,N-dimethylaminomethyl)-5-nitrobenzofuran as a yellow oil (1.0g) which was used without further purification. To a suspension of crude 2-(N,N-dimethylaminomethyl)-5-nitrobenzofuran (1.0 g) in methanol (degassed, 60 mL) was added $Na_2S_2O_4$ (0.50 g) and 10% Pd/C (100 mg). The reaction mixture was stirred under an atmosphere of H_2 for 10h. Solids were removed by filtration through Celite® filter aid, and the filter cake was washed several times with methanol. Concentration gave dark yellow oil. The product, 5-amino-2-(N,N-dimethylaminomethyl)benzofuran, was obtained after purification by column chromatography over silica gel (mobile phase: 0% to 5% Methanol (containing 2N NH_3)/dichloromethane). ^1H NMR (CD_3OD): δ 7.24 (d, 1H, J= 8.7 Hz), 6.91 (d, 1H, J= 2.4 Hz), 6.76 (dd, 1H, J= 2.4 and 8.7 Hz), 6.65 (s, 1H), 3.87 (s. 2H), 2.48 (s, 6H).
	Bis-SNAr and Subsequent Reactions	
7.4.101	(±) N2-(2-Carboxyl-2,3-dihydrobenzofuran-5-yl)-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926957)	The reaction of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(2-methoxycarbonyl-2,3-dihydrobenzofuran-5-yl)-2,4-pyrimidinediamine and lithium hydroxide(LiOH) in THF:H_2O at room temperature followed by acidification with 2N HCl aqueous solution gave N2-(2-carboxyl-2,3-dihydrobenzofuran-5-yl)-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.62 (s, 1H), 9.14 (s, 1H), 8.11 (dd, J= 3.6 and 7.5 Hz, 2H), 7.81 (dd, J= 3.0 and 9.3 Hz, 1H), 7.49-7.44 (m, 2H), 7.22 (dd, J= 2.4 and 8.1 Hz, 1H), 6.72 (d, J= 9.0 Hz, 1H), 5.21-5.13 (m, 1H), 3.48 (dd, J= 10.5 and 15.6 Hz, 1H), 3.17 (dd, J= 6.0 and 15.6 Hz, 1H); LCMS: purity: 98%; MS (m/e): 486 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.102	(±) N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2-(N-2,3-dihydroxypropylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine (R926958)	In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, racemic N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(2-methoxycarbonyl-2,3-dihydrobenzofuran-5-yl)-2,4-pyrimidinediamine and racemic 2,3-dihydroxypropyl amine were reacted to provide a mixture of two racemates of N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2-(N-2,3-dihydroxypropylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.06 (d, J= 2.4 Hz, 1H), 7.92 (dd, J= 2.4 and 4.2 Hz, 1H), 7.68 (dd, J= 3.0 and 9.3 Hz, 1H), 7.41-7.37 (m, 1H), 7.34-7.29 (m, 1H), 7.26-7.19 (m, 1H), 6.82 (d, J= 8.7 Hz, 1H), 5.18-5.11 (m, 1H), 3.74-3.66 (m, 1H), 3.60-3.52 (m, 1H), 3.50-3.42 (m, 2H), 3.38-3.35 (m, 1H), 3.21 (dd, J= 7.2 and 13.5 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD): -169.15, -60.23; LCMS: purity: 98%; MS (m/e): 559 (MH^+).
7.4.103	(±) N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2-(N-2-hydroxyethylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine (R926959)	In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, racemic N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(2-methoxycarbonyl-2,3-dihydrobenzofuran-5-yl)-2,4-pyrimidinediamine and ethanolamine were reacted to provide (±) N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2-(N-2-hydroxyethylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.65-8.05 (m, 1H), 7.94-7.90 (m, 1H), 7.68 (dd, J=3.0 and 9.3 Hz, 1H), 7.39-7 35 (m, 1H), 7.31 (dd, J= 1.2 and 8.7 Hz, 1H), 6.82 (d, J= 8.1 Hz, 1H), 5.18-5.10 (m, 1H), 3.64-3.21 (m, 7H); ^{19}F NMR (282 MHz, CD_3OD): -169.19, -60.24; LCMS: purity: 98%; MS (m/e): 529 (MH^+).
7.4.104	(±) N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2-(N-2-hydroxyethyl-N-methylamino]carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine (R926960)	In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, racemic N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(2-methoxycarbonyl-2,3-dihydrobenzofuran-5-yl)-2,4-pyrimidinediamine and N-methylethanolamine were reacted to provide (±) N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2-(N-2-hydroxyethyl-N-methylamino]carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine. LCMS: purity: 95%; MS (m/e): 543 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.105	N4-(3-Chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2-(N-isopropylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine (R926961)	In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, racemic N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-(2-methoxycarbonyl-2,3-dihydrobenzofuran-5-yl)-2,4-pyrimidinediamine and isopropyl amine were reacted to provide (±) N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-N2-[2-(N-isopropylamino)carbonyl-2,3-dihydrobenzofuran-5-yl]-2,4-pyrimidinediamine. LCMS: purity: 94%; MS (m/e): 526 (MH^+).
7.4.106	5-Fluoro-N4-(2-isopropoxypyridin-5-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926962)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-5-fluoro-N4-(2-isopropoxypyridin-5-yl)-4-pyrimidineamine with 3-(N-methylamino)carbonylmethyleneoxyaniline in isopropanol gave 5-fluoro-N4-(2-isopropoxypyridin-5-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d_6): δ 9.34 (s, 1H), 9.22 (s, 1H), 8.60-8 56 (m, 1H), 8.07 (d, 3.6 Hz, 1H), 8.02-7.92 (m, 2H), 7.36 (bs, 1H), 7.25 (d, J= 8.4 Hz, 1H), 7.08 (t, J= 8.1 Hz, 1H), 6.72 (d, J= 8.7 Hz, 1H), 6.46 (dd, J= 2.1 and 8.1 Hz, 1H), 5.17 (quintet, J= 6.3 Hz, 1H), 4.34 (s, 2H), 2.63 (d, J= 3.9 Hz, 3H), 1.27 (d, J= 6.6 Hz, 6H); LCMS: purity: 93%; MS (m/e): 427 (MH^+).
7.4.107	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926963)	In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and ethanolamine were reacted to provide N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[3-(N-2-hydroxyethylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.90 (d, J= 3.3 Hz, 1H), 7.76 (d, J= 3.3 Hz, 1H), 7.54 (dd, J= 2.1 and 8.7 Hz, 1H), 7.34-7.29 (m, 1H), 7.17-7.14 (m , 2H), 7.03 (d, J= 8.7 Hz, 1H), 6.62-6.56 (m, 1H), 4.39 (s, 2H), 3.87 (s, 3H), 3.62 (t, J= 5.7 Hz, 2H), 3.40 (t, J= 5.7 Hz, 2H); ^{19}F NMR (282 MHz, CD_3OD): -168.65; LCMS: purity: 97%; MS (m/e): 462 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.108	(±) N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926964)	In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and racemic 2,3-dihydroxypropyl amine were reacted to provide (±) N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[3-(N-2,3-dihydroxypropylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.35 (s, 1H), 9.23 (s, 1H), 8.09 (d, J= 4.2Hz, 1H), 7.87-7.78 (m, 2H), 7.70 (dd, J= 2.4 and 9.0 Hz, 1H), 7.32-7.27 (m, 2H), 7.15-7.08 (m, 2H), 6.48 (dd, J= 2.4 and 9.0 Hz, 1H), 4.38 (s, 2H), 3.82 (s, 3H), 3.55-3.21 (m, 5H), 3.08-2.98 (m, 2H); LCMS: purity: 98%; MS (m/e): 493(MH^+).
7.4.109	N2,N4-Bis(4-benzyloxy-3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R926965)	In a like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloro-4-benzyloxyaniline were reacted to provide N2,N4-bis(4-benzyloxy-3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.43 (s, 1H), 9.27 (s, 1H), 8.09 (d, J= 4.2 Hz, 1H), 7.76 (dd, J= 2.1 and 5.4 Hz, 2H), 7.62 (dd, J= 2.4 and 9.6 Hz, 1H), 7.48-7.29 (m, 11H), 7.17 (d, J= 8.7 Hz, 1H), 7.09 (d, J= 8.7 Hz, 1H), 5.18 (s, 2H), 5.12 (s, 2H); LCMS: purity: 97%; MS (m/e): 562 (MH^+).
7.4.110	N4-(4-Benzyloxy-3-chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926966)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of N4-(4-benzyloxy-3-chlorophenyl)-2-chloro-5-fluoro-4-pyrimidineamine with 3-[(N-methylamino)carbonylmethyleneoxy]aniline gave N4-(4-benzyloxy-3-chlorophenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.64 (s, 1H), 9.53 (s, 1H), 8.13 (d, J= 4.2 Hz, 1H), 7.99-7.94 (m, 1H), 7.81 (d, J= 2.4 Hz, 1H), 7.67 (dd, J= 2.7 and 8.7 Hz, 1H), 7.48-7.07 (m, 9H), 6.52 (dd, J= 1.8 and 8.1 Hz, 1H), 5.18 (s, 2H), 4.35 (s, 2H), 2.62 (d, J= 4.8 Hz, 3H); LCMS: purity: 98%; MS (m/e): 509(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.111	N4-(3-Chloro-4-methoxyphenyl)-N2-[3-(N-cyclopropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R926967)	In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and cyclopropylamine were reacted to provide N4-(3-chloro-4-methoxyphenyl)-N2-[3-(N-cyclopropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.88 (s, 1H), 9.70 (s, 1H), 8.17 (d, J= 4.8 Hz, 1H), 8.06 (d, J= 3 9 Hz, 1H), 7.79-7.76 (m, 1H), 7.65 (dd, J= 2.4 and 8.1 Hz, 1H), 7.22-7.11 (m, 4H), 6.57-6.52 (m, 1H), 4.32 (s, 2H), 3.82 (s, 3H), 2.69-2.61 (m, 1H), 0.63-0.56 (m, 2H), 0.47-0.43 (m, 2H); LCMS: purity: 92%; MS (m/e): 459 (MH^+).
7.4.112	N2-(3-Chloro-4-hydroxy-5-methylphenyl)-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926968)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine with 3-chloro-4-hydroxy-5-methylaniline gave N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.49 (s, 1H), 9.17 (s, 1H), 8.66 (m, 1H), 8.07 (d, J= 4.2 Hz, 1H), 7.71-7.62 (m, 2H), 7.46 (bs, 1H), 7.18 (bs, 1H), 7.09 (d, J= 9.0, 1H), 3.82 (s, 3H), 2.09 (s, 3H); LCMS: purity: 95%; MS (m/e): 410 (MH^+).
7.4.113	N4-(3-Chloro-4-methoxyphenyl)-N2-[3-(N-cyclobutylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R926969)	In a like manner to the preparation of N4-(3,5-dichloro-4-hydroxyphenyl)-5-fluoro-N2-[3-(N-morpholino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine and cyclobutylamine were reacted to provide N4-(3-chloro-4-methoxyphenyl)-N2-[3-(N-cyclobutylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.52 (s, 1H), 9.37 (s, 1H), 8.21 (d, J= 7.8 Hz, 1H), 8.11 (d, J= 3.3 Hz, 1H), 7.79 (d, J= 3.3 Hz, 1H), 7.69 (dd, J= 2.4 and 9.6 Hz, 1H), 7.27-7.22 (m, 2H), 7.16-7.08 (m, 2H), 6.50 (dd, J= 2.4 and 8.1 Hz, 1H), 4.32 (s, 2H), 4.24 (q, 8.1 Hz, 1H), 3.82 (s, 3H), 2.18-2.05 (m, 2H), 2.00-1.89 (m, 2H), 1.64-1.53 (m, 2H); LCMS: purity: 95%; MS (m/e): 473(MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.114	N4-(2,2-Difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926970)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine with 3,5-dimethoxyaniline gave N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 11.92 (s, 1H), 9.55 (s, 1H), 9.09 (s, 1H), 8.12 (d, J= 6.0 Hz, 1H), 7.52-7.46 (m, 2H), 7.22 (d, J= 8.7 Hz, 1H), 6.91 (d, J= 2.4 Hz, 1H), 6.05 (t, J= 2.4 Hz, 1H), 3.61 (s, 6H); ^{19}F NMR (282 MHz, DMSO-d_6): -164.56, -76.64; LCMS: purity: 98%; MS (m/e): 448 (MH^+).
7.4.115	N2-(3-Chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R926971)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine with 3-chloro-4-hydroxy-5-methylaniline gave N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 11.95 (s, 1H), 9.50 (s, 1H), 9.00 (s, 1H), 8.56 (s, 1H), 8.09 (d, J= 3.6 Hz, 1H), 7.57 (d, J= 2.4 Hz, 1H), 7.49-7.40 (m, 2H), 7.24 (s, 1H), 7.22-7.19 (m, 1H), 2.07 (s, 3H); ^{19}F NMR (282 MHz, DMSO-d_6): --165.46, -76.51; LCMS: purity: 94%; MS (m/e): 453 (MH^+).
7.4.116	N4-(3-Chloro-4-methoxyphenyl)-N2-(3-chloro-4-methoxy-5-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926972)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine with 3-chloro-4-methoxy-5-methylaniline gave N4-(3-chloro-4-methoxyphenyl)-N2-(3-chloro-4-methoxy-5-methylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.38 (s, 1H), 9.25 (s, 1H), 8.09 (d, J= 3.6 Hz, 1H), 7.70 (d, J= 2.4, 1H), 7.66-7.58 (m, 2H), 7.33 (d, J= 2.4 Hz, 1H), 7.11 (d, J= 8.7 Hz, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 2.14 (s, 3H); LCMS: purity: 94%; MS (m/e): 424 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.117	N4-(3-Chloro-4-isopropoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R926973)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-isopropoxyphenyl)-5-fluoro-4-pyrimidineamine. with 3-(N-methylamino)carbonylmethyleneoxyaniline gave N4-(3-chloro-4-isopropoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.30 (s, 1H), 9.21 (s, 1H), 8.08 (d, J= 3.6 Hz, 1H), 7.95-7.88 (m, 1H), 7.81-7.79 (m, 1H), 7.69 (dd, J= 3.0 and 8.7 Hz, 1H), 7.32-7.28 (m, 2H), 7.13-7.07 (m, 2H), 6.49-6.44 (m, 1H), 4.57 (quintet, J= 6.0 Hz, 1H), 4.34 (s, 2H), 2.63 (d, J= 4.8 Hz, 3H), 1.26 (d, J= 6.0 Hz, 6H); LCMS: purity: 99%; MS (m/e): 461 (MH^+).
7.4.118	N4-(3-Chloro-4-methoxy-5-methylphenyl)-5-fluoro-N2-[3-[(N-methylamino)carbonylmethyleneoxy]phenyl]-2,4-pyrimidinediamine (R926974)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-methoxy-5-methylphenyl)-5-fluoro-4-pyrimidineamine with 3-(N-methylamino)carbonylmethyleneoxyaniline gave N4-(3-chloro-4-methoxy-5-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.01 (d, J= 5.4 Hz, 1H), 7.60 (d, J= 2.4 Hz, 1H), 7.40-7.29 (m, 2H), 7.10-7.04 (m, 2H), 6.89-6.84 (m, 1H), 4.38 (s, 2H), 3.79 (s, 3H), 2.79 (s, 3H), 2.25 (s, 3H); LCMS: purity: 96%; MS (m/e): 447(MH^+).
7.4.119	N4-(3,4-Dichlorophenyl)-5-fluoro-N2-(indol-6-yl)-2,4-pyrimidinediamine (R926975)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine with 6-aminoindole gave N4-(3,4-dichlorophenyl)-5-fluoro-N2-(indol-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.99 (d, J= 2.4, 1H), 7.91 (d, J= 3.6 Hz, 1H), 7.72 (dd, J= 3.0 and 8.7 Hz, 1H), 7.60 (d, J= 1.2 Hz, 1H), 7.46 (d, J= 8.7 Hz, 1H), 7.25 (d, J= 9.0 Hz, 1H), 7.17 (d, J= 3.0 Hz, 1H), 7.06 (dd, J= 1.8 Hz, 1H), 6.40 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, CD_3OD): -169.48; LCMS: purity: 96%; MS (m/e): 390 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.120	N4-(3-Chloro-4-methoxyphenyl)- 5-fluoro-N2-(indol-6-yl)-2,4-pyrimidinediamine (R926976)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine with 6-aminoindole gave N4-(3-chloro-4-methoxyphenyl)- 5-fluoro-N2-(indol-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.82 (s, 1H), 9.22 (s, 1H), 9.02 (s, 1H), 8.05 (d, J= 3.6 Hz, 1H), 7.85 (d, J= 2.4 Hz, 1H), 7.81-7.76 (m, 2H), 7.36 (d, J= 8.7 Hz, 1H), 7.21 (d, J= 1.8 Hz, 1H), 7.19-7.15 (m, 1H), 7.03 (d, J= 8.7 Hz, 1H), 6.30 (bs, 1H), 3.81 (s, 3H); LCMS: purity: 93%; MS (m/e): 384(MH^+).
7.4.121	N4-(2,2-Difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(indol-6-yl)-2,4-pyrimidinediamine (R926977)	In a like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine with 6-aminoindole gave N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(indol-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 11.91 (s, 1H), 10.83 (s, 1H), 9.48 (s, 1H), 8.91 (s, 1H), 8.09 (d, J= 3.6 Hz, 1H), 7.84 (bs, 1H), 7.68 (dd, J= 3.0 and 9.3 Hz, 1H), 7.54-7.51 (m, 1H), 7.34 (d, J= 8.7 Hz, 1H), 7.20 (s, 1H), 7.18-7.14 (m, 2H), 6.32-6.28 (m, 1H); LCMS: purity: 98%; MS (m/e): 427 (MH^+).
7.4.122	N4-(3-Chloro-4-methoxyphenyl)-N2-[2-(N,N-dimethylaminomethyl)benzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R926978)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 5-amino-2-(N,N-dimethylaminomethyl)benzofuran were reacted to provide N4-(3-chloro-4-methoxyphenyl)-N2-[2-(N,N-dimethylaminomethyl)benzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.27 (s, 1H), 9.15 (s, 1H), 8.06 (d, J= 3.6 Hz, 1H), 7.85 (s, 1H), 7.79 (d, J= 3.0 Hz, 1H), 7.69-7.63 (m, 1H), 7.35 (bs, 1H), 7.07 (d, J= 8.7 Hz, 1H), 6.59 (s, 1H), 3.83 (s, 3H), 3.56 (s, 2H), 2.21 (s, 6H); LCMS: purity: 97%; MS (m/e): 443 (MH^+).
7.4.123	N4-(2,2-Difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[2-(N,N-dimethylaminomethyl)benzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R926979)	In like manner to the preparation 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 5-amino-2-(N,N-dimethylaminomethyl)benzofuran were reacted to provide N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[2-(N,N-dimethylaminomethyl)benzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 99%; MS (m/e): 483 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.124	N4-(3,4-Dichlorophenyl)-N2-[2-(N,N-dimethylaminomethyl)benzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R926980)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine and 5-amino-2-(N,N-dimethylaminomethyl)benzofuran were reacted to provide N4-(3,4-dichlorophenyl)-N2-[2-(N,N-dimethylaminomethyl)benzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.99 (bs, 1H), 7.89 (d, J= 2.4 Hz, 1H), 7.72 (d, J= 2.4 Hz, 1H), 7.43 (d, J= 8.7 Hz,, 1H), 7.40-7.33 (m, 2H), 7.26 (dd, J= 1.8 and 8.7 Hz, 1H), 6.97 (s, 1H), 6.75 (d, J= 2,4 Hz, 1H), 6.58 (s, 1H), 3.67 (s, 2H), 2.38 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$): -47438; LCMS: purity: 94%; MS (m/e): 445 (M-1).
7.4.125	N2-(3-Chloro-4-methoxyphenyl)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R926981)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and 3-chloro-4-methoxyaniline were reacted to provide N2-(3-chloro-4-methoxyphenyl)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 12.07 (s, 1H), 10.09 (s, 1H), 9.75 (s, 1H), 8.20 (d, J= 4.2 Hz, 1H), 7.75 (d, J= 2.4 Hz, 1H), 7.52 (bs, 1H), 7.44-7.34 (m, 2H), 7.27 (d, J= 8.7 Hz, 1H), 7.03 (d, J= 9.3 Hz, 1H), 3.77 (s, 3H); LCMS: purity: 96%; MS (m/e): 453 (MH^+).
7.4.126	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(indol-6-yl)-2,4-pyrimidinediamine (R926982)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 6-aminoindole were reacted to provide N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(indol-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.81 (s, 1H), 10.54 (s, 1H), 9.24 (s, 1H), 8.81 (s, 1H), 8.03 (d, J= 3.3 Hz, 1H), 7.81 (bs, 1H), 7.45-7.38 (m, 1H), 7.34-7.31 (m, 2H), 7.21-7.14 (m, 2H), 6.83 (d, J= 9.0 Hz, 1H), 6.28 (d, J= 2.4 Hz, 1H), 1.38 (s, 3H); LCMS: purity: 98%; MS (m/e): 419 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.127	N4-(2,2-Difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[2-(N,N-dimethylaminocarbonyl)-2,3-dihydrobenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine (R926983)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 5-amino-2-(N,N-dimethylaminocarbonyl)-2,3-dihydrobenzofuran were reacted to provide N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[2-(N,N-dimethylaminocarbonyl)-2,3-dihydrobenzofuran-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 12.09 (s, 1H), 10.15 (s, 1H), 9.59 (s, 1H), 8.15 (d, J= 3.9 Hz, 1H), 7.52-7.39 (m, 3H), 7.26 (d, J= 8.7 Hz, 1H), 7.13 (d, J= 8.4 Hz, 1H), 6.69 (d, J= 8.7 Hz, 1H), 5.64-5.57 (m, 1H), 3.43-3.27 (m, 2H), 3.06 (s, 3H), 2.85 (s, 3H); LCMS: purity: 96%; MS (m/e): 501(MH^+).
7.4.128	N4-(2,2-Difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(3-methoxy-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926984)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3-methoxy-5-trifluoromethylaniline were reacted to provide N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(3-methoxy-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 11.92 (s, 1H), 9.61 (s, 1H), 9.50 (s, 1H), 8.18 (d, J= 3.6 Hz, 1H), 7.65 (s, 1H), 7.59 (s, 1H), 7.48-7.41 (m, 2H), 7.22 (d, J= 8.7 Hz, 1H), 6.71 (bs, 1H), 3.70 (s, 3H); ^{19}F NMR (282 MHz, DMSO-d_6): -163.55, -76.50, -61.83; LCMS: purity: 98%; MS (m/e): 486 (MH^+).
7.4.129	N2-(3,5-Dichlorophenyl)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R926985)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3,5-dichloroaniline were reacted to provide N2-(3,5-dichlorophenyl)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 11.95 (bs, 1H), 9.65 (d, J= 3.3 Hz, 2H), 8.19 (d, J= 3.9 Hz, 1H), 7.71 (d, J= 1.8 Hz, 2H), 7.41-7.35 (m, 2H), 7.27 (d, J= 9.3 Hz, 1H), 6.99 (t, J= 1.8 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): -163.24, -76.23; LCMS: purity: 92%; MS (m/e): 457 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.130	N4-[3-Chloro-4-(N-morpholino)phenyl]-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926986)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-[3-chloro-4-(N-morpholino)phenyl]-5-fluoro-4-pyrimidineamine and 3,5-dimethoxyaniline were reacted to provide N4-[3-chloro-4-(N-morpholino)phenyl]-5-fluoro-N2-(3,5-dimethoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.80 (bs, 1H), 9.53 (bs, 1H), 8.16 (d, J= 4.2 Hz, 1H), 7.78-7.71 (m, 2H), 7.10 (d, J= 8.7 Hz, 1H), 6.81 (bs, 2H),6.16-6.11 (m, 1H), 3.75-3.71 (m, 4H), 3.63 (s, 6H), 2.96-2.91 (m, 4H); LCMS: purity: 95%; MS (m/e): 460 (MH^+).
7.4.131	N4-[3-Chloro-4-(N-morpholino)phenyl]-5-fluoro-N2-(3-methoxy-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926987)	In like manner to the preparation of 5-fluoro-N4-(3-hydroxyphenyl)-N2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-2,4-pyrimidinediamine, 2-chloro-N4-[3-chloro-4-(N-morpholino)phenyl]-5-fluoro-4-pyrimidineamine and 3-methoxy-5-trifluoromethylaniline were reacted to provide N4-[3-chloro-4-(N-morpholino)phenyl]-5-fluoro-N2-(3-methoxy-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.53 (s, 1H), 9.45 (s, 1H), 8.16 (d, J= 3.6 Hz, 1H), 7.77-7.73 (m, 2H), 7.64-7.57 (m, 2H), 7.10 (d, J= 8.7 Hz, 1H), 6.72 (bs, 1H), 3.76-3.70 (m, 7H), 2.95-2.91 (m, 4H); ^{19}F NMR (282 MHz, DMSO-d_6): -163.57, -61.62; LCMS: purity: 99%; MS (m/e): 498 (MH^+).
7.4.132	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine p-Toluenesulfonic Acid Salt (R926989)	In a like manner to the preparation of N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-4H-benz[1,4-oxazin-3-oxo-6-yl)-5-fluoro-2,4-pyrimidinediamine p-toluenesulfonic acid salt, N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine was reacted with p-toluenesulfonic acid monohydrate to provide N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine p-toluenesulfonic acid salt. ^{1}H NMR (DMSO-d_6): δ 9.91 (bs, 1H), 9.65 (bs, 1H), 8.16 (d, J= 4.5 Hz, 1H), 8.02-7.94 (m, 1H), 7.78 (d, J= 2.7 Hz, 1H), 7.64 (dd, J= 2.7 and 9.0 Hz, 1H), 7.45 (d, J= 8.1 Hz, 2H), 7.22-7.06 (m, 6H), 6.63-6.56 (,m, 1H), 4.34 (s, 2H), 3.83 (s, 3H), 2.63 (d, J= 4.5 Hz, 3H), 2.28 (s, 3H).

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Section Number	Name of compound and reference number	Experimental
7.4.133	N4-(3-Chloro-4-methoxyphenyl)-N2-(3,5-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R926990)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine with 3,5-dichloroaniline gave N4-(3-chloro-4-methoxyphenyl)-N2-(3,5-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.68 (s, 1H), 9.53 (s, 1H), 8.16 (d, J= 3.9 Hz, 1H), 7.69 (d, J= 1.8 Hz, 2H), 7.66-7.58 (m, 2H), 7.13 (d, J= 9.3 Hz, 1H), 7.01 (t, J= 2.1 Hz, 1H), 3.83 (s, 3H); LCMS: purity: 97%; MS (m/e): 415 (MH^+).
7.4.134	N4-(3-Chloro-4-methoxyphenyl)-N2-(3,5-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926991)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine with 3,5-dimethylaniline gave N4-(3-chloro-4-methoxyphenyl)-N2-(3,5-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.10 (bs, 1H), 9.79 (bs, 1H), 8.21 (d, J= 4.8 Hz, 1H), 7.71 (d, J= 2.4 Hz, 1H), 7.59 (dd, J= 2.4 and 9.0 Hz, 1H), 7.14 (d, J= 9.0 Hz, 1H), 7.09 (bs, 2H), 6.65 (s, 1H), 3.85 (s, 3H), 2.16 (s, 6H); LCMS: purity: 99%; MS (m/e): 374 (MH^+).
7.4.135	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-(3-methoxy-5-trifluoromethylphenyl)-2,4-pyrimidinediamine (R926992)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine with 3-methoxy-5-trifluoromethylaniline gave N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(3-methoxy-5-trifluoromethylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.52 (s, 1H), 9.40 (s, 1H), 8.14 (d, J= 3.9 Hz, 1H), 7.72 (d, J= 2.4 Hz, 1H), 7.68 (dd, J= 2.7 and 9.0 Hz, 1H), 7.64-7.60 (m, 1H), 7.59-7.55 (m, 1H), 3.84 (s, 3H), 3.72 (s, 3H); LCMS: purity: 95%; MS (m/e): 444 (MH^+).
7.4.136	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-(3,4,5-trimethylphenyl)-2,4-pyrimidinediamine (R926993)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine with 3,4,5-trimethylaniline gave N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(3,4,5-trimethylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.23 (bs, 1H), 8.91 (bs, 1H), 8.04 (d, J= 3.6 Hz, 1H), 7.78-7.66 (m, 2H), 7.22 (s, 2H), 7.07 (d, J= 8.7 Hz, 1H), 3.83 (s, 3H), 2.12 (s, 6H), 2.03 (s, 3H); LCMS: purity: 98%; MS (m/e): 388 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.137	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethylphenyl)-2,4-pyrimidinediamine (R926994)	In a like manner to the preparation of N4-(4-chloro-3-methoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, the reaction of 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine with 3,4,5-trimethylaniline gave N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(3,4,5-trimethylphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.57 (s, 1H), 9.24 (s, 1H), 8.78 (s, 1H), 8.02 (d, J= 3.9 Hz, 1H), 7.31 (dd, J= 2.1 and 8.4 Hz, 1H), 7.26-7.22 (m, 3H), 6.86 (d, J= 8.7 Hz, 1 H), 2.11 (s, 6H), 2.02 (s, 3H), 1.40 (s, 6H); LCMS: purity: 99%; MS (m/e): 422 (MH^+).
7.4.138	5-Fluoro-N4-[1-(N-methylaminocarbonyl)indol-6-yl]-N2-(3,5-dimethoxyphenyl)-2,4-pyrimidinediamine (R926995)	To a suspension of 5-fluoro-N4-[(1H)-indol-6-yl]-N2-(3,5-dimethoxyphenyl)-2,4-pyrimidinediamine (0.045mg, 0.12 mmol), in THF (0.75 mL) at 0 °C were added triethylamine (0.025 mL, 0.12 mmol), 4-N,N-dimethylaminopyridine (0.5 mg) followed by diphosgene (8.5 µL, 0.071 mmol). The resulting reaction mixture was then stirred at room temperature for 1 hour, quenched with an aqueous solution of methylamine (40%, 1.5 mL), stirred for 5 minutes and diluted with water. The aqueous solution was extracted with ethyl acetate, solvent was evaporated and the residue was chromatographed (silica gel; CH_2Cl_2 then 2-5% of 2M NH_3/MeOH in CH_2Cl_2) to yield 5-fluoro-N4-[1-(N-methylaminocarbonyl)indol-6-yl]-N2-(3,5-dimethoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.90 (bs, 1H), 9.62 (bs, 1H), 9.49-9.42 (m, 1H), 8.08 (d, J= 3.3 Hz, 1H), 7.40 (bs, 1H), 7.35 (d, J= 8.7 Hz, 1H), 7.30 (t, J= 2.7 Hz, 1H), 7.09 (dd, J= 1.5 and 8.7 Hz, 1H), 6.49 (t, J= 2.4 Hz, 1H), 6.41-6.36 (m, 1H), 6.29 (d, J= 2.4 Hz, 1H), 3.69 (s, 6H), 2.47 (d, J= 4.2 Hz, 3H); LCMS: purity: 94%; MS (m/e): 437 (MH^+).
	Snthesis of Anilines	
7.4.139	2-Chloro-6-methyl-4-nitrophenol	To a suspenssion of commercially available 6-methyl-4-nitrophenol (5g, 32.6 mmol) in water (300 mL) at room temperature was added N-chlorosuccinimide (8.7 g, 32.6 mmol) followed by an aqueous solution of potassium hydroxyde 5N (13 mL, 65.2 mmol). After stirred at room temperature for 2 hours, the resulting reaction was acidified with 2N HCl (pH >2) and extracted with ethyl acetate (3 x 200 mL). The organic phase was separated, washed with brine, dried (Na_2SO_4), concentrated and the resulting residue was purified by flash chromatography (EtOAc:n-hexanes 15 : 85; v/v) to afford 2-chloro-6-methyl-4-nitrophenol (3.7 g, 60%). ^{1}H NMR (DMSO-d6): δ 10.84 (1H, s), 8.20 (1H, d, J= 3.3 Hz), 8.13 (1H, dt, J= 2.7 Hz, J= 0.6 Hz), 2.39 (3H, s); LCMS: purity: 96.69%.

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Section Number	Name of compound and reference number	Experimental
7.4.140	4-Amino-2-chloro-6-methylphenol	2-Chloro-6-methyl-4-nitrophenol (2.5 g, 13.32 mmol) was dissolved in glacial AcOH (22 mL), and iron powder (2.23 g, 40 mmol) was added. The mixture was heated at 90 °C with mechanical stirring for 2 hours, then was cooled to room temperature and diluted with EtOAc (200 mL). The mixture was filtered through a pad of Celite. The filtrate was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by chromatography on silica gel with CH_2Cl_2 to give 4-amino-2-chloro-6-methylphenol (1.03 g, 50%). ^{1}H NMR (DMSO-d6): δ 8.02 (1H, d, J= 0.9 Hz), 6.47 (1H, d, J= 2.1 Hz), 6.38 (1H, d, J= 2.4 Hz), 4.74 (2H, s), 2.16 (3H, s).
7.4.141	3-Chloro-4-methoxy-5-methylnitrobenzene	To a solution of 2-chloro-6-methyl-4-nitrophenol (1.2 g, 6.5 mmol) in acetone (10 mL), was added potassium carbonate (1.34 g, 9.75 mmol) followed by dimethyl sulfate (1.33 mL, 7.8 mmol). The mixture was stirred under reflux for 2 hours. Ammonium hydroxyde (1 mL) was added and the mixture was heated under reflux for 30 minutes. The mixture was cooled to room temperature and the solvent was removed in *vacuo*. The residue was poured into water, saturated with sodium chloride and the resulting solid was filtered to give the desired 3-chloro-4-methoxy-5-methylnitrobenzene (1.1 g, 84%). ^{1}H NMR (DMSO-d6): δ 8.28 (1H, d, J= 2.7 Hz), 8.24 (1H, dt, J= 2.7 Hz, J= 0.75 Hz), 3.95 (3H, d, J= 0.9 Hz), 2.48 (3H, d, J= 0.9 Hz); LCMS: purity: 98%.
7.4.142	3-Chloro-4-methoxy-5-methylaniline	3-Chloro-4-methoxy-5-methylnitrobenzene (1.1g, 5.4 mmol) was dissolved in glacial AcOH (9 mL), and iron powder (0.917 g, 16.4 mmol) was added. The mixture was heated at 90 °C under a mechanical stirring for 2 hours, then was cooled to room temperature and diluted with EtOAc (200 mL). The mixture was filtered through a pad of Celite. The filtrate was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel with CH_2Cl_2 to give 3-chloro-4-methoxy-5-methylaniline. ^{1}H NMR (DMSO-d6): δ 6.51 (1H, d, J= 2.7 Hz), 6.41 (1H, dd, J= 1.8 Hz, J= 0.9 Hz), 5.11 (2H, s), 3.68 (3H, d, J= 0.9 Hz), 2.21 (3H, s); LCMS: purity: 95%.

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Section Number	Name of compound and reference number	Experimental
7.4.143	(±) 2-Ethoxycarbonyl-2-methyl-6-nitro-3-oxo-4H-benz[1,4]oxazine	A mixture of potassium fluoride (KF) (1.8 g, 32.4 mmol), DMF (10 mL), diethyl-2-bromo-2-methylmalonate (3.2 g, 12.9 mmol), and 4-nitro-2-aminophenol (2 g, 12.9 mmol) was stirred for 16 hours, then poured into water, and extracted with EtOAc. The extract was washed with brine, dried, and concentrated to give the desired (±) 2-ethoxycarbonyl-2-methyl-6-nitro-3-oxo-4H-benz[1,4]oxazine , which was recrystallized from EtOH (2.2 g, 62%). ^{1}H NMR (DMSO-d6): δ 11.47 (1H, s), 7.99 (1H, dd, J= 9 Hz, J= 2.7 Hz), 7.85 (1H, d, J= 2.7 Hz), 7.36 (1H, d, J= 8.7 Hz), 4.23 (2H, q, J= 7 Hz), 1.85 (3H, s), 1.17 (3H, t, J= 7.2 Hz); LCMS: purity: 98 %; MS (m/e): 281 (MH^+).
7.4.144	(±) 6-Amino-2-ethoxycarbonyl-2-methyl-3-oxo-4H-benz[1,4]oxazine	A solution of (±) 2-ethoxycarbonyl-2-methyl-6-nitro-3-oxo-4H-benz[1,4]oxazine (0.5 g, 1.78 mmol) in methanol was hydrogenated at 30 PSI for 1 hour in the presence of 10% Pd/C (0.05 g, 10% by weight). After the filtration through a Celite pad, the solvent was removed under reduced pressure to obtain (±) 6-amino-2-ethoxycarbonyl-2-methyl-3-oxo-4H-benz[1,4]oxazine. ^{1}H NMR (DMSO-d6): δ 10.73 (1H, s), 6.76 (1H, d, J= 12 Hz), 6.23-6.20 (2H, m), 5.0 (2H, s), 4.16 (2H, q, J= 6.9 Hz), 1.69 (3H, s), 1.15 (3H, t, J= 6.9 Hz); LCMS: purity: 99 %; MS (m/e): 251 (MH^+).
7.4.145	3,5-Dimethy-4-methoxynitrobenzene	To a solution of 2,6-dimethyl-4-nitrophenol (1 g, 5.9 mmol) in acetone (9 mL), was added potassium carbonate (1.22 g, 8.85 mmol) followed by dimethyl sulfate (0.68 mL, 7.1 mmol). The mixture was stirred under reflux for 2 hours. Ammonium hydroxyde (1 mL) was added and the mixture was heated under reflux for an extra 30 minutes. The mixture was cooled to room temperature and the solvent was removed in *vacuo*. The residue was poured into water, saturated with sodium chloride and the resulting solid was filtered to give the desired 3,5-dimethyl-4-methoxynitrobenzene. ^{1}H NMR (DMSO-d6): δ 8.06 (2H, s), 3.84 (3H, s), 2.42 (6H, s); LCMS: purity: 91%.
7.4.146	3,5-Dimethyl-4-methoxyaniline	A solution of 3,5-dimethyl-4-methoxynitrobenzene (0.83 g, 4.5 mmol) in methanol was hydrogenated at 30 PSI for 1 hour in the presence of 10% Pd/C (0.1 g, 10% by weight). After the filtration through a Celite pad, the solvent was removed under reduced pressure to obtain 3,5-dimethyl-4-methoxyaniline. ^{1}H NMR (DMSO-d6): δ 6.28 (2H, s), 4.69 (2H, brads), 3.60 (3H, d, J= 0.9 Hz), 2.16 (6H, s); LCMS: purity: 100 %.

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Section Number	Name of compound and reference number	Experimental
7.4.147	N2-(3-Chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazın-6-yl)-5-fluoro-2,4-pyrimidınediamine R940358	To a solution of 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine (0.1 g, 0.3 mmol) in (2 mL) was added 4-amino-2-chloro-6-methylphenol (0.146 g, 0.9 mmol). The mixture was heated in a sealed tube at 100 °C for 24 hours. The resultıng reaction was diluted wıth H_2O (10 mL), acıdified with 2N HCl (pH >2), saturated with sodium chloride and the resultıng solid was fıltered to gıve the desired N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimıdinediamine. Purification can be done by fıltration through a pad of sılica gel usıng 1-5% MeOH ın CH_2Cl_2 or by crystallization using an appropriate solvent system. Alternatıvely, the reaction of equimolar amount of 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazın-3-6-yl)-5-fluoro-4-pyrımidineamine wıth 4-amino-2-chloro-6-methylphenol ın MeOH ın a pressure tube at 110 °C for 24 hours or, in EtOH using microwave at 175 °C for 30-60 min followed by aqueous work up, also gave N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.78 (1H, s), 10.00 (1H, s), 9.58 (1H, s), 8.91 (1H, s), 8.23 (1H, d, J= 4.8 Hz), 7.57 (1H, s), 7.37 (1H, dd, J= 8.7 Hz, J= 2.1 Hz), 7.27 (2H, m), 6.98 (1H, d, J= 8.7 Hz), 2.22 (3H, s), 1.50 (6H, s); LCMS: purity: 98 %; MS (m/e): 444 (MH^+).
7.4.148	N2-(3-Chloro-4-methoxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine R940361	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3-chloro-4-methoxy-5-methylaniline were reacted to yield N2-(3-chloro-4-methoxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidınediamıne ^{1}H NMR (DMSO-d6): δ 10.72 (1H, s), 9.55 (1H, s), 9.35 (1H, s), 8.20 (1H, d, J= 4.2 Hz), 7.75 (1H, d, J= 2.4 Hz), 7.46 (1H, d, J= 2.1 Hz), 7.36 (1H, m), 7.28 (1H, m), 7.00 (1H, d, J= 8.7 Hz), 3.76 (3H, s), 2.25 (3H, s), 1.50 (6H, s); LCMS: purity: 98.99 %; MS (m/e): 458 (MH^+).
7.4.149	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(indazolin-6-yl)-2,4-pyrimidinediamıne R940363	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazın-6-yl)-5-fluoro-2,4-pyrimıdinediamıne, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrımidıneamine and 6-aminoındazole were reacted to yield N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(indazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.71 (1H, s), 9.64 (1H, s), 9.42 (1H, s), 8.24 (1H, d, J= 3.9 Hz), 8.09 (1H, s), 8.01 (1H, s), 7.66 (1H, d, J= 9 Hz), 7.52 (1H, d, J= 8.7 Hz), 7.37 (2H, m), 7.00 (1H, d, J= 8.7 Hz), 1.50 (6H, s); LCMS: purity: 96.09 %; MS (m/e): 420 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.150	N4-(2,2-Difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(indazolin-6-yl)-2,4-pyrimidinediamine R940364	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]-oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]-oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 6-aminoindazole were reacted to yield N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(indazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 12.07 (1H, s), 9.73 (1H, s), 9.40 (1H, s), 8.29 (1H, d, J= 3.6 Hz), 8.12 (1H, s), 8.00 (1H, s), 7.78 (1H, dd, J= 8.7 Hz, J= 2.4 Hz), 7.60 (1H, s), 7.36 (2H, m); LCMS: purity: 94.39 %; MS (m/e): 428 (MH^+).
7.4.151	(±) 2-Chloro-N4-(2-ethoxycarbonyl-2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine	The reaction flask equipped with a magnetic stirring bar and a rubber septum and N_2 inlet was charged with (±) 6-amino-2-ethoxycarbonyl-2-methyl-3-oxo-4H-benz[1,4]oxazine (0.45 g, 1.8 mmol), MeOH (4mL), H_2O (2 mL) and 2,4-dichloro-5-fluoropyrimidine (0.36 g, 2.2 mmol). The reaction mixture was stirred at 60 °C for 1 hour, diluted with H_2O (50 mL), acidified with 2N HCl (6 mL) and sonicated. The solid obtained was filtered, washed with H_2O and dried. The crude was recrystallized from EtOAc:n-hexanes to produce (±) 2-chloro-N4-(2-ethoxycarbonyl-2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 11.21 (1H, s), 10.05 (1H, s), 8.39 (1H, d, J= 3.6 Hz), 7.41-7.34 (2H, m), 7.13 (1H, d, J= 9Hz), 4.20 (2H, q, J= 7.2 Hz), 1.78 (3H, s), 1.17 (3H, t, J= 7.2 Hz); LCMS: purity: 95 %; MS (m/e): 381 (MH^+).
7.4.152	(±) N4-(2-Ethoxycarbonyl-2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2-ethoxycarbonyl-2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3-(methoxycarbonylmethyleneoxy)aniline were reacted to yield (±) N4-(2-ethoxycarbonyl-2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-[3-(methoxycarbonylmethyleneoxy)phenyl]-2,4-pyrimidinediamine.

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Section Number	Name of compound and reference number	Experimental
7.4.153	5-Fluoro-N4-[2-methyl-2-(N-methylaminocarbonyl)-3-oxo-4H-benz[1,4]oxazin-6-yl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine R940365	A mixture of N4-(2-ethoxycarbonyl-2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (0.069 g, 1.3 mmol), methylamine hydrochloride salt (0.088 g, 1.3 mmol) and diisopropylethylamine (230 µL, 1.3 mmol) in MeOH (2 mL) was stirred in a pressure vial at 90 °C for 4 hours. The reaction was cooled to room temperature, diluted with water (20 mL), the solid formed was filtered, washed with water and dried. The resulting residue was purify by chromatography on silica gel (CH_2Cl_2: MeOH; 95:5 v/v) to get the desired 5-fluoro-N4-[2-methyl-2-(N-methylaminocarbonyl)-3-oxo-4H-benz[1,4]oxazin-6-yl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.80 (1H, s), 9.44 (1H, s), 9.21 (1H, s), 8.22 (1H, m), 8.18 (1H, d, J= 3.9 Hz), 8.06 (1H, m), 7.51-7.41 (3H, m), 7.31 (1H, m), 7.20 (1H, t, J= 8.2 Hz), 7.11 (1H, d, J= 9 Hz), 5.57 (1H, dd, J= 8.1 Hz, J= 2.7 Hz), 4.46 (2H, s), 2.74 (3H, d, J= 4.8 Hz), 2.62 (3H, d, J= 4.8 Hz), 1.72 (3H, s); LCMS: purity: 94 %; MS (m/e): 510 (MH^+).
7.4.154	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(N1-methylindazolin-6-yl) -2,4-pyrimidinediamine R940366	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 6-amino-N1-methylindazole were reacted to yield N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(N1-methylindazolin-6-yl) -2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.74 (1H, s), 9.48 (1H, s), 9.42 (1H, s), 8.24 (1H, d, J= 3.6 Hz), 8.16 (1H, s), 7.94 (1H, s), 7.63 (1H, d, J= 8.4 Hz), 7.46 (1H, dd, J= 8.4 Hz, J= 2.4 Hz), 7.36-7.32 (2H, m), 6.99 (1H, d, J= 9 Hz), 3.86 (3H, s), 1.50 (6H, s); LCMS: purity: 96.80 %; MS (m/e): 434 (MH^+).
7.4.155	N4-(2,2-Difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine R940367	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]-oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 6-amino-2,2-dimethyl-3-oxo-4H-benz[1,4]oxazine were reacted to yield N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-(2,2-dimethyl-3-oxo-4H-benz[1,4]-oxazin-3-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 12.04 (1H, s), 10.64 (1H, s), 9.61 (1H, s), 9.12 (1H, s), 8.17 (1H, d, J= 3.6 Hz), 7.54 (1H, dd, J= 9 Hz, J= 2.7 Hz), 7.55 (1H, d, J= 2.7 Hz), 7.32-7.26 (3H, m), 6.87 (1H, d, J= 9.3 Hz), 1.46 (6H, s); LCMS: purity: 92.68 %; MS (m/e): 487 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.156	N4-(2,2-Difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine R940368	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4-oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 6-amino-1-methylindazole were reacted to yield N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(1-methylindazolin-6-yl) -2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 12.09 (1H, s), 9.71 (1H, s), 9.49 (1H, s), 8.31 (1H, d, J= 3.9 Hz), 8.18 (1H, s), 7.95 (1H, s), 7.72-7.69 (1H, m), 7.65 (1H, d, J= 9 Hz), 7.59 (1H, m), 7.36 (2H, t, J= 8.7 Hz), 3.85 (3H, s); LCMS: purity: 94.55 %; MS (m/e): 442 (MH^+).
7.4.157	N4-(2,2-Dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-N2-(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine R940371	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]-oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3-chloro-4-methoxyaniline were reacted to yield N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-N2-(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.20 (1H, s), 9.39 (1H, s), 9.34 (1H, s), 8.22 (1H, d, J= 3.3 Hz), 7.90 (1H, s), 7.62-7.54 (2H, m), 7.47 (1H, d, J= 8.4 Hz), 7.08 (1H, d, J= 9 Hz), 3.87 (3H, s), 1.53 (6H, s); LCMS: purity: 97.92 %; MS (m/e): 445 (MH^+).
7.4.158	N4-(2,2-Dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine R940372	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]-oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3,5-dimethoxyaniline were reacted to yield N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.15 (1H, s), 9.34 (1H, s), 9.30 (1H, s), 8.23 (1H, d, J= 3.3 Hz), 7.74 (1H, dd, J= 8.7 Hz, J= 3.9 Hz), 7.43 (1H, d, J= 8.7 Hz), 7.02 (2H, s), 6.16 (1H, s), 3.75 (6H, s), 1.53 (6H, s); LCMS: purity: 100 %; MS (m/e): 441 (MH^+).
7.4.159	N2-(3,4-Dichlorophenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine R940373	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]-oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3,4-dichloroaniline were reacted to yield N2-(3,4-dichlorophenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.20 (1H, s), 9.68 (1H, s), 9.54 (1H, s), 8.27 (1H, d, J= 3.6 Hz), 8.14 (1H, d, J= 2.1 Hz), 7.64 (1H, dd, J= 8.7 Hz, J= 2.1 Hz), 7.53-7.47 (3H, m), 1.53 (6H, s); LCMS. purity: 100 %; MS (m/e): 449 (M^+).

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Section Number	Name of compound and reference number	Experimental
7.4.160	N4-[(2,2-Dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-(indazolin-6-yl)-2,4-pyrimidinediamine R940380	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 6-aminoindazole were reacted to yield N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-*fluoro*-N2-(indazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.16 (1H, s), 9.48 (1H, s), 9.28 (1H, s), 8.27 (1H, d, J= 3.3 Hz), 8.17 (1H, s), 7.98 (1H, s), 7.84 (1H, m), 7.65 (1H, d, J= 9 Hz), 7.47 (1H, d, J= 8.7 Hz), 7.36 (1H, d, J= 8.7 Hz), 1.53 (6H, s); LCMS: purity: 100 %; MS (m/e): 421 (MH^+).
7.4.161	N2-(3-*tert*-Butylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine R940381	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3-*tert*-butylaniline were reacted to yield N2-(3-*tert*-butylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.16 (1H, s), 9.27 (1H, s), 9.23 (1H, s), 8.22 (1H, d, J= 3.6 Hz), 7.74 (1H, m), 7.70 (1H, d, J= 8.4 Hz), 7.57 (1H, s), 7.44 (1H, d, J= 8.7 Hz), 7.205 (1H, t, J= 7.9 Hz), 7.01 (1H, d, J= 7.8 Hz), 1.53 (6H, s), 1.33 (9H, s); LCMS: purity: 100 %; MS (m/e): 437 (MH^+).
7.4.162	N4-[(2,2-Dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine R940382	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3-aminophenol were reacted to yield N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.16 (1H, s), 9.29 (1H, s), 9.25 (1H, s), 9.23 (1H, s), 8.20 (1H, d, J= 3.6 Hz), 7.74 (1H, d, J= 8.4 Hz), 7.44 (1H, d, J= 8.7 Hz), 7.23 (1H, t, J= 1.25 Hz), 7.16 (1H, d, J= 8.1 Hz), 7.04 (1H, t, J= 7.9 Hz), 6.40 (1H, dd, J= 6.9 Hz, J= 1.2 Hz), 1.53 (6H, s); LCMS: purity: 100 %; MS (m/e): 397 (MH^+).
7.4.163	N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-N2-(3-fluoro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine R940384	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3-fluoro-4-methoxyaniline were reacted to yield N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-N2-(3-fluoro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.20 (1H, s), 9.42 (1H, s), 9.35 (1H, s), 8.21 (1H, d, J= 3.6 Hz), 7.75 (1H, dd, J= 14.4 Hz, J= 2.4 Hz), 7.56 (1H, d, J= 8.1 Hz), 7.46 (1H, d, J= 8.7 Hz), 7.37 (1H, d, J= 9.6 Hz), 7.08 (1H, t, J= 9.3 Hz), 3.85 (3H, s), 1.53 (6H, s); LCMS: purity: 97 %; MS (m/e): 429 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.164	N2-(3-Chlorophenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine R940386	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3-chloroaniline were reacted to yield N2-(3-chlorophenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.10 (1H, s), 9.50 (1H, s), 9.43 (1H, s), 8.16 (1H, d, J= 3.3 Hz), 7.85 (1H, t, J= 1.95 Hz), 7.47 (2H, d, J =8.7 Hz), 7.38 (1H, d, J= 8.7 Hz), 7.18 (1H, t, J= 8.1 Hz), 6.89 (1H, ddd, J= 7.8 Hz, J= 2.1 Hz, J= 1.2 Hz), 1.43 (6H, s); LCMS: purity: 100 %; MS (m/e): 415 (MH^+).
7.4.165	N2-(3,5-Dichlorophenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine R940387	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3,5-dichloroaniline were reacted to yield N2-(3,5-dichlorophenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.10 (1H, s), 9.66 (1H, s), 9.49 (1H, s), 8.19 (1H, m), 7.70 (2H, m), 7.39 (2H, m), 6.99 (1H, t. J= 1.95 Hz), 1.42 (6H, s); LCMS: purity: 96 %; MS (m/e): 450 (MH^+).
7.4.166	N4-(2,2-Dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-(1-methylindazolin-6-yl) -2,4-pyrimidinediamine R940389	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 6-amino-1-methylindazole were reacted to yield N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.22 (1H, s), 9.60 (1H, s), 9.43 (1H, s), 8.29 (1H, d, J= 3.6 Hz), 8.13 (1H, s), 7.95 (1H, s), 7.72 (1H, d, J= 8.4 Hz), 7.64 (1H, d, J= 9 Hz), 7.47 (1H, d, J= 8.1 Hz), 7.34 (1H, dd, J= 8.7 Hz, J= 1.8 Hz), 3.19 (3H, s), 1.53 (6H, s); LCMS: purity: 100 %; MS (m/e): 435 (MH^+).
7.4.167	N2-(3-Chloro-4-trifluoromethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine R940390	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3-chloro-4-trifluoromethoxyaniline were reacted to yield N2-[3-chloro-4-trifluoromethoxyphenyl]-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.24 (1H, s), 9.76 (1H, s), 9.60 (1H, s), 8.28 (1H, d, J= 3.6 Hz), 8.14 (1H, d, J= 2.4 Hz), 7.70 (1H, dd, J= 9 Hz, J= 2.7 Hz), 7.54-7.43 (3H, m), 1.53 (6H, s); LCMS: purity: 94.6 %; MS (m/e): 499 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.168	N2-(3-Chloro-4-methoxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine R940391	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3-chloro-4-methoxy-5-methylaniline were reacted to yield N2-(3-chloro-4-methoxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.20 (1H, s), 9.24 (1H, s), 9.40 (1H, s), 8.23 (1H, dd, J= 3.3 Hz, J= 0.9 Hz), 7.76 (1H, d, J= 2.7 Hz), 7.61 (1H, d, J= 8.4 Hz), 7.47 (1H, d, J= 8.1 Hz), 7.42 (1H, d, J= 2.7 Hz), 3.76 (3H, d, J= 1.2 Hz), 2.27 (3H, s), 1.53 (6H, s); LCMS: purity: 100 %; MS (m/e): 459 (MH^+).
7.4.169	N4-(2,2-Dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine R940392	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3-(methoxycarbonylmethyleneoxy)aniline were reacted to yield N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)5-fluoro-N2-[3-methoxycarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.16 (1H, s), 9.36 (1H, s), 9.34 (1H, s), 8.23 (1H, d, J= 3.3 Hz), 7.69 (1H, d, J= 8.7 Hz), 7.47 (1H, d, J= 8.7 Hz), 7.42 (1H, s), 7.37 (1H, d, J= 8.1 Hz), 7.17 (1H, t, J= 8.1 Hz), 6.53 (1H, dd, J= 8.4 Hz, J= 2.4 Hz), 4.78 (2H, s), 3.79 (3H, s), 1.53 (6H, s); LCMS: purity: 94.69 %; MS (m/e): 469 (MH^+).
7.4.170	N2-(3-Chloro-4-hydroxy-5-methylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine R940393	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 4-amino-2-chloro-6-methylphenol were reacted to yield N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.19 (1H, d, J= 1.5 Hz), 9.05 (1H, s), 8.64 (1H, s), 8.10 (1H, d, J= 3.9 Hz), 7.62 (1H, d, J= 2.7 Hz), 7.36 (1H, d, J= 1.8 Hz), 7.31 (1H, m), 7.27 (1H, d, J= 2.7 Hz), 6.87 (1H, d, J= 8.4 Hz), 4.31 (4H, s), 2.22 (3H, s); LCMS: purity: 96.98%; MS (m/e): 403 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.171	N2-(3-Chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine R940394	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 4-amino-2-chloro-6-methylphenol were reacted to yield N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.16 (1H, s), 9.27 (1H, s), 9.15 (1H, s), 8.67 (1H, s), 8.19 (1H, d, J= 3.6 Hz), 7.64 (2H, m), 7.42 (1H, d, J= 8.4 Hz), 7.29 (1H, d, J= 2.7 Hz), 2.22 (3H, s), 1.53 (6H, s); LCMS: purity: 97.69%; MS (m/e): 444 (M^+).
7.4.172	N2-(3,5-Dimethyl-4-methoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine R940395	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3,5-dimethyl-4-methoxyaniline were reacted to yield N2-(3,5-dimethyl-4-methoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 11.16 (1H, s), 9.23 (1H, s), 9.11 (1H, s), 8.19 (1H, d, J= 3.6 Hz), 7.69 (1H, d, J= 8.1 Hz), 7.44 (1H, d, J= 8.4 Hz), 7.33 (2H, s), 3.68 (3H, s), 2.23 (6H, s), 1.53 (6H, s); LCMS: purity: 99%; MS (m/e): 439 (MH^+).
7.4.173	N2-(3,5-Dimethyl-4-methoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine R940396	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3,5-dimethyl-4-methoxyaniline were reacted to yield N2-(3,5-dimethyl-4-methoxyphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.06 (1H, s), 9.85 (1H, s), 8.25 (1H, d, J= 4.8 Hz), 7.33 (1H, d, J= 2.4 Hz), 7.24 (2H, s), 7.20 (1H, d, J= 2.7 Hz), 6.91 (1H, d, J= 8.4 Hz), 4.32 (4H, s), 3.71 (3H, s), 2.25 (6H, s); LCMS: purity: 96.69%; MS (m/e): 397 (MH^+).
7.4.174	N2-(3-Chloro-4-methoxy-5-methylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine R940397	In like manner to the preparation of N2-(3-chloro-4-hydroxy-5-methylphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 3-chloro-5-methyl-4-metoxyaniline were reacted to yield N2-(3-chloro-4-methoxy-5-methylphenyl)-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.88 (2H, broad s), 8.26 (1H, d, J= 4.2 Hz), 7.64 (1H, s), 7.41 (1H, s), 7.30-7.28 (1H, m), 7.25-7.20 (1H, m), 6.92 (1H, d, J= 10.2 Hz), 4.32 (4H, s), 3.79 (3H, s), 2.29 (3H, s); LCMS: purity: 94.81%; MS (m/e): 417 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.175	5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(N-morpholino)carbonyl-4-trifluoromethoxyphenyl]-2,4-pyrimidinediamine (R950411)	A solution of N4-(3-carboxy-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DMF was treated with PyBroP and morpholine. The mixture was stirred for 1 hour at 22 °C and purified by flash chromatography on silica gel to give 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(N-morpholino)carbonyl-4-trifluoromethoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO-d6): δ 9.62 (s, 1H), 9.29 (s, 1H), 7.77-8.17 (m, 7H), 7.12 (t, 1H, J= 8.1 Hz), 6.48 (m, 1H), 4.36 (s, 2H), 3.02-4.36 (m, 8H), 2.64 (s, 3H); LCMS: purity: 92.9%; MS (m/e): 565.34 (MH^+).
7.4.176	N4-[3-(N-2-Aminoethylamino)carbonyl-3-trifluoromethoxyphenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950406)	A solution of N4-(3-carboxy-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DMF was treated with PyBroP and 1,2-diaminoethane. The mixture was stirred for 1 hour at 22 °C and purified by flash chromatography on silica gel to give N4-[3-(N-2-aminoethylamino)carbonyl-3-trifluoromethoxyphenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 100%; MS (m/e): 538.5 (MH^+).
7.4.177	5-Fluoro-N4-[3-(N-methylamino)carbonyl-4-trifluoromethoxyphenyl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950407)	A solution of N4-(3-carboxy-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DMF was treated with PyBroP and N-methylamine. The mixture was stirred for 1 hour at 22 °C and purified by flash chromatography on silica gel to give 5-fluoro-N4-[3-(N-methylamino)carbonyl-4-trifluoromethoxyphenyl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.3%; MS (m/e): 496.27 (MH^+).
7.4.178	5-Fluoro-N4-(3-[N-(2-(N-methylamino)ethyleneamino)carbonyl-4-trifluoromethoxyphenyl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950408)	A solution of N4-(3-carboxy-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DMF was treated with PyBroP and N1-methylamino-2-aminoethane. The mixture was stirred for 1 hour at 22 °C and purified by flash chromatography on silica gel to give 5-fluoro-N4-(3-[N-(2-(N-methylamino)ethyleneamino)carbonyl-4-trifluoromethoxyphenyl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 81.6%; MS (m/e): 552.37 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.179	5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(N-piperidinocarbonyl-4-trifluoromethoxyphenyl]-2,4-pyrimidinediamine (R950409) 5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(N-piperidinocarbonyl-4-trifluoromethoxyphenyl]-2,4-pyrimidinediamine (R950409)	A solution of N4-(3-carboxy-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DMF was treated with PyBroP and piperidine. The mixture was stirred for 1 hour at 22 °C and purified by flash chromatography on silica gel to give 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[3-(N-piperidinocarbonyl-4-trifluoromethoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity. 90.4%; MS (m/e): 563.36 (MH^+).
7.4.180	(R)-N4-(3-[N-(1,2-Dihydroxyproypylamino)carbonyl-4-trifluoromethoxyphenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950410)	A solution of N4-(3-carboxy-4-trifluoromethoxyphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in DMF was treated with PyBroP and (R)-1,2-dihydroxypropylamine. The mixture was stirred for 1 hour at 22 °C and purified by flash chromatography on silica gel to give (R)-N4-(3-[N-(1,2-dihydroxyproypylamino)carbonyl-4-trifluoromethoxyphenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 82.6%; MS (m/e): 569.34 (MH^+).
7.4.181	(±) 4-(N-tert-Butoxycarbonyl)amino-6-nitro-1-benzopyran	A solution of (±) 4-amino-6-nitro-1-benzopyran in dioxane-water was treated with di-tert-butyl carbonate and sodium bicarbonate. The mixture was stirred for 2 hours at 0 °C and diluted with hexane. The mixture was filtered, and the remaining solids were carefully washed with hexane and dried under reduced pressure to give (±) 4-(N-tert-butoxycarbonyl)amino-6-nitro-1-benzopyran as a pale yellow solid. ^1H NMR ($CDCl_3$): δ 8.23 (d, 1H, J= 2.7 Hz), 8.04 (dd, 1H, J= 2.7, 9.6 Hz), 6.88 (d, 1H, J= 9.6 Hz), 4.89 (bs, 1H), 4.81 (bs, 1H), 4.26-4.38 (m, 2H), 2.03-2.26 (m, 2H).
7.4.182	(±) N4-[4-(N-tert-Butoxycarbonyl)amino-1-benzopyran-6-yl)-2-chloro-5-fluoro-2,4-pyrimidineamine	A mixture (±) 4-(N-tert-butoxycarbonyl)amino-6-nitro-1-benzopyran and Pd/C (10%) in MeOH was hydrogenated at 22 °C for 3 hours (40psi). The mixture was filtered and concentrated to dryness to give 6-amino-4-(N-tert-butoxycarbonyl)amino-1-benzopyran as a brown oil. The resulting oil of 6-amino-4-(N-tert-butoxycarbonyl)amino-1-benzopyran was reacted with 2,4-dichloro-5-fluoro-pyrimidine in MeOH at 70 °C for 2 hours. The reaction mixture was diluted with water and the resulting precipitate was filtered to give (±) N4-[4-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl)-2-chloro-5-fluoro-2,4-pyrimidineamine as a pale yellow solid. ^1H NMR (DMSO-d6): δ 9.85 (s, 1H), 8.22 (d, 1H, J= 2.4 Hz), 7.38 (m, 3H), 6.75 (d, 1H, J= 9.6 Hz), 4.15-4.72 (m, 3H), 1.88-2.01 (m, 2H), 1.42 (s, 9H); LCMS: purity: 92.3%; MS (m/e): 397.02 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.183	(±) N4-[4-(N-tert-Butoxycarbonyl)amino-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950405)	A solution of equimolar amount of (±) N4-[4-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl)-2-chloro-5-fluoro-2,4-pyrimidineamine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH and heated in a sealed tube at 110 °C for 24 hours. The resulting reaction mixture was diluted with water and the solid was isolated by filtration to give (±) N4-[4-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO-d6): δ 9.24 (s, 1H), 9.04 (s, 1H), 8.01 (d, 1H, J= 2.4 Hz), 7.93 (d, 1H, J= 4.5 Hz), 7.60 (d, 1H, J= 7.2 Hz), 7.22-7.36 (m, 3H), 7.07 (t, 1H, J= 8.4 Hz), 6.69 (d, 1H, J= 9.0 Hz), 6.56 (m, 1H), 4.70 (m, 1H), 4.29 (s, 2H), 4.17 (m, 2H), 2.64 (s, 3H), 1.88-2.08 (m, 2H), 1.40 (s, 9H); LCMS: purity: 93.7%; MS (m/e): 537.28 (M$^+$).
7.4.184	(±) 4-(N-tert-Butoxycarbonyl-N-methyl)amino-6-nitro-1-benzopyran	A solution of 4-amino-6-nitro-1-benzopyran in THF was treated with sodium hydride followed by methyl iodide. The mixture was stirred for 24 hours at 0 °C. The mixture was diluted with water and extracted with dichloromethane. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure to give (±) 4-(N-tert-butoxycarbonyl-N-methyl)amino-6-nitro-1-benzopyran as a pale yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.98 (dd, 1H, J= 3.4, 9.3 Hz), 7.90 (bs, 1H), 6.82 (d, 1H, J= 9.3 Hz), 5.65 (bs, 1H), 4.18-4.44 (m, 2H), 1.98-2.06 (m, 2H), 2.55 (s, 3H).
7.4.185	(±) N4-[4-(N-tert-Butoxycarbonyl-N-methyl)amino-1-benzopyran-6-yl]-2-chloro-5-fluoro-2,4-pyrimidineamine	A mixture (±) 4-(N-tert-butoxycarbonyl-N-methyl)amino-6-nitro-1-benzopyran and Pd/C (10%) in MeOH was hydrogenated at 22 °C for 3 hours (40psi). The mixture was filtered and concentrated to dryness to give 6-amino-4-(N-tert-butoxycarbonyl-N-methyl)amino-1-benzopyran as a brown oil. The resulting (±) 6-amino-4-(N-tert-butoxycarbonyl-N-methyl)amino-1-benzopyran was reacted with 2,4-dichloro-5-fluoro-pyrimidine in MeOH at 70 °C for 2 hours. The mixture was diluted with water and the resulting precipitate was filtered to give (±) N4-[4-(N-tert-butoxycarbonyl-N-methyl)amino-1-benzopyran-6-yl]-2-chloro-5-fluoro-2,4-pyrimidineamine as a pale yellow solid. LCMS: purity: 88.0%; MS (m/e): 408.14 (M$^+$).

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Section Number	Name of compound and reference number	Experimental
7.4.186	(±) 5-Fluoro-N4-[4-(N-methyl)amino-1-benzopyran-6-yl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950412)	A solution of equimolar amount of (±) N4-[4-(N-tert-butoxycarbonyl-N-methyl)amino-1-benzopyran-6-yl]-2-chloro-5-fluoro-2,4-pyrimidineamine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH was heated in a sealed tube in the presence of a catalytic amount of trifluoroacetic acid at 110 °C for 24 hours. The reaction mixture was diluted with water and the solid was isolated by filtration to give (±) 5-fluoro-N4-[(4-N-methyl)amino-1-benzopyran-6-yl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 9.62 (s, 1H), 9.46 (s, 1H), 8.71 (bs, 3H), 8.01-8.12 (m, 3H), 7.47 (s, 1H), 7.39(m, 1H), 7.27 (d, 1H, J= 7.2 Hz), 7.11 (t, 1H, J= 7.2 Hz), 6.86 (d, 1H, J 7.0 Hz), 6.46 (m, 1H), 4.20-4.46 (m, 3H), 4.31 (s, 3H), 2.64 (d, 3H, J= 4.8 Hz), 2.55 (s, 3H), 2.05-2.19 (m, 2H); LCMS: purity: 94.8%; MS (m/e): 451.17 (M⁺).
7.4.187	(±) N4-[4-(N-tert-Butoxycarbonyl-N-methyl)amino-1-benzopyran-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950415)	A solution of equimolar amount of (±) N4-[4-(N-tert-butoxycarbonyl-N-methyl)amino-1-benzopyran-6-yl]-2-chloro-5-fluoro-2,4-pyrimidineamine and 3-(N-methylamino)carbonylmethyleneoxyaniline in MeOH was heated in a sealed tube at 80 °C for 7 days. Aqueous work up gave (±) N4-[4-(N-tert-butoxycarbonyl-N-methyl)amino-1-benzopyran-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^1H NMR (DMSO-d6): δ 10.22-10.34 (m, 2H), 8.23 (d, 1H, J= 5.1 Hz), 7.99 (d, 1H, J= 4.2 Hz), 6.98-7.56 (m 3H), 6.74 (d, 1H, J= 9.0 Hz), 6.65 (d, 1H, J= 7.8 Hz), 5.41 (bs, 1H), 5.18 (bs, 1H), 4.15-4.36 (m, 5H), 2.63 (s, 3H), 1.90-2.20 (m, 2H), 1.44 (s, 9H); LCMS: purity: 97.3%; MS (m/e): 551.25 (M⁺).
7.4.188	(±) 4-(N-Acetyl)amino-6-nitro-1-benzopyran	A solution of 4-hydroxy-6-nitro-1-benzopyran in dry acetonitrile was treated with concentrated sulfuric acid. The mixture was stirred for 1 hour at 22 °C to give (±) 4-(N-acetyl)amino-6-nitro-1-benzopyran as a pale brownish precipitate, which was filtered off and dried. ^1H NMR ($CDCl_3$): δ 8.13 (d, 1H, J= 2.8 Hz), 8.04 (dd, 1H, J= 2.8, 8.7 Hz), 6.88 (d, 1H, J= 8.7 Hz), 5.87 (bs, 1H), 5.17-5.24 (m, 1H), 4.25-4.39 (m, 2H), 2.04-2.26 (m, 2H), 2.08 (s, 3H).
7.4.189	(±) 4-Amino-6-nitro-1-benzopyran	A solution of (±) 4-(N-acetyl)amino-6-nitro-1-benzopyran in concentrated HCl was refluxed for 16 hours. The reaction mixture was concentrated to dryness under reduced pressure and basified by addition of potassium carbonate. Water was added and the aqueous phase was extracted with methylene chloride and dried over magnesium sulfated. Removal of the volatiles under reduced pressure gave (±) 4-amino-6-nitro-1-benzopyran as a yellow solid, which used in the next step without further purification. ^1H NMR ($CDCl_3$): δ 8.23 (d, 1H, J= 3.0 Hz), 7.96 (dd, 1H, J= 3.0, 9.0 Hz), 6.80 (d, 1H, J= 9.0 Hz), 4.04-4.41 (m, 3H), 1.78-2.14 (m, 2H).

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Section Number	Name of compound and reference number	Experimental
7.4.190	(S)-4-Amino-6-nitro-1-benzopyran (L)-(+)-Tartaric Acid Salt	A solution of (±)-4-amino-6-nitro-1-benzopyran in ethanol-water was treated with L-(+)-tartaric acid and heated to give a clear solution. The mixture was kept for 3 days at 22 °C and the resulting precipitate was filtered and washed carefully with ethanol to give enantiomerically pure (S)-4-amino-6-nitrobenzo-1-pyran (L)-(+)-tartaric acid salt. ^{1}H NMR (DMSO-d6): δ 8.44 (d, 1H, J= 2.7 Hz), 8.08 (dd, 1H, J= 2.7, 9.3 Hz), 7.01 (d, 1H, J= 9.3 Hz), 4.32-4.39 (m, 3H), 3.97 (s, 2H), 1.90-2.26 (m, 2H).
7.4.191	(R)-4-Amino-6-nitro-1-benzopyran (D)-(-)-Tartaric Acid Salt	A solution of (±)-4-amino-6-nitrobenzopyran in ethanol-water was treated with D-(-)-tartaric acid and heated to give a clear solution. The mixture was kept for 3 days at 22 °C and the resulting precipitate was filtered and washed carefully with ethanol to give enantiomerically pure (R)-4-amino-6-nitro-1-benzopyran (D)-(-)-tartaric acid salt. ^{1}H NMR (DMSO-d6): δ 8.44 (d, 1H, J= 2.7 Hz), 8.08 (dd, 1H, J= 2.7, 9.3 Hz), 7.01 (d, 1H, J= 9.3 Hz), 4.32-4.39 (m, 3H), 3.97 (s, 2H), 1.90-2.26 (m, 2H).
7.4.192	(S)-N4-[4-(N-Benzyloxycarbonyl)amino-1-benzopyran-6-yl]-2-chloro-5-fluoro-4-pyrimidineamine (R950413)	A solution of (S)-4-amino-6-nitro-1-benzopyran in dioxane-water was treated with benzylchloroformate and sodium bicarbonate. The mixture was stirred for 1 hour at 0 °C and diluted with hexane. The mixture was filtered, and the remaining solid was carefully washed with hexane and dried under reduced vacuum to give (S)-4-(N-benzyloxycarbonyl)amino-6-nitro-1-benzopyran as a pale yellow solid. The crude material was dissolved in EtOH and treated with iron powder and ammonium chloride. The mixture was stirred for 2 hours at 85 °C and filtered to give a clear solution, which was diluted with water. The aqueous phase was extracted with dichloromethane and the organic phase was dried over magnesium sulfate. Removal of the volatiles under reduced pressure gave (S)-6-amino-4-(N-benzyloxycarbonyl)amino-1-benzopyran as a brown oil. The reaction of (S)-6-amino-4-(N-benzyloxycarbonyl)amino-1-benzopyran with 2,4-dichloro-5-fluoropyrimidine in MeOH for 2 hours at 70 °C followed by dilution with water and fitration of the resulting residue gave (S)-2-chloro-N4-[4-(N-benzyloxycarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-4-pyrimidineamine as a pale yellow solid. ^{1}H NMR (DMSO-d6): δ 9.87 (s, 1H), 9.23 (d, 1H, J= 2.4 Hz), 7.85 (d, 1H, J= 9.0 Hz), 7.25-7.45 (m, 7H), 6.77 (d, 1H, J= 8.4 Hz), 5.08 (s, 2H), 4.78 (bs, 1H), 4.19 (s, 2H), 1.93-2.06 (m, 2H); LCMS: purity: 97.2%; MS (m/e): 429.4 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.193	(R)-2-Chloro-N4-[4-(N-benzyloxycarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-4-pyrimidineamine (R950413)	A solution of (R)-4-amino-6-nitro-1-benzopyran in dioxane-water was treated with benzylchloroformate and sodium bicarbonate. The mixture was stirred for 1 hour at 0 °C and diluted with hexane. The mixture was filtered, and the remaining solid was carefully washed with hexane and dried under reduced vacuum to give (R)-4-(N-benzyloxycarbonyl)amino-6-nitro-1-benzopyran as a pale yellow solid. The crude material was dissolved in EtOH and treated with iron powder and ammonium chloride. The mixture was stirred for 2 hours at 85 °C and filtered to give a clear solution, which was diluted with water. The aqueous phase was extracted with dichloromethane and the organic phase was dried over magnesium sulfate. Removal of the volatiles under reduced pressure gave (R)-6-amino-4-(N-benzyloxycarbonyl)amino-1-benzopyran as a brown oil. The reaction of (R)-6-amino-4-(N-benzyloxycarbonyl)amino-1-benzopyran with 2,4-dichloro-5-fluoropyrimidine in MeOH for 2 hours at 70 °C followed by dilution with water and filtration of the resulting residue gave (R)-2-chloro-N4-[4-(N-benzyloxycarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-4-pyrimidineamine as a pale yellow solid. ^{1}H NMR (DMSO-d6): δ 9.87 (s, 1H), 9.23 (d, 1H, J= 2.4 Hz), 7.85 (d, 1H, J= 9.0 Hz), 7.25-7.45 (m, 7H), 6.77 (d, 1H, J= 8.4 Hz), 5.08 (s, 2H), 4.78 (bs, 1H), 4.19 (s, 2H), 1.93-2.06 (m, 2H); LCMS: purity: 96.1%; MS (m/e): 429.4 (MH^+).
7.4.194	(S)-N4-[4-(N-Benzyloxycarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950417)	(S)-2-chloro-N4-[4-(N-benzyloxycarbonyl)amino-1-benzopyran-6-yl)-5-fluoro-4-pyrimidineamine and equimolar amounts of 3-(N-methylamino)carbonylmethyleneoxyaniline were dissolved in MeOH and heated in a sealed tube at 110 °C for 24 hours. Aqueous work up gave (S)-N4-[4-(N-benzyloxycarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO-d6): δ 9.83 (bs, 1H), 9.58 (bs, 1H), 8.12 (d, 1H, J= 2.4 Hz), 7.94 (m, 1H), 7.80 (d, 1H, J= 8.7 Hz), 7.56 (m, 1H), 7.11-7.36 (m, 8H), 6.72 (d, 1H, J= 8.7 Hz), 6.56 (m, 1H), 5.04 (m, 2H), 4.79 (m, 1H), 4.17-4.30 (m, 4H), 2.63 (s, 3H), 1.91-2.08 (m, 2H); LCMS: purity: 93.6%; MS (m/e): 571.26 (M^+).

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Section Number	Name of compound and reference number	Experimental
7.4.195	(R)-N4-[4-(N-Benzyloxycarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950418)	(R)-2-chloro-N4-[4-(N-benzyloxycarbonyl)amino-1-benzopyran-6-yl)-5-fluoro-4-pyrimidineamine and equimolar amounts of 3-(N-methylamino)carbonylmethyleneoxyaniline were dissolved in MeOH and heated in a sealed tube at 110 °C for 24 hours. Aqueous work up gave (R)-N4-[4-(N-benzyloxycarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO-d6): δ 9.83 (bs, 1H), 9.58 (bs, 1H), 8.12 (d, 1H, J= 2.4 Hz), 7.94 (m, 1H), 7.80 (d, 1H, J= 8.7 Hz), 7.56 (m, 1H), 7.11-7.36 (m, 8H), 6.72 (d, 1H, J= 8.7 Hz), 6.56 (m, 1H), 5.04 (m, 2H), 4.79 (m, 1H), 4.17-4.30 (m, 4H), 2.63 (s, 3H), 1.91-2.08 (m, 2H); LCMS: purity: 92.5%; MS (m/e): 571.26 (M^-).
7.4.196	(S)-N4-(4-Amino-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950420)	(S)-N4-[4-(N-Benzyloxycarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and Pd/C 10% (50% water content) were suspended in MeOH and hydrogenated in a Parr apparatus for 14 hours (22 °C, 40 psi). The suspension was filtered over celite and washed with MeOH. The combined filtrates were concentrated under reduced pressure to give (S)-N4-(4-amino-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO-d6): δ 9.60 (s, 1H), 9.46 (s, 1H), 8.73 (bs, 3H), 8.00-8.10 (m, 3H), 7.47 (s, 1H), 7.42 (m, 1H), 7.29 (d, 1H, J= 7.2 Hz), 7.11 (t, 1H, J= 7.2 Hz), 6.82 (d, 1H, J 7.0 Hz), 6.46 (m, 1H), 4.23-4.46 (m, 3H), 4.31 (s, 3H), 2.63 (d, 3H, J= 4.8 Hz), 2.09-2.29 (m, 2H); LCMS: purity: 98.1%; MS (m/e): 437.20 (M^-).
7.4.197	(R)-N4-(4-Amino-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950421)	(R)-N4-[4-(N-Benzyloxycarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and Pd/C 10% (50% water content) were suspended in MeOH and hydrogenated in a Parr apparatus for 14 hours (22 °C, 40 psi). The suspension was filtered over celite and washed with MeOH. The combined filtrates were concentrated under reduced pressure to give (R)-N4-(4-amino-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO-d6): δ 9.60 (s, 1H), 9.46 (s, 1H), 8.73 (bs, 3H), 8.00-8.10 (m, 3H), 7.47 (s, 1H), 7.42 (m, 1H), 7.29 (d, 1H, J= 7.2 Hz), 7.11 (t, 1H, J= 7.2 Hz), 6.82 (d, 1H, J 7.0 Hz), 6.46 (m, 1H), 4.23-4.46 (m, 3H), 4.31 (s, 3H), 2.63 (d, 3H, J= 4.8 Hz), 2.09-2.29 (m, 2H); LCMS: purity: 98.6%; MS (m/e): 437.20 (M^-).

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Section Number	Name of compound and reference number	Experimental
7.4.198	(±) N4-[4-(N-tert-Butoxycarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-N2-(indazol-6-yl)-2,4-pyrimidinediamine (R950422)	A mixture of equimolar amounts of (±) N4-[4-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl]-2-chloro-5-fluoro-4-pyrimidineamine and 6-aminoindazole in MeOH was stirred in a sealed tube for 24 hours at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give (±) N4-[4-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-N2-(indazol-6-yl)-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.7%; MS (m/e): 490.23 (M^-).
7.4.199	(±) N4-(4-Amino-1-benzopyran-6-yl)-5-fluoro-N2-(indazol-6-yl)-2,4-pyrimidinediamine (R950423)	(±) N4-[4-(N-tert-Butoxycarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-N2-(indazol-6-yl)-2,4-pyrimidinediamine was suspended in dichloromethane and treated with trifluoroacetic acid. The mixture was stirred for 30 minutes at 22 °C and concentrated to dryness under reduced pressure. The residue was neutralized with sodium bicarbonate and crystallized from MeOH-water to give (±) N4-(4-amino-1-benzopyran-6-yl)-5-fluoro-N2-(indazol-6-yl)-2,4-pyrimidinediamine as a white solid. LCMS: purity: 89.0%; MS (m/e): 390.21 (M^-).
7.4.200	(±) N4-(4-Amino-1-benzopyran-6-yl)-N2-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950424)	A mixture of equimolar amounts of (±) N4-[4-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl]-2-chloro-5-fluoro-4-pyrimidineamine and the HCl salt of 3,5-dichloro-4-methoxyaniline in MeOH was stirred in a sealed tube for 24 hours at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give (±) N4-(4-amino-1-benzopyran-6-yl)-N2-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO-d6): δ 9.42 (s, 1H), 9.33 (s, 1H), 8.08 (d, 1H, J= 2.4 Hz), 7.76 (s, 2H), 7.61 (m, 1H), 7.36 (d, 1H, J= 2.7, 8.4 Hz), 6.78 (d, 1H, J= 8.7 Hz), 3.72-4.23 (m, 3H), 3.72 (s, 3H), 1.85-2.18 (m, 2H); LCMS: purity: 97.3%; MS (m/e): 448.12 (M^-).
7.4.201	(±) N4-[4-(N-tert-Butoxycarbonyl)amino-1-benzopyran-6-yl]-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950425)	A mixture of equimolar amounts of (±) N4-[4-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl]-2-chloro-5-fluoro-4-pyrimidineamine and 3,5-dimethoxyaniline in MeOH was stirred in a sealed tube for 24 hours at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give (±) N4-[4-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl]-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO-d6): δ 9.24 (s, 1H), 8.96 (s, 1H), 8.02 (d, 1H, J= 2.4 Hz), 7.61 (m, 1H), 7.28 (m, 2H), 6.91 (s, 2H), 6.68 (d, 1H, J= 8.7 Hz), 6.03 (m, 1H), 4.68 (m, 1H), 4.17 (m, 2H), 1.80-2.05 (m, 2H), 1.41 (s, 9H); LCMS: purity: 93.9%; MS (m/e): 510.24 (M^-).

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Section Number	Name of compound and reference number	Experimental
7.4.202	(±) N4-(4-Amino-1-benzopyran-6-yl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950426)	(±) N4-[4-(N-tert-Butoxycarbonyl)amino-1-benzopyran-6-yl]-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine was suspended in dichloromethane and treated with trifluoroacetic acid. The mixture was stirred for 30 minutes at 22 °C and concentrated to dryness under reduced pressure. The residue was neutralized with sodium bicarbonate and crystallized from MeOH-water to give N4-(4-amino-1-benzopyran-6-yl)-N2-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.1%; MS (m/e): 410.23 (M^-).
7.4.203	(±) N4-[4-(N-tert-Butoxycarbonyl)amino-1-benzopyran-6-yl]-N2-(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950427)	A mixture of equimolar amounts of (±) N4-[4-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl]-2-chloro-5-fluoro-4-pyrimidineamine and 3-chloro-4-methoxyaniline in MeOH was stirred in a sealed tube for 24 hours at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give (±) N4-[4-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl]-N2-(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 93.7%; MS (m/e): 514.21 (M^-).
7.4.204	(±) N4-(4-Amino-1-benzopyran-6-yl)-N2-(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950428)	(±) N4-[4-(N-tert-Butoxycarbonyl)amino-1-benzopyran-6-yl)-N2-(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine was suspended in dichloromethane and treated with trifluoroacetic acid. The mixture was stirred for 30 minutes at 22 °C and concentrated to dryness under reduced pressure. The residue was neutralized with sodium bicarbonate and crystallized from MeOH-water to give (±) N4-(4-amino-1-benzopyran-6-yl)-N2-(3-chloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 91.4%; MS (m/e): 414.13 (M^-).
7.4.205	(±) N4-[4-(N-tert-Butoxycarbonyl)amino-1-benzopyran-6-yl]-N2-(3,4-dichlorophenyl)-5-fluoro 2,4-pyrimidinediamine (R950429)	A mixture of equimolar amounts of (±) N4-[4-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl]-2-chloro-5-fluoro-4-pyrimidineamine and 3,4-dichloroaniline in MeOH was stirred in a sealed tube for 24 hours at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give (±) N4-[4-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl]-N2-(3,4-dichlorophenyl)-5-fluoro 2,4-pyrimidinediamine as a white solid. LCMS: purity: 86.7%; MS (m/e): 518.17 (M^-).

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Section Number	Name of compound and reference number	Experimental
7.4.206	(±) N4-(4-Amino-1-benzopyran-6-yl)-N2-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R950430)	(±) N4-[4-(N-tert-Butoxycarbonyl)amino-1-benzopyran-6-yl]-N2-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine was suspended in dichloromethane and treated with trifluoroacetic acid. The mixture was stirred for 30 minutes at 22 °C and concentrated to dryness under reduced pressure. The residue was neutralized with sodium bicarbonate and crystallized from MeOH-water to give (±) N4-(4-amino-1-benzopyran-6-yl)-N2-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 88.3%; MS (m/e): 418.16 (M^-).
7.4.207	(±) N2-[4-(N-tert-Butoxycarbonylamino-1-benzopyran-6-yl]-N4-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950432)	A mixture of equimolar amounts of 2-chloro-N4-(3,5-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine and (±) 6-amino-4-(N-tert-butoxycarbonyl)amino-1-benzopyran in MeOH was stirred in a sealed tube for 24 hours at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give (±) N2-[4-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl]-N4-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. LCMS: purity: 97.2%; MS (m/e): 510.3 (M^-).
7.4.208	(±) N2-[4-(N-tert-Butoxycarbonyl)amino-1-benzopyran-6-yl]-N4-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R950433)	A mixture of equimolar amounts of 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine and (±) 6-amino-4-(N-tert-butoxycarbonyl)amino-1-benzopyran in MeOH was stirred in a sealed tube for 24 hours at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give (±) N2-[4-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl]-N4-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO-d6): δ 9.51 (s, 1H), 9.12 (s, 1H), 8.12 (d, 1H. J= 2.4 Hz), 8.06 (d, 1H, J= 3.6 Hz), 7.82 (m, 1H), 7.49 (d, 1H, J= 8.7 Hz), 7.43 (m, 1H), 7.32 (d, 1H, J= 9.0 Hz), 7.25 (m, 1H), 6.67 (d, 1H, J= 8.7 Hz), 4.12-4.65 (m, 3H), 1.84-1.99 (m, 2H), 1.40 (s, 9H); LCMS: purity: 97.2%; MS (m/e): 518.3 (M^-).
7.4.209	N2-[4(R,S)-(N-tert-Butoxycarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-N4-[2-(S)-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl]-2,4-pyrimidinediamine (R950434)	A mixture of equimolar amounts of (S)-2-chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and (±) 6-amino-4-(N-tert-butoxycarbonyl)amino-1-benzopyran in MeOH was stirred in a sealed tube for 24 hours at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N2-[4-(R,S)-(N-tert-butoxycarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-N4-[2-(S)-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 89.3%; MS (m/e): 537.42 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.210	(±) N2-(4-Amino-1-benzopyran-6-yl]-N4-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950436)	(±) N2-[4-(N-tert-Butoxycarbonylamino-1-benzopyran-6-yl]-N4-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine was suspended in dichloromethane and treated with trifluoroacetic acid. The mixture was stirred for 30 minutes at 22 °C and concentrated to dryness under reduced pressure. The residue was neutralized with sodium bicarbonate and crystallized from MeOH-water to give (±) N2-(4-amino-1-benzopyran-6-yl]-N4-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 92.4%; MS (m/e): 410.17 (M^-).
7.4.211	(±) N2-(4-Amino-1-benzopyran-6-yl)-N4-(3,4-dichlorophenyl)-5-fluoro 2,4-pyrimidinediamine (R950437)	(±) N2-[4-(N-tert-Butoxycarbonyl)amino-1-benzopyran-6-yl]-N4-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine was suspended in dichloromethane and treated with trifluoroacetic acid. The mixture was stirred for 30 minutes at 22 °C and concentrated to dryness under reduced pressure. The residue was neutralized with sodium bicarbonate and crystallized from MeOH-water to give (±) N2-(4-amino-1-benzopyran-6-yl)-N4-(3,4-dichlorophenyl)-5-fluoro 2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.51 (s, 1H), 8.99 (s, 1H), 8.09 (d, 1H, J= 2.4 Hz), 8.07 (d, 1H, J= 3.6 Hz), 7.45-7.81 (m, 2H), 7.30 (dd, 1H, J= 2.4, 9.0 Hz), 6.62 (d, 1H, J= 8.7 Hz), 3.78-4.20 (m, 3H), 1.73-2.05 (m, 2H); LCMS: purity: 100%; MS (m/e): 420.29 (M^-, 100).
7.4.213	N2-[4(R,S)-Amino-1-benzopyran-6-yl)-5-fluoro-N4-(2(S)-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl]-2,4-pyrimidinediamine (R950438)	N2-[4 (R,S)-(N-tert-Butoxycarbonyl)amino-1-benzopyran-6-yl]5-fluoro-N4-(2 (S)-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine was suspended in dichloromethane and treated with trifluoroacetic acid. The mixture was stirred for 30 minutes at 22 °C and concentrated to dryness under reduced pressure. The residue was neutralized with sodium bicarbonate and crystallized from MeOH-water to give N2-[4(R,S)-amino-1-benzopyran-6-yl)-5-fluoro-N4-(2(S)-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl]-2,4-pyrimidinediamine. LCMS: purity: 97.9%; MS (m/e): 435.37 (M^-).
7.4.214	N2-[(1R,2R)-2-Aminocyclohex-1-yl)-N4-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950439)	A mixture of 2-chloro-N4-(3,5-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine and 5 equivalents of (R,R)-1,2-diaminocyclohexane in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N2-[(1R,2R)-2-aminocyclohex-1-yl)-N4-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 94.6%; MS (m/e): 360.20 (M^-).

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Section Number	Name of compound and reference number	Experimental
7.4.215	N2-[(1R,2R)-2-Aminocyclohex-1-yl)-N4-(3,5-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R950440)	A mixture of N4-(3,4-dichlorophenyl)-2-chloro-5-fluoro-4-pyrimidineamine and 5 equivalents of (R,R)-1,2-diaminocyclohexane in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N2-[(1R,2R)-2-aminocyclohex-1-yl)-N4-(3,5-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.49 (s, 1H), 9.26 (s, 1H), 8.02, 7.44-7.54 (m, 3H), 6.81 (d, 1H, J= 9.0 Hz), 3.31 (m, 1H), 2.78 (m, 1H), 1.15-1.98 (m, 8H); LCMS: purity: 98.3%; MS (m/e): 368.07 (M^-, 100).
7.4.216	N2-((1R,2R)-2-Aminocyclohex-1-yl)-5-fluoro-N4-[(2S)-2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R950441)	A mixture of (S)-2-chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and 5 equivalents of (R,R)-1,2-diaminocyclohexane in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N2-((1R,2R)-2-aminocyclohex-1-yl)-5-fluoro-N4-[(2S)-2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. LCMS: purity: 91.8%; MS (m/e): 385.15 (M^-).
7.4.217	(R,R)-N4-(4,4-Dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-N2-(2-aminocyclohexan-1-yl)-2,4-pyrimidinediamine (R950442)	A mixture of N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-2-chloro-5-fluoro-4-pyrimidineamine and 5 equivalents of (R,R)-1,2-diaminocyclohexane in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give (R,R)-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-N2-(2-aminocyclohexan-1-yl)-2,4-pyrimidinediamine LCMS: purity: 92.1%; MS (m/e): 411.14 (M^-).
7.4.218	N2-((1R,2R)-2-Aminocyclohex-1-yl)-5-fluoro-N4-[(2R,S)-2-(2-hydroxy)ethyl-3-oxo-4H-benz[1,4]oxazin-6-yl]-2,4-pyrimidinediamine (R950443)	An mixture of (±)-2-chloro-N4-[2-(2-hydroxy)ethyl-3-oxo-4H-benz[1,4]oxazin-6-yl]-4-pyrimidineamine and 5 equivalents of (R,R)-1,2-diaminocyclohexane in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N2-((1R,2R)-2-aminocyclohex-1-yl)-5-fluoro-N4-[(2R,S)-2-(2-hydroxy)ethyl-3-oxo-4H-benz[1,4]oxazin-6-yl]-2,4-pyrimidinediamine. LCMS: purity: 86.1%; MS (m/e): 415.17 (M^-).
7.4.219	N4-(3,5-Dimethoxyphenyl)-N2-[4-(2-N,N-diethylaminoethyleneamino)carbonylphenyl]-5-fluoro-2,4-pyrimidinediamine (R950444)	A mixture of equimolar amounts of 2-chloro-N4-(3,5-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine and 4-[(2-N,N-diethylaminoethyleneamino)carbonyl]aniline in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N4-(3,5-dimethoxyphenyl)-N2-[4-(2-N,N-diethylaminoethyleneamino)carbonylphenyl]-5-fluoro- 2,4-pyrimidinediamine. LCMS: purity: 89.1%; MS (m/e): 481.19 (M^-).

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Section Number	Name of compound and reference number	Experimental
7.4.220	N4-(3,4-Dichlorophenyl)-N2-[4-(2-N,N-diethylaminoethyleneamino)carbonylphenyl]-5-fluoro 2,4-pyrimidinediamine (R950445)	A mixture of equimolar amounts of 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine and 4-[(2-N,N-diethylaminoethyleneamino)carbonyl]aniline in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N4-(3,4-dichlorophenyl)-N2-[4-(2-N,N-diethylaminoethyleneamino)carbonylphenyl]-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 93.2%; MS (m/e): 489.12 (M^-).
7.4.221	(S)-N2-[4-(2-N,N-Diethylaminoethyleneamino)carbonylphenyl]-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R950446)	A mixture of equimolar amounts of (S)-2-chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and 4-[(2-N,N-diethylaminoethyleneamino)carbonyl]aniline in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give (S)-N2-[4-(2-N,N-diethylaminoethyleneamino)carbonylphenyl]-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. LCMS: purity: 93.9%; MS (m/e): 506.15 (M^-).
7.4.222	N4-(4,4-Dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-N2-[4-(N,N-diethylaminoethylenaminocarbonyl)phenyl]-2,4-pyrimidinediamine (R950447)	A mixture of equimolar amounts of N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-2-chloro-5-fluoro-4-pyrimidineamine and 1-amino-4-(N,N-diethylaminoethylenaminocarbonyl)benzene in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-N2-[4-(N,N-diethylaminoethylenaminocarbonyl)phenyl]-2,4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 11.32 (s, 1H), 9.96 (s, 1H), 9.70 (s, 1H), 9.55 (s, 1H), 8.66 (m, 1H), 7.67-8.24 (m, 7H), 3.59 (m, 2H), 3.17 (m, 6H), 1.53 (s, 6H), 1.22 (t, 6H, J= 7.2 Hz); LCMS: purity 94.7%; MS (m/e): 532.21 (M^-).
7.4.223	(±)-N2-[4-(2-N,N-Diethylaminoethyleneamino)carbonylphenyl]-5-fluoro-N4-[(2-hydroxyethyl)-3-oxo-4H-benz[1,4]oxazin-6-yl]-2,4-pyrimidinediamine (R950448)	A mixture of equimolar amounts of (±)-2-chloro-5-fluoro-N4-[(2-hydroxyethyl)-3-oxo-4H-benz[1,4]oxazin-6-yl]-4-pyrimidineamine and 4-[(2-N,N-diethylaminoethyleneamino)carbonyl]aniline in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give (±)-N2-[4-(2-N,N-diethylaminoethyleneamino)carbonylphenyl]-5-fluoro-N4-[(2-hydroxyethyl)-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. LCMS: purity: 93.7%; MS (m/e): 536.17 (M^-).

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Section Number	Name of compound and reference number	Experimental
7.4.224	N2-[4-(2-N,N-Diethylaminoethyleneamino)carbonylphenyl]-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950449)	A mixture of equimolar amounts of 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidineamine and 4-[(2-N,N-diethylaminoethyleneamino)carbonyl]aniline in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N2-[4-(2-N,N-diethylaminoethyleneamino)carbonylphenyl]-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 86.8%; MS (m/e): 528.18 (M^-).
7.4.225	N2-(4-Aminocarbonylphenyl)-N4-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950450)	A mixture of equimolar amounts of 2-chloro-N4-(3,5-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine and 4-aminocarbonylaniline in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N2-(4-aminocarbonylphenyl)-N4-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.34 (s, 1H), 10.14 (s, 1H), 8.30 (d, 1H, J= 2.4 Hz), 7.75 (d, 2H, J= 9.0 Hz), 7.62 (d, 2H, J= 8.7 Hz), 7.25-7.35 (m, 2H), 6.90 (m, 2H), 6.35 (m, 1H), 3.73 (s, 3H), 3.70 (s, 3H); LCMS: purity: 89.2%; MS (m/e): 382.16 (M^-).
7.4.226	N2-(4-Aminocarbonylphenyl)-N4-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R950451)	A mixture of equimolar amounts of 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine and 4-aminocarbonylaniline in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N2-(4-aminocarbonylphenyl)-N4-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 93.9%; MS (m/e): 390.09 (M^-).
7.4.227	(S)-N2-(4-Aminocarbonylphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R950452)	A mixture of equimolar amounts of (S)-2-chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and 4-aminocarbonylaniline in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give (S)-N2-(4-aminocarbonylphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. LCMS: purity: 92.3%; MS (m/e): 407.18 (M^-).
7.4.228	N4-(4,4-Dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-N2-(4-aminocarbonylphenyl)-2,4-pyrimidinediamine (R950453)	A mixture of equimolar amounts of N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-2-chloro-5-fluoro-4-pyrimidineamine and 1-amino-4-aminocarbonylbenzene in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-N2-(4-aminocarbonylphenyl)-2,4-pyrimidinediamine LCMS: purity: 92.2%; MS (m/e): 433.17 (M^-).

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Section Number	Name of compound and reference number	Experimental
7.4.229	(±)-N2-(4-Aminocarbonylphenyl)-5-fluoro-N4-[(2-hydroxyethylene)-3-oxo-4H-benz[1,4]oxazin-6-yl]-2,4-pyrimidinediamine (R950454)	A mixture of equimolar amounts of (±)-2-chloro-N4-[(2-hydroxyethylene)-3-oxo-4H-benz[1,4]oxazin-6-yl]-4-pyrimidineamine and 4-aminocarbonylaniline in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give (±)-N2-(4-aminocarbonylphenyl)-5-fluoro-N4-[(2-hydroxyethylene)-3-oxo-4H-benz[1,4]oxazin-6-yl]-2,4-pyrimidinediamine. LCMS: purity: 90.4%; MS (m/e): 437.14 (M^-).
7.4.230	N2-(4-Aminocarbonylphenyl)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950455)	A mixture of equimolar amounts of 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4}oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 4-aminocarbonylaniline in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N2-(4-aminocarbonylphenyl)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 90.8%; MS (m/e): 429.14 (M^-).
7.4.231	N2-[4-(N-tert-Butoxycarbonylamino)methylenephenyl]-N4-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950456)	A mixture of equimolar amounts of 2-chloro-N4-(3,5-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine and 4-(tert-butoxycarbonylaminomethylene)aniline in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N2-[4-(N-tert-butoxycarbonylamino)methylenephenyl]-N4-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 84.3%; MS (m/e): 468.26 (M^-).
7.4.232	N2-[4-(N-tert-Butoxycarbonylamino)methylenephenyl]-N4-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R950458)	A mixture of equimolar amounts of 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine and 4-(tert-butoxycarbonylaminomethylene)aniline in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N2-[4-(N-tert-butoxycarbonylamino)methylenephenyl]-N4-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 91.3%; MS (m/e): 476.13 (M^-).
7.4.233	(S)-N2-[4-(N-tert-Butoxycarbonylamino)methylenephenyl]-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R950460)	A mixture of equimolar amounts of (S)-2-chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and 4-(tert-butoxycarbonylaminomethylene)aniline in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give (S)-N2-[4-(N-tert-butoxycarbonylamino)methylenephenyl]-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. LCMS: purity: 93.5%; MS (m/e): 493.22 (M^-).

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Section Number	Name of compound and reference number	Experimental
7.4.234	N2-[4-(N-tert-Butoxycarbonylamino)methylenephenyl]-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-2,4-pyrimidinediamine (R950462)	A mixture of equimolar amounts of N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-2-chloro-5-fluoro-4-pyrimidineamine and 4-amino-N-tert-butoxycarbonylbenzylamine in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N2-[4-(N-tert-butoxycarbonylamino)methylenephenyl]-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 92.2%; MS (m/e): 519.21 (M^-, 100).
7.4.235	N2-[4-(N-tert-Butoxycarbonylaminomethylene)phenyl]-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950464)	A mixture of equimolar amounts of 2-chloro-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 4-(tert-butoxycarbonylaminomethylene)aniline in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N2-[4-(N-tert-butoxycarbonylaminomethylene)phenyl]-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 89.2%; MS (m/e): 515.18 (M^-).
7.4.236	N2-(4-Aminomethylenephenyl)-N4-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R950457)	N2-[4-(N-tert-Butoxycarbonylamino)methylenephenyl]-N4-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine was suspended in dichloromethane and treated with trifluoroacetic acid. The mixture was stirred for 30 minutes at 22 °C and concentrated to dryness under reduced pressure. The residue was neutralized with sodium bicarbonate and crystallized from MeOH-water to give N2-(4-aminomethylenephenyl)-N4-(3,5-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 92.2%; MS (m/e): 368.20 (M^-).
7.4.237	N2-(4-Aminomethylenephenyl)-N4-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R950459)	N2-[4-(N-tert-Butoxycarbonylamino)methylenephenyl]-N4-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine was suspended in dichloromethane and treated with trifluoroacetic acid The mixture was stirred for 30 minutes at 22 °C and concentrated to dryness under reduced pressure. The residue was neutralized with sodium bicarbonate and crystallized from MeOH-water to give N2-(4-aminomethylenephenyl)-N4-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 94.0%; MS (m/e): 376.06 (M^-).
7.4.238	(S)-N2-(4-Aminomethylenephenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R950461)	(S)-N2-[4-(N-tert-Butoxycarbonylamino)methylenephenyl]-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine was suspended in dichloromethane and treated with trifluoroacetic acid. The mixture was stirred for 30 minutes at 22 °C and concentrated to dryness under reduced pressure. The residue was neutralized with sodium bicarbonate and crystallized from MeOH-water to give (S)-N2-(4-aminomethylenephenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. LCMS: purity: 94.7%; MS (m/e): 393.15 (M^-).

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Section Number	Name of compound and reference number	Experimental
7.4.239	N2-(4-Aminomethylenphenyl)-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-2,4-pyrimidinediamine (R950463)	N4-(4,4-Dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-N2-[4-(N-tert-butoxycarbonylaminomethylen)phenyl]-2,4-pyrimidinediamine was suspended in dichloromethane and treated with trifluoroacetic acid. The mixture was stirred for 30 minutes at 22 °C and concentrated to dryness under reduced pressure. The residue was neutralized with sodium bicarbonate and crystallized from MeOH-water to give N2-(4-aminomethylenphenyl)-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 92.3%; MS (m/e): 419.49 (M^-).
7.4.240	N2-(4-Aminomethylenephenyl)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R950465)	N2-[4-(N-tert-Butoxycarbonylaminomethylene)phenyl]-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine was suspended in dichloromethane and treated with trifluoroacetic acid. The mixture was stirred for 30 minutes at 22 °C and concentrated to dryness under reduced pressure. The residue was neutralized with sodium bicarbonate and crystallized from MeOH-water to give N2-(4-aminomethylenephenyl)-N4-(2,2-difluoro-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 93.9%; MS (m/e): 415.3 (M^-).
7.4.241	N4-(3,5-Dimethoxyphenyl)-N2-(3-N,N-diethylaminopropyl)-5-fluoro-2,4-pyrimidinediamine (R950469)	A mixture of equimolar amounts of 2-chloro-N4-(3,5-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine and 3-N,N-diethylaminopropylamine in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N4-(3,5-dimethoxyphenyl)-N2-(3-N,N-diethylaminopropyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 94.3%; MS (m/e): 378.33 (MH^+).
7.4.242	N4-(3,4-Dichlorophenyl)-N2-(3-N,N-diethylaminopropyl)-5-fluoro-2,4-pyrimidinediamine (R950470)	A mixture of equimolar amounts of 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine and 3-N,N-diethylaminopropylamine in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N4-(3,4-dichlorophenyl)-N2-(3-N,N-diethylaminopropyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 100%; MS (m/e): 386.18 (MH^+).
7.4.243	(S)-N2-(3-N,N-Diethylaminopropyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R950471)	A mixture of equimolar amounts of (S)-2-chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidineamine and 3-N,N-diethylaminopropylamine in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give (S)-N2-(3-N,N-diethylaminopropyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. LCMS: purity: 86.3%; MS (m/e): 403.34 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.244	N4-(4,4-Dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-N2-(3-N,N-diethylaminopropyl)-5-fluoro-2,4-pyrimidinediamine (R950472)	A mixture of equimolar amounts of N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-2-chloro-5-fluoro-4-pyrimidineamine and 3-N,N-diethylaminopropylamine in MeOH was stirred in a sealed tube for 3 days at 100 °C. Aqueous work up gave a brown solid which was further purified by column chromatography on silica gel to give N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-N2-(3-N,N-diethylaminopropyl)-5-fluoro-2,4-pyrimidinediamine. LCMS: purity: 95.9%; MS (m/e): 429.51 (MH^+).
7.4.245	(±)-5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[4-(N-p-toluenesulfonyl)amino-1-benzopyran-6-yl)-2,4-pyrimidinediamine (R950493)	A solution of (±)-N4-(4-amino-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine in THF:DMF was treated with p-tolunesulfonyl chloride and triethylamine. The mixture was stirred for 1 hour at 0 °C and diluted with hexane. The reaction mixture was filtered, and the remaining solids were dried and subjected to column chromatography to (±)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-[4-(N-p-toluenesulfonyl)amino-1-benzopyran-6-yl)-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO-d6): δ 9.24 (s, 1H), 9.00 (s, 1H), 8.01 (d, 1H, J= 2.4 Hz), 8.16 (d, 1H, J= 7.8 Hz), 7.63-8.05 (m, 4H), 7.21-7.37 (m, 5H), 7.08 (t, 1H, J= 7.8 Hz), 6.69 (d, 1H, J= 8.4 Hz), 6.46 (d, 1H, J= 6.9 Hz), 4.40 (m, 1H0, 4.29 (s, 1H), 4.10 (m, 2H), 3.33 (s, 3H), 2.64 (s, 3H), 1.88-2.08 (m, 2H); LCMS: purity: 94.0%; MS (m/e): 591.16 (M^-).
7.4.246	(±)-2-Chloro-5-fluoro-N4-[4-(N-methansulfonyl)amino-1-benzopyran-6-yl)-4-pyrimidineamine	A solution of (±)-4-amino-6-nitro-1-benzopyran in DMF was treated with triethylamine and methanesulfonyl chloride. The mixture was stirred for 30 minutes at 0 °C and diluted with dichloromethane. Aqueous workup gave the expected (±)-4-(N-methanesulfonyl)amino-6-nitro-1-benzopyran as a yellow solid. This solid and Pd/C (10%) were suspended in MeOH and the mixture was hydrogenated at 22 °C for 3 hours (40psi). The mixture was filtered and concentrated to dryness to give (±)-4-(N-methanesulfonyl)amino-6-amino-1-benzopyran as a brown oil, which was reacted with 2,4-dichloro-5-fluoropyrimidine in MeOH for 2 hours at 70 °C. The mixture was diluted with water and the resulting precipitate was filtered to give (±)-2-chloro-5-fluoro-N4-[4-(N-methansulfonyl)amino-1-benzopyran-6-yl)-4-pyrimidineamine as a pale yellow solid. LCMS: purity: 91.3%; MS (m/e): 373.02 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.247	(±)-5-Fluoro N4-[4-(N-methanesulfonyl)amino-1-benzopyran-6-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950494)	A solution of equimolar amount of (±)-2-chloro-5-fluoro-N4-[4-(N-methansulfonyl)amino-1-benzopyran-6-yl)-4-pyrimidineamine and 3-(N-methylamino)carbonylmethyleneoxyaniline were dissolved in MeOH and heated in a sealed tube at 110 °C for 24 hours. Aqueous work up gave (±)-5-fluoro N4-[4-(N-methanesulfonyl)amino-1-benzopyran-6-yl)-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO-d6): δ 9.33 (s, 1H), 8.91 (s, 1H), 8.03 (d, 1H, J= 2.4 Hz), 7.94 (m, 1H), 7.78 (m, 1H), 7.66 (d, 1H, J= 8.4 Hz), 7.22-7.62 (m, 3H), 7.09 (t, 1H, J= 8.1 Hz), 6.72 (d, 1H, J= 8.7 Hz), 6.45 (m 1H), 4.56 (m, 1H), 4.32 (s, 2H), 4.17 (m, 2H), 3.29 (s, 3H), 2.65 (s, 3H), 1.75-2.16 (m, 2H); LCMS: purity: 95.6%; MS (m/e): 515.05 (M^-).
7.4.248	(±)-N4-[4-N-(N,N-Dimethylaminomethylencarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950416)	A solution of (±)-N4-(4-amino-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and N,N-diaminoglycine in DMF was treated with PyBroP followed by diisopropylethylamine. The mixture was stirred for 30 minutes at 22 °C and diluted with hexane. The mixture was filtered, and the remaining solid was dried and subjected to column chromatography to give (±)-N4-[4-N-(N,N-dimethylaminomethylencarbonyl)amino-1-benzopyran-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. LCMS: purity: 95.6%; MS (m/e): 522.26 (M^-).
7.4.249	(±)-N4-[4-N-(N,N-Dimethylaminomethylencarbonyl)-N-methylamino-1-benzopyran-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R950419)	A solution of (±)-N4-(4-amino-1-benzopyran-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine and N,N-diaminoglycine in DMF was treated with PyBroP followed by diisopropylethylamine. The mixture was stirred for 30 minutes at 22 °C and diluted with hexane. The mixture was filtered, and the remaining solids were dried and subjected to column chromatography to give (±)-N4-[4-N-(N,N-dimethylaminomethylencarbonyl)-N-methylamino-1-benzopyran-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine as a white solid. ^{1}H NMR (DMSO-d6, 2 rotamers): δ 9.28 (s, 1H), 9.19 (s, 1H), 9.03 (s, 1H), 8.92 (s, 1H), 7.01-8.04 (14H), 6.74 (d, 2H, J= 9.0 Hz), 6.45 (m, 2H), 5.80 (m, 1H), 5.51 (m, 1H), 4.08-4.31 (m, 8H), 3.15-3.39 (m, 4H), 3.32 (s, 6H), 3.30 (s, 3H), 3 27 (m, 3H), 2.64 (s, 6H), 1.90-2.12 (m, 4H); LCMS: purity: 94.3%; MS (m/e): 536.30 (M^-).

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Section Number	Name of compound and reference number	Experimental
7.4.250	N4-Cyclopropyl-5-fluoro-N2-(4-morpholinophenyl)-2,4-pyrimidinediamine (R945356)	In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine (100 mg, 0.6 mmol) and cyclopropylamine (50 mg) were reacted to yield 2-chloro-N4-cyclopropyl-5-fluoro-4-pyrimidineamine. In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-morpholinoaniline (150 mg) and 2-chloro-N4-cyclopropyl-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N4-cyclopropyl-5-fluoro-N2-(4-morpholinophenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 0.63 (m, 2H), 0.88 (m, 2H), 2.82 (m, 1H), 3.10 (t, J= 4.8 Hz, 4H), 3.86 (t, J= 4.8 Hz, 4H), 5.16 (s, 1H), 6.89 (d, J= 9.0 Hz, 2H), 6.94 (s, 1H), 7.55 (d, J= 9.0 Hz, 2H), 7.74 (d, J= 3.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 169.88; LCMS: ret. time: 7.13 min.; purity: 91.61%; MS (m/e): 330.26 (MH^+).
7.4.251	N2-Cyclopropyl-5-fluoro-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine (R945357)	In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine (300 mg, 1.8 mmol) and 4-morpholinoaniline (200 mg) were reacted at room temperature to yield 2-chloro-5-fluoro-N4-(4-morpholinophenyl)-4-pyrimidineamine. In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, cyclopropylamine(200 mg) and 2-chloro-5-fluoro-N4-(4-morpholinophenyl)-4-pyrimidineamine (100 mg) were reacted to give N2-cyclopropyl-5-fluoro-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$). δ 0.52 (m, 2H), 0.77 (m, 2H), 2.69 (m, 1H), 3.12 (t, J= 4.8 Hz, 4H), 3.85 (t, J= 4.8 Hz, 4H), 5.16 (s, 1H), 6.66 (s, 1H), 6.89 (d, J= 9.0 Hz, 2H), 7.60 (d, J= 9.0 Hz, 2H), 7.84 (d, J= 3.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 170.72; LCMS: ret. time: 6.77 min.; purity: 88.87%; MS (m/e): 330.22 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.252	N2-Cyclobutyl-5-fluoro-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine (R945358)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, cyclobutylamine (200 mg) and 2-chloro-5-fluoro-N4-(4-morpholinophenyl)-4-pyrimidineamine (100 mg) were reacted to give N2-cyclobutyl-5-fluoro-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 1.68-1.90 (m, 4H), 2.34-2.43 (m, 2H), 3.14 (t, J= 4.8 Hz, 4H), 3.87 (t, J= 4.8 Hz, 4H), 4.32 (m, J= 7.8 Hz, 1H), 5.18 (s, 1H), 6.61 (s, 1H), 6.92 (d, J= 9.0 Hz, 2H), 7.53 (d, J= 9.0 Hz, 2H), 7.78 (d, J= 3.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 171.07; LCMS: ret. time: 8.05 min.; purity: 79.69%; MS (m/e): 344.22 (MH^+).
7.4.253	N2-[3-(N-Cyclopropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine (R945360)	3-(Methoxycarbonylmethyleneoxy)nitrobenzene (2 g), cyclopropylamine (1 g) and triethylamine (1 mL) were dissolved in methanol (10 mL) and heated in a sealed tube at 100 °C overnight. The reaction solution was then diluted with 1N HCl aq. solution (80 mL). The white precipitation was collected by filtration and washed with water, dried to give 3-(N-cyclopropylaminocarbonylmethyleneoxy)nitrobenzene. ^{1}H NMR ($CDCl_3$): δ 0.60 (m, 2H), 0.85 (m, 2H), 2.80 (m, J= 3.6 Hz, 1H), 4.53 (s, 2H), 6.61 (br, 1H, NH), 7.23 (ddd, J= 0.6 and 2.7 and 8.4 Hz, 1H), 7.49 (t, J= 8.4 Hz, 1H), 7.77 (t, J= 2.4 Hz, 1H), 7.90 (ddd, J= 0.9 and 2.1 and 8.1 Hz, 1H). 3-(N-Cyclopropylaminocarbonylmethyleneoxy)nitrobenzene was reduced under hydrogenolysis conditions using 10% Pd-C in methanol at 40 psi for 2h. The catalyst was filtered off. The filtrate was evaporated to give 3-(N-cyclopropylaminocarbonylmethyleneoxy)aniline. ^{1}H NMR ($CDCl_3$): δ 0.38 (m, 2H), 0.58 (m, 2H), 2.56 (m, J= 3.6 Hz, 1H), 4.19 (s, 2H), 6.08 (m, 2H), 6.15 (d, J= 8.1 Hz, 1H), 6.83 (t, J= 8.1 Hz, 1H), 7.09 (br, 1H, NH). In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(N-cyclopropylaminocarbonylmethyleneoxy)aniline (200 mg) and 2-chloro-5-fluoro-N4-(4-morpholinophenyl)-4-pyrimidineamine (100 mg) were reacted to give N2-[3-(N-cyclopropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 0.55 (m, 2H), 0.81 (m, 2H), 2.77 (m, J= 3.6 Hz, 1H), 3.14 (t, J= 4.8 Hz, 4H), 3.87 (t, J= 4.8 Hz, 4H), 4.40 (s, 2H), 6.52 (ddd, J= 0.9 and 2.4 and 8.1 Hz, 1H), 6.61 (br, 1H, NH), 6.79 (d, J= 2.4 Hz, 1H), 6.92 (d, J= 9.0 Hz, 2H), 7.02 (dt, J= 0.9 and 8.1 Hz, 1H), 7.11 (br, 1H, NH), 7.18 (t, J= 8.4 Hz, 1H), 7.40 (t, J= 2.4 Hz, 1H), 7.48 (d, J= 9.3 Hz, 2H), 7.92 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 166.86; LCMS: ret. time: 8.57 min.; purity: 88.55%; MS (m/e): 479.31 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.254	5-Fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine (R945361)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-[(4-morpholinophenyl)aminocarbonylmethyleneoxy]aniline (200 mg) and 2-chloro-5-fluoro-N4-(4-morpholinophenyl)-4-pyrimidineamine (100 mg) were reacted in methanol to give 5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 3.15 (t, J= 4.8 Hz, 4H), 3.80 (s, 3H), 3.88 (t, J= 4.8 Hz, 4H), 4.55 (s, 2H), 6.55 (ddd, J= 0.9 and 2.7 and 8.1 Hz, 1H), 6.76 (br, 1H, NH), 6.94 (d, J= 9.0 Hz, 2H), 7 06 (ddd, J= 0.9 and 2.1 and 8.4 Hz, 1H), 7.17 (t, J= 8.4 Hz, 1H), 7.20 (br, 1H, NH), 7.33 (t, J= 2.1 Hz, 1H), 7.49 (d, J= 9.0 Hz, 2H), 7.90 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 167.19; LCMS: ret. time: 9.32 min.; purity: 97.10%; MS (m/e): 454.27 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.255	N2-[3-(N-Cyclobutylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine (R945362)	In a manner similar to the preparation of 3-(N-cyclopropylaminocarbonylmethyleneoxy)nitrobenzene, 3-(methoxycarbonylmethyleneoxy)nitrobenzene (2 g) and cyclobutylamine (1 g) were reacted to give 3-(N-cyclobutylaminocarbonylmethyleneoxy)nitrobenzene. ^{1}H NMR ($CDCl_3$): δ 1.69-1.80 (m, 2H), 1.88-2.02 (m, 2H), 2.34-2.44 (m, 2H), 4.50 (m, J= 8.7 Hz, 1H), 4.52 (s, 2H), 6.62 (br, 1H, NH), 7.26 (ddd, J= 0.9 and 3.6 and 9.0 Hz, 1H), 7.50 (t, J= 8.4 Hz, 1H), 7.80 (t, J= 2.4 Hz, 1H), 7.91 (ddd, J= 0.9 and 2.1 and 8.4 Hz, 1H). 3-(N-Cyclobutylaminocarbonylmethyleneoxy)nitrobenzene was reduced under hydrogenolysis conditions using 10% Pd-C in methanol at 40 psi for 2h. The catalyst was filtered off. The filtrate was evaporated to give 3-(N-cyclobutylaminocarbonylmethyleneoxy)aniline. ^{1}H NMR ($CDCl_3$): δ 1.60-1.70 (m, 2H), 1.80-1.93 (m, 2H), 2.62 (m, 2H), 4.31 (s, 2H), 4.36 (m, J= 8.4 Hz, 1H), 6.20 (s, 1H), 6.23 (d, J= 8.4 Hz, 1H), 6.28 (d, J= 8.1 Hz, 1H), 6.85 (br, 1H, NH), 6.99 (t, J= 8.1 Hz, 1H). In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(N-cyclobutylaminocarbonylmethyleneoxy)aniline (200 mg) and 2-chloro-5-fluoro-N4-(4-morpholinophenyl)-4-pyrimidineamine (100 mg) were reacted to give N2-[3-(N-cyclobutylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 1.65-1.76 (m, 2H), 1.84-1.97 (m, 2H), 2.29-2.39 (m, 2H), 3.12 (t, J= 4.8 Hz, 4H), 3.86 (t, J= 4.8 Hz, 4H), 4.37 (s, 2H), 4.46 (q, J= 8.1 Hz, 1H), 6.54 (ddd, J= 0.9 and 2.4 and 8.4 Hz, 1H), 6.68 (d, J= 8.1 Hz, 1H), 6.85 (dd, J= 3.0 and 5.4 Hz, 1H), 6.90 (d, J= 9.0 Hz, 2H), 7.04 (ddd, J= 0.9 and 2.4 and 7.8 Hz, 1H), 7.16 (br, 1H, NH), 7.17 (t, J= 8.1 Hz, 1H), 7.40 (t, J= 2.1 Hz, 1H), 7.48 (d, J= 9.0 Hz, 2H), 7.92 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 167.01; LCMS: ret. time: 9.54 min.; purity: 88.80%; MS (m/e): 493.34 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.256	N4-Cyclopropyl-N2-[3-(N-cyclopropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R945363)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(N-cyclopropylaminocarbonylmethyleneoxy)aniline (200 mg) and 2-chloro-N4-cyclopropyl-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N4-cyclopropyl-N2-[3-(N-cyclopropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 0.55 (m, 2H), 0.72-0.79 (m, 4H), 0.89-0.96 (m, 2H), 2.72 (m, J= 3.6 Hz, 1H), 3.03 (m, J= 3.6 Hz, 1H), 4.50 (s, 2H), 6.82 (ddd, J= 0.9 and 2.1 and 8.4 Hz, 1H), 7.17 (ddd, J= 1.8 and 7.8 Hz, 1H), 7.33 (m, 2H), 7.80 (d, J= 5.7 Hz, 1H), 8.20 (br, 1H, NH); ^{19}F NMR (282 MHz, CD_3OD): δ - 164.97; LCMS: ret. time: 7.47 min.; purity: 97.25%; MS (m/e): 358.23 (MH^+).
7.4.257	N2-[3-(N-Cyclobutylamino)carbonylmethyleneoxyphenyl]-N4-cyclopropyl-5-fluoro-2,4-pyrimidinediamine (R945364)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(N-cyclobutylaminocarbonylmethyleneoxy)aniline (200 mg) and 2-chloro-N4-cyclopropyl-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N4-cyclopropyl-N2-[3-(N-cyclobutylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 0.72 (m, 2H), 0.87-0.94 (m, 2H), 1.68-1.79 (m, 2H), 1.97-2.11 (m, 2H), 2.23-2.33 (m, 2H), 2.99 (m, J= 3.6 Hz, 1H), 4.39 (m, J= 8.1 Hz, 1H), 4.48 (s, 2H), 6.77 (ddd, J= 0.9 and 2.4 and 7.8 Hz, 1H), 7.18 (ddd, J= 0.9 and 1.8 and 8.1 Hz, 1H), 7.29 (t, J= 8.1 Hz, 1H), 7.43 (d, J= 2.1 Hz, 1H), 7.78 (d, J= 4.8 Hz, 1H), 8.19 (br, 1H, NH); ^{19}F NMR (282 MHz, CD_3OD): δ - 166.31; LCMS: ret. time: 8.72 min.; purity: 97.16%; MS (m/e): 372.24 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.258	N4-Cyclopropyl-5-fluoro-N2-[3-(4-morpholinophenyl)aminocarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R945365)	3-(Methoxycarbonylmethyleneoxy)nitrobenzene (2 g), 4-morpholinoaniline (1 g) and triethylamine (1 mL) were dissolved in methanol (10 mL) and heated at 100 °C for 3 days. The reaction solution was then diluted with 1N HCl aq. solution (80 mL) and ethyl acetate (60 mL). The white precipitation was collected by filtration and washed with water, dried to give 3-[(4-morpholinophenyl)aminocarbonylmethyleneoxy]nitrobenzene. ^{1}H NMR (DMSO-d_6): δ 3.24 (s, 4H), 3.85 (s, 4H), 4.85 (s, 2H), 7.27 (m, 2H), 7.48 (dd, J= 2.4 and 8.4 Hz, 1H), 7.57-7.63 (m, 3H), 7.80-7.86 (m, 2H), 10.22 (br, 1H, NH). 3-[(4-Morpholinophenyl)aminocarbonylmethyleneoxy]nitrobenzene was reduced under hydrogenolysis conditions using 10% Pd-C in methanol at 40 psi for 2h. The catalyst was filtered off. The filtrate was evaporated to give 3-[(4-morpholinophenyl)aminocarbonylmethyleneoxy]aniline. ^{1}H NMR ($CDCl_3$): δ 3.12 (t, J= 4.8 Hz, 4H), 3.86 (t, J= 4.8 Hz, 4H), 4.54 (s, 2H), 6.31-6.38 (m, 3H), 6.90 (d, J= 9.0 Hz, 2H), 7.09 (t, J= 7.8 Hz, 1H), 7.45 (d, J= 9.0 Hz, 2H), 8.19 (br, 1H, NH). In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-[(4-morpholinophenyl)aminocarbonylmethyleneoxy]aniline (200 mg) and 2-chloro-N4-cyclopropyl-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N4-cyclopropyl-5-fluoro-N2-[3-(4-morpholinophenyl)aminocarbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 0.64-0.69 (m, 2H), 0.88-0.96 (m, 2H), 2.87 (m, J= 3.3 Hz, 1H), 3.12 (t, J= 4.8 Hz, 4H), 3.86 (t, J= 4.8 Hz, 4H), 4.61 (s, 2H), 6.60 (ddd, J= 0.9 and 2.4 and 8.1 Hz, 1H), 6.90 (d, J= 9.0 Hz, 2H), 7.11 (dd, J= 1.8 and 8.1 Hz, 1H), 7.23 (t, J= 8.4 Hz, 1H), 7.31 (s, 1H), 7.46 (d, J= 9.0 Hz, 2H), 7.75 (t, J= 2.7 Hz, 1H), 7.79 (d, J= 3.3 Hz, 1H), 8.16 (br, 1H, NH); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 168.10; LCMS: ret. time: 9.03 min.; purity: 99.97%; MS (m/e): 479 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.259	N4-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R945366)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(methylaminocarbonylmethyleneoxy)aniline (200 mg) and 2-chloro-N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 2.17 (s, 3H), 2.62 (d, J= 4.8 Hz, 3H), 4.35 (s, 2H), 6.56 (d, J= 8.4 Hz, 1H), 7.14 (m, 2H), 7.29 (d, J= 8.4 Hz, 1H), 7.41 (t, J= 3.3 Hz, 1H), 7.54 (t, J= 3.3 Hz, 1H), 7.94 (br, 1H), 8.12 (d, J= 4.2 Hz, 1H), 8.98 (br, 1H), 9.55 (br, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 167.17; LCMS: ret. time: 8.56 min.; purity: 95.27%; MS (m/e): 432.15 (MH^+).
7.4.260	5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine (R945367)	In a manner similar to the preparation of 3-(N-cyclopropylaminocarbonylmethyleneoxy)nitrobenzene, 5-fluoro-N2-(3-methoxycarbonylmethyleneoxyphenyl)-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine (30 mg) and methylamine (30 mg) were reacted to give 5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-N4-(4-morpholinophenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 2.63 (d, J= 4.5 Hz, 3H), 3.04 (t, J= 4.8 Hz, 4H), 3.72 (t, J= 4.8 Hz, 4H), 4.32 (s, 2H), 6.46 (dd, J= 7.8 Hz, 1H), 6.90 (d, J= 9.0 Hz, 2H), 7.08 (t, J= 8.1 Hz, 1H), 7.26 (d, J= 7.8 Hz, 1H), 7.37 (s, 1H), 7.60 (dd, J= 3.3 and 8.7 Hz, 2H), 7.94 (br, 1H), 8.02 (d, J= 3.9 Hz, 1H), 9.12 (br, 1H), 9.15 (br, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 167.17; LCMS: ret. time: 7.88 min.; purity: 99.47%; MS (m/e): 453.21 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.261	5-Fluoro-N4-[4-(4-methoxycarbonylpiperazino)phenyl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945368)	1-(4-Nitrophenyl)piperazine (1 g), methyl chloroformate (1 mL) and triethylamine (1 mL) were reacted at room temperature in dichloromethane (10 mL) overnight. After extraction between ethyl acetate and water, the organic layer was evaporated and recrystallized from dichloromethane and hexanes to give 4-(4-methoxycarbonylpiperazino)nitrobenzene as yellow solid. It was reduced under hydrogenolysis conditions using 10% Pd-C in methanol at 60 psi for 1h. The catalyst was filtered off. The filtrate was evaporated to give 4-(4-methoxycarbonylpiperazino)aniline. ^{1}H NMR ($CDCl_3$): δ 2.94 (t, J= 5.1 Hz, 4H), 3.59 (t, J= 5.1 Hz, 4H), 3.70 (s, 3H), 6.62 (d, J= 8.7 Hz, 2H), 6.78 (d, J= 9.0 Hz, 2H). In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine (300 mg, 1.8 mmol) and 4-(4-methoxycarbonylpiperazino)aniline (300 mg) were reacted to yield 2-chloro-5-fluoro-N4-[4-(4-methoxycarbonylpiperazino)phenyl]-4-pyrimidineamine. In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(methylaminocarbonylmethyleneoxy)aniline (150 mg) and 2-chloro-5-fluoro-N4-[4-(4-methoxycarbonylpiperazino)phenyl]-4-pyrimidineamine (100 mg) were reacted to give 5-fluoro-N4-[4-(4-methoxycarbonylpiperazino)phenyl]-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 2.63 (d, J= 4.8 Hz, 3H), 3.04 (t, J= 5.1Hz, 4H), 3.50 (t, J= 5.1 Hz, 4H), 3.61 (s, 3H), 4.32 (s, 2H), 6.46 (dd, J= 2.1 and 7.8 Hz, 1H), 6.92 (d, J= 9.0 Hz, 2H), 7.08 (t, J= 5.1 Hz, 1H), 7.24 (dd, J= 0.9 and 8.4 Hz, 1H), 7.38 (t, J= 2.1 Hz, 1H), 7.60 (d, J= 9.0 Hz, 2H), 7.95 (d, J= 3.9 Hz, 1H), 8.02 (d, J= 3.6 Hz, 1H), 9.13 (s, 1H, NH), 9.17 (s, 1H, NH); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 164.93; LCMS: ret. time: 8.50 min.; purity: 94.49%; MS (m/e): 510.28 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.262	N2-[4-(N-Acetyl-N-methylamino)phenyl]-N4-cyclopropyl-5-fluoro-2,4-pyrimidinediamine (R945369)	In a manner similar to the preparation of 4-(4-methoxycarbonylpiperazino)nitrobenzene, N-methyl-4-nitroaniline (1 g) and acetyl chloride (1 mL) were reacted to yield N-acetyl-N-methyl-4-nitroaniline. ^{1}H NMR ($CDCl_3$): δ 2.03 (s, 3H), 3.35 (s, 3H), 7.39 (d, J= 9.0 Hz, 2H), 8.28 (d, J= 9.0 Hz, 2H). N-Acetyl-N-methyl-4-nitroaniline was reduced under hydrogenolysis conditions using 10% Pd-C in methanol at 60 psi for 1h. The catalyst was filtered off. The filtrate was evaporated to give 4-(N-acetyl-N-methylamino)aniline. ^{1}H NMR ($CDCl_3$): δ 1 80 (s, 3H), 3.14 (s, 3H), 6 63 (d, J= 8.1 Hz, 2H), 6.88 (d, J= 8.7 Hz, 2H). In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(N-acetyl-N-methylamino)aniline (200 mg) and 2-chloro-N4-cyclopropyl-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N2-[4-(N-acetyl-N-methylamino)phenyl]-N4-cyclopropyl-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 0.67 (m, 2H), 0.83-0.97 (m, 2H), 1.88 (s, 3H), 2.85 (m, J= 3.3 Hz, 1H), 3.24 (s, 3H), 5.31 (br, 1H), 7.10 (d, J= 8.7 Hz, 2H), 7.36 (br, 1H), 7.73 (d, J= 8.7 Hz, 2H), 7.78 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 168.13; LCMS: ret. time: 6.65 min.; purity: 100%; MS (m/e): 316.22 (MH^+).

Section Number	Name of compound and reference number	Experimental
7.4.263	N2-[4-(4-Acetylpiperazino)phenyl]-N4-cyclopropyl-5-fluoro-2,4-pyrimidinediamine (R945370)	In a manner similar to the preparation of 4-(4-methoxycarbonylpiperazino)nitrobenzene, 1-(4-nitrophenyl)piperazine (1 g) and acetyl chloride (1 mL) were reacted to yield 4-(4-acetylpiperazino)nitrobenzene. ^{1}H NMR ($CDCl_3$): δ 2.16 (s, 3H), 3.46 (br, 4H), 3.68 (br, 2H), 3.80 (br, 2H), 6.84 (d, J= 9.6 Hz, 2H), 8.15 (d, J= 9.6 Hz, 2H). 4-(4-Acetylpiperazino)nitrobenzene was reduced under hydrogenolysis conditions using 10% Pd-C in methanol at 60 psi for 1h. The catalyst was filtered off. The filtrate was evaporated to give 4-(4-acetylpiperazino)aniline. ^{1}H NMR ($CDCl_3$): δ 2.10 (s, 3H), 2.97 (p, J= 4.8 Hz, 4H), 3.58 (t, J= 4.8 Hz, 2H), 3.72 (t, J= 5.1 Hz, 2H), 6.64 (d, J= 8.7 Hz, 2H), 6.78 (d, J= 8.4 Hz, 2H). In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(4-acetylpiperazino)aniline (200 mg) and 2-chloro-N4-cyclopropyl-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N2-[4-(4-acetylpiperazino)phenyl]-N4-cyclopropyl-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 0.66 (m, 2H), 0.90 (m, 2H), 2.14 (s, 3H), 2.84 (m, J= 3.3 Hz, 1H), 3.10 (p, J= 5.1 Hz, 4H), 3.62 (t, J= 5.1 Hz, 2H), 3.77 (t, J= 5.1 Hz, 2H), 5.33 (br, 1H), 6.90 (d, J= 9.0 Hz, 2H), 7.43 (br, 1H), 7.57 (d, J= 9.0 Hz, 2H), 7.71 (d, J= 3.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 168.95; LCMS: ret. time: 6.79 min.; purity: 93.14%; MS (m/e): 371.50 (MH^+).
7.4.264	N4-Cyclopropyl-5-fluoro-N2-[4-(4-methoxycarbonylpiperazino)phenyl]-2,4-pyrimidinediamine (R945371)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(4-methoxycarbonylpiperazino)aniline (200 mg) and 2-chloro-N4-cyclopropyl-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N4-cyclopropyl-5-fluoro-N2-[4-(4-methoxycarbonylpiperazino)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 0.65 (m, 2H), 0.88 (m, 2H), 2.84 (m, J= 3.3 Hz, 1H), 3.07 (t, J= 4.8 Hz, 4H), 3.63 (t, J= 5.1 Hz, 4H), 3.73 (s, 3H), 5.29 (br, 1H), 6.90 (d, J= 9.0 Hz, 2H), 7.38 (br, 1H), 7.56 (d, J= 8.7 Hz, 2H), 7.71 (d, J= 3.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 169.13; LCMS: ret. time: 7.86 min.; purity: 91.63%; MS (m/e): 387.20 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.265	N4-Cyclopropyl-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945372)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(methylaminocarbonylmethyleneoxy)aniline (200 mg) and 2-chloro-N4-cyclopropyl-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N4-cyclopropyl-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 0.66 (m, 2H), 0.91 (m, 2H), 2.87 (m, 1H), 2.90 (d, J= 5.1 Hz, 3H), 4.50 (s, 2H), 5.32 (br, 1H), 6.52 (ddd, J= 0.9 and 2.4 and 7.8 Hz, 1H), 6.60 (br, 1H), 7.13 (ddd, J= 1.2 and 8.1 Hz, 1H), 7.20 (t, J= 8.1 Hz, 1H), 7.31 (br, 1H), 7.61 (t, J= 2.1 Hz, 1H), 7.80 (d, J= 3.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 168.24; LCMS: ret. time: 6.78 min.; purity: 89.65%; MS (m/e): 332.19 (MH^+).
7.4.266	N2-Cyclopropyl-5-fluoro-N4-[4-(4-methoxycarbonylpiperazino)phenyl]-2,4-pyrimidinediamine (R945373)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, cyclopropylamine (150 mg) and 2-chloro-5-fluoro-N4-[4-(4-methoxycarbonylpiperazino)phenyl]-4-pyrimidineamine (100 mg) were reacted to give N2-cyclopropyl-5-fluoro-N4-[4-(4-methoxycarbonylpiperazino)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 0.60 (m, 2H), 0.81 (m, 2H), 2.72 (m, J= 3.3 Hz, 1H), 3.13 (t, J= 5.1 Hz, 4H), 3.64 (t, J= 5.1 Hz, 4H), 3.73 (s, 3H), 6.92 (d, J= 9.0 Hz, 2H), 7.63 (d, J= 9.0 Hz, 2H), 7.76 (d, J= 3.0 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 168.70; LCMS: ret. time: 7.59 min.; purity: 92.07%; MS (m/e): 387.27 (MH^+).
7.4.267	N2-Cyclobutyl-5-fluoro-N4-[4-(4-methoxycarbonylpiperazino)phenyl]-2,4-pyrimidinediamine (R945374)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, cyclobutylamine (150 mg) and 2-chloro-5-fluoro-N4-[4-(4-methoxycarbonylpiperazino)phenyl]-4-pyrimidineamine (100 mg) were reacted to give N2-cyclobutyl-5-fluoro-N4-[4-(4-methoxycarbonylpiperazino)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 1.68-1.78 (m, 2H), 1.82-1.92 (m, 2H), 2.33-2.43 (m, 2H), 3.12 (t, J= 5.1 Hz, 4H), 3.64 (t, J= 5.1 Hz, 4H), 3.74 (s, 3H), 4.31 (m, J= 7.8 Hz, 1H), 5.42 (br, 1H), 6.69 (br, 1H), 6.93 (d, J= 9.3 Hz, 2H), 7.53 (d, J= 9.0 Hz, 2H), 7.76 (d, J= 3.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 170.64; LCMS: ret. time: 8.34 min.; purity: 82.53%; MS (m/e): 401.28 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.268	N4-[4-(N-Acetyl-N-methylamino)phenyl]-N2-cyclopropyl-5-fluoro-2,4-pyrimidinediamine (R945375)	In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine (300 mg, 1.8 mmol) and 4-(N-acetyl-N-methylamino)aniline (300 mg) were reacted to yield N4-[4-(N-acetyl-N-methylamino)phenyl]-2-chloro-5-fluoro-4-pyrimidineamine. In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, cyclopropylamine (150 mg) and N4-[4-(N-acetyl-N-methylamino)phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N4-[4-(N-acetyl-N-methylamino)phenyl]-N2-cyclopropyl-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 0.66 (m, 2H), 0.85 (m, 2H), 1.90 (s, 3H), 2.74 (m, 1H), 3.27 (s, 3H), 7.22 (d, 2H), 7.84 (d, 3H); LCMS: ret. time: 5.91 min.; purity: 79.74%; MS (m/e): 316.23 (MH^+).
7.4.269	N2,N4-Bis(cyclopropyl)-5-fluoro-2,4-pyrimidinediamine (R945376)	During the preparation of N4-[4-(N-acetyl-N-methylamino)phenyl]-N2-cyclopropyl-5-fluoro-2,4-pyrimidinediamine, the formation of N2,N4-bis(cyclopropyl)-5-fluoro-2,4-pyrimidinediamine as a by product was observed. ^{1}H NMR ($CDCl_3$): δ 0.49-0.59 (m, 4H), 0.73-0.84 (m, 4H), 2.67-2.79 (m, 2H), 5.04 (br, 1H), 5.14 (br, 1H), 7.73 (d, J= 3.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 171.76; LCMS: ret. time: 2.63 min.; purity: 96.91%; MS (m/e): 209.16 (MH^+).
7.4.270	N4-[4-(N-Acetyl-N-methylamino)phenyl]-5-fluoro-N2-[3-N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine (R945377)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(N-methylamino)carbonylmethyleneoxyaniline (150 mg) and N4-[4-(N-acetyl-N-methylamino)phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N4-[4-(N-acetyl-N-methylamino)phenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 1.89 (s, 3H), 2.89 (d, J= 5.1 Hz, 3H), 3.26 (s, 3H), 4.47 (s, 2H), 6.59 (dd, J= 2.4 and 8.1 Hz, 1H), 7.12-7.24 (m, 4H), 7.30 (br, 1H), 7.35 (t, J= 2.1 Hz, 1H), 7.70 (d, J= 8.4 Hz, 2H), 8.01 (d, J= 3.0 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 165.91; LCMS: ret. time: 7.94 min., purity. 89.78%; MS (m/e): 439.50 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.271	N2,N4-Bis(3-methylaminocarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R945378)	During the synthesis of N4-[4-(N-acetyl-N-methylamino)phenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine, the formation of N2,N4-bis(3-methylaminocarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine as a by product was observed. ^{1}H NMR ($CDCl_3$): δ 2.87 (d, J= 4.8 Hz, 3H), 2.90 (d, J= 4.8 Hz, 3H), 4 46 (s, 2H), 4.54 (s, 2H), 6.53 (ddd, J= 0.9 and 2.4 and 7.8 Hz, 2H), 6.69 (ddd, J= 0.9 and 2.7 and 8.1 Hz, 2H), 6.82 (dd, J= 1.2 and 7.8 Hz, 1H), 6.92 (d, J= 3.0 Hz, 1H), 7.19-7.30 (m, 3H), 7.65 (t, J= 2.1 Hz, 1H), 8.00 (d, J= 3.3 Hz, 1H), 8.04 (br, 1H), 8.12 (t, J= 2.1 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 167.11; LCMS: ret. time: 7.93 min.; purity: 96.85%; MS (m/e): 455.50 (MH^+).
7.4.272	N4-[4-(N-Acetyl-N-methylamino)phenyl]-N2-cyclobutyl-5-fluoro-2,4-pyrimidinediamine (R945379)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, cyclobutylamine (150 mg) and N4-[4-(N-acetyl-N-methylamino)phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N4-[4-(N-acetyl-N-methylamino)phenyl]-N2-cyclobuyl-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 1.70-1.97 (m, 4H), 1.89 (s, 3H), 2.36-2.45 (m, 2H), 3.26 (s, 3H), 4.33 (m, J= 7.8 Hz, 1H), 5.13 (d, J= 7.2 Hz, 1H), 6.87 (br, 1H), 7.16 (d, J= 8.7 Hz, 2H), 7.73 (d, J= 9.0 Hz, 2H), 7.86 (d, J= 3.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 170.61; LCMS: ret. time: 7.03 min.; purity: 93.04%; MS (m/e): 330.16 (MH^+).
7.4.273	N2,N4-Bis(cyclobutyl)-5-fluoro-2,4-pyrimidinediamine (R945380)	During the preparation of N4-[4-(N-acetyl-N-methylamino)phenyl]-N2-cyclobuyl-5-fluoro-2,4-pyrimidinediamine, the formation of N2,N4-bis(cyclobutyl)-5-fluoro-2,4-pyrimidinediamine as a by product was observed. ^{1}H NMR ($CDCl_3$): δ 1.64-1.96 (m, 8H), 2.32-2.46 (m, 4H), 4.31 (m, J= 7.8 Hz, 1H), 4.50 (m, J= 7.8 Hz, 1H), 4.99 (br, 2H), 7.63 (d, J= 3.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 172.68; LCMS: ret. time: 8.35 min.; purity: 96.68%; MS (m/e): 237.20 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.274	N4-[4-(4-Acetylpiperazino)phenyl]-N2-cyclopropyl-5-fluoro-2,4-pyrimidinediamine (R945381)	In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine (300 mg, 1.8 mmol) and 4-(4-acetylpiperazino)aniline (300 mg) were reacted to yield N4-[4-(4-acetylpiperazino)phenyl]-2-chloro-5-fluoro-4-pyrimidineamine. In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, cyclopropylamine (150 mg) and N4-[4-(4-acetylpiperazino)phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N4-[4-(4-acetylpiperazino)phenyl]-N2-cyclopropyl-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 0.73 (m, 2H), 0.84 (m, 2H), 2.18 (s, 3H), 2.76 (m, J= 3.3 Hz, 1H), 3.23 (p, J= 5.4 Hz, 4H), 3.68 (t, J= 5.1 Hz, 2H), 3.82 (t, J= 5.1 Hz, 2H), 6.98 (d, J= 9.0 Hz, 2H), 7.45 (d, J= 3.0 Hz, 1H), 7.65 (d, J= 5.1 Hz, 1H), 7.71 (d, J= 9.0 Hz, 2H), 9.70 (br, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 166.00; LCMS: ret. time: 6.50 min.; purity: 93.56%; MS (m/e): 371.24 (MH^+).
7.4.275	N4-[4-(4-Acetylpiperazino)phenyl]-N2-cyclobutyl-5-fluoro-2,4-pyrimidinediamine (R945382)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, cyclobutylamine (150 mg) and N4-[4-(4-acetylpiperazino)phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N4-[4-(4-acetylpiperazino)phenyl]-N2-cyclobutyl-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 1.69-1.88 (m, 2H), 2.07-2.37 (m, 4H), 2.18 (s, 3H), 3.25 (p, J= 5.4 Hz, 4H), 3.68 (t, J= 5.1 Hz, 2H), 3.83 (t, J= 5.1 Hz, 2H), 4.27 (m, J= 7.2 Hz, 1H), 6.99 (d, J= 9.3 Hz, 2H), 7.40 (br, 1H), 7.55 (d, J= 9.0 Hz, 2H), 7.62 (d, J= 5.1 Hz, 1H), 9.69 (br, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 166.57; LCMS: ret. time: 7.23 min.; purity: 89.04%; MS (m/e): 385.25 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.276	N2-[4-(N-Acetyl-N-methylamino)phenyl]-N4-cyclobutyl-5-fluoro-2,4-pyrimidinediamine (R945383)	In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine (400 mg, 2.4 mmol) and cyclobutylamine (200 mg) were reacted at room temperature to yield 2-chloro-N4-cyclobutyl-5-fluoro-4-pyrimidineamine. In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(N-acetylN-methylamino)aniline (100 mg) and 2-chloro-N4-cyclobutyl-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N2-[4-(N-acetyl-N-methylamino)phenyl]-N4-cyclobutyl-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 1.75-2.02 (m, 4H), 1.88 (s, 3H), 2.41-2.51 (m, 2H), 3.24 (s, 3H), 4.53 (m, J= 7.8 Hz, 1H), 5.17 (d, J= 6.3 Hz, 1H), 7.06 (br, 1H), 7.10 (d, J= 8.7 Hz, 2H), 7.63 (d, J= 9.0 Hz, 2H), 7.78 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 168.52; LCMS: ret. time: 7.41 min.; purity: 97.56%; MS (m/e): 330.19 (MH^+).

Section Number	Name of compound and reference number	Experimental
7.4.277	*cis/trans*-N4-[4-[4-(tert-Butoxycarbonylamino)cyclohexyloxy]-3-chlorophenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945384)	*cis/trans*-4-Aminocyclohexanol hydrogen chloride salt (10 g), di-tert-butyl dicarbonate (20 g) and sodium bicarbonate (20 g) were dissolved in THF (50 mL) and water (50 mL). The reaction solution was stirred at rt overnight. The solution was extracted with ethyl acetate (100 mL) and the organic layer was evaporated to give 4-tert-butoxycarbonylamino-cyclohexanol. *cis/trans*-4-tert-Butoxycarbonylaminocyclohexanol (10 g) was dissolved in dichloromethane (100 mL). P-Tolunesulfonyl chloride (10 g), DMAP (5 g) and triethylamine (10 mL) were added to the solution. It was stirred at rt overnight. The reaction mixture was washed with 1N HCl aq. (3 x 100 mL), dried and evaporated to give *cis/trans*-O-p-tolunesulfonyl-4-tert-butoxycarbonylaminocyclohexanol. *cis/trans*-O-p-Tolunesulfonyl-4-tert-butoxycarbonylaminocyclohexanol (10 g), 2-chloro-4-nitrophenol (10 g) and potassium carbonate (10 g) were heated at 60 °C in DMF (50 mL) for 4 h. The solution was diluted with ethyl acetate (100 mL) and washed with water (3 x 100 mL). The organic layer was dried, evaporated to give 4-[4-(tert-butoxycarbonylamino)cyclohexyloxy]-3-chloronitrobenzene. It was reduced under hydrogenolysis conditions using 10% Pd-C in methanol at 60 psi for 1h. The catalyst was filtered off. The filtrate was evaporated to give 4-[4-(tert-butoxycarbonylamino)cyclohexyloxy]-3-chloroaniline. In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-[4-(tert-butoxycarbonylamino)cyclohexyloxy]-3-chloroaniline were reacted to yield N4-[4-[4-(tert-butoxycarbonylamino)cyclohexyloxy]-3-chlorophenyl]-2-chloro-5-fluoro-4-pyrimidineamine. In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(methylaminocarbonylmethyleneoxy)aniline and N4-[4-[4-(tert-butoxycarbonylamino)cyclohexyloxy]-3-chlorophenyl]-2-chloro-5-fluoro-4-pyrimidineamine were reacted to give N4-[4-[4-(tert-butoxycarbonylamino)cyclohexyloxy]-3-chlorophenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. LCMS: ret. time: 12.83 min.; purity: 96.20%; MS (m/e): 615.32 (M^+).

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Section Number	Name of compound and reference number	Experimental
7.4.278	N2-[4-(4-Acetylpiperazino)phenyl]-N4-cyclobutyl-5-fluoro-2,4-pyrimidinediamine (R945385)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(4-acetylpiperazino)aniline (100 mg) and 2-chloro-N4-cyclobutyl-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N2-[4-(4-acetylpiperazino)phenyl]-N4-cyclobutyl-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 1.72-1.99 (m, 4H), 2.13 (s, 3H), 2.39-2.49 (m, 2H), 3.09 (p, J= 5.1 Hz, 4H), 3.61 (t, J= 5.1 Hz, 2H), 3.77 (t, J= 5.1 Hz, 2H), 4.51 (m, J= 7.8 Hz, 1H), 5.10 (d, J= 6.9 Hz, 1H), 6.85 (br, 1H), 6.90 (d, J= 9.0 Hz, 2H), 7.46 (d, J= 9.0 Hz, 2H), 7.73 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 170.01; LCMS: ret. time: 7.26 min.; purity: 90.49%; MS (*m/e*): 385.25 (MH^+).
7.4.279	N4-Cyclobutyl-5-fluoro-N2-[4-(4-methoxycarbonylpiperazino)phenyl]-2,4-pyrimidinediamine (R945386)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(4-methoxycarbonylpiperazino)aniline (100 mg) and 2-chloro-N4-cyclobutyl-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N4-cyclobutyl-5-fluoro-N2-[4-(4-methoxycarbonylpiperazino)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 1.72-1.85 (m, 2H), 1.88-1.99 (m, 2H), 2.38-2.48 (m, 2H), 3.06 (t, J= 5.1 Hz, 4H), 3.62 (t, J= 5.1 Hz, 4H), 3.72 (s, 3H), 4.51 (m, J= 7.8 Hz, 1H), 5.09 (d, J= 6.3 Hz, 1H), 6.90 (d, J= 9.0 Hz, 2H), 6.91 (br, 1H), 7.45 (d, J= 9.0 Hz, 2H), 7.73 (d, J= 3.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 170.12; LCMS: ret. time: 8.48 min.; purity: 94.18%; MS (m/e): 401.21 (MH^+).
7.4.280	N4-Cyclobutyl-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945387)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(methylaminocarbonylmethyleneoxy)aniline (100 mg) and 2-chloro-N4-cyclobutyl-5-fluoro-4-pyrimidineamine (100 mg) were reacted to give N4-cyclobutyl-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.71 (m, 2H), 2.14 (m, 2H), 2.25 (m, 2H), 2.64 (d, J= 4.2 Hz, 3H), 4.45 (s, 2H), 4.51 (m, 1H), 6.70 (dd, J= 8.1 Hz, 1H), 7.13 (d, J= 8.1 Hz, 1H), 7.26 (t, J= 8.1 Hz, 1H), 7.32 (t, 1H), 8.03 (d, J= 4.5 Hz, 1H), 8.10 (d, J= 5.4 Hz, 1H), 9.04 (br, 1H), 10.18 (br, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 163.00; LCMS: ret. time: 7.50 min.; purity: 95.47%; MS (m/e): 346.20 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.281	N2-[3-(N-Cyclobutylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945389)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(N-cyclobutylaminocarbonylmethyleneoxy)aniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-[3-(N-cyclobutylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.53-1.65 (m, 2H), 1.90-2.03 (m, 2H), 2.07-2.17 (m, 2H), 4.25 (q, J= 8.1 Hz, 1H), 4.32 (s, 2H), 4.61 (s, 2H), 6.46 (dd, J= 1.8 and 8.1 Hz, 1H), 7.10 (t, J= 8.1 Hz,1H), 7.23 (dd, J= 0.9 and 8.4 Hz, 1H), 7.38 (m, 2H), 7.60 (d, J= 8.7 Hz, 1H), 8.13 (d, J= 3.6 Hz, 1H), 8.22 (d, J= 8.1 Hz, 1H), 9.23 (s, 1H), 9.26 (s, 1H), 11.12 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 163.26; LCMS: ret. time: 9.98 min.; purity: 92.21%; MS (m/e): 480.25 (MH^+).
7.4.282	N2-[3-(N-Cyclopropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945390)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(N-cyclopropylaminocarbonylmethyleneoxy)aniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-[3-(N-cyclopropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 0.47 (m, 2H), 0.61 (m, 2H), 2.66 (m, J= 3.6 Hz, 1H), 4.32 (s, 2H), 4.62 (s, 2H), 6.44 (dd, J= 2.4 and 7.5 Hz, 1H), 7.09 (t, J= 8.1 Hz, 1H), 7.22 (dd, J= 0.9 and 8.1 Hz, 1H), 7.37 (m, 2H), 7.59 (d, J= 8.4 Hz, 1H), 8.05 (d, J= 4.5 Hz, 1H), 8.13 (d, J= 3.6 Hz, 1H), 9.22 (s, 1H), 9.26 (s, 1H), 11.12 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 163.27; LCMS: ret. time: 8.89 min.; purity: 83.29%; MS (m/e): 466.24 (MH^+).
7.4.283	N2-[4-(4-Acetylpiperazino)phenyl]-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945391)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(4-acetylpiperazino)aniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-[4-(4-acetylpiperazino)phenyl]-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 2.02 (s, 3H), 2.96 (t, J= 5.1 Hz, 2H), 3.02 (t, J= 5.1 Hz, 2H), 3.55 (br, 4H), 4.62 (s, 2H), 6.84 (d, J= 9.0 Hz, 2H), 7.36 (d, J= 8.4 Hz, 1H), 7.48 (d, J= 9.0 Hz, 2H), 7.57 (d, J= 8.7 Hz, 1H), 8.07 (d, J= 3.6 Hz, 1H), 9.01 (s, 1H), 9.13 (s, 1H), 11.14 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 164.84; LCMS: ret. time: 7.29 min.; purity: 88.46%; MS (m/e): 479.27 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.284	5-Fluoro-N2-[4-(4-methoxycarbonylpiperazino)phenyl]-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945392)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(4-methoxycarbonylpiperazino)aniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give 5-fluoro-N2-[4-(4-methoxycarbonylpiperazino)phenyl]-N4-(2H-3-oxo-4H-5-pyrid[1,4]-oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 2.98 (t, J= 5.1 Hz, 4H), 3.48 (t, J= 5.1 Hz, 4H), 3.60 (s, 3H), 4.62 (s, 2H), 6.83 (d, J= 9.3 Hz, 2H), 7.36 (d, J= 8.4 Hz, 1H), 7.47 (d, J= 9.0 Hz, 2H), 7.56 (d, J= 8.4 Hz, 1H), 8.06 (d, J= 3.6 Hz, 1H), 9.01 (s, 1H), 9.13 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 164.84; LCMS: ret. time: 8.61 min.; purity: 83.00%; MS (m/e): 495.25 (MH^+).
7.4.285	N4-Cyclobutyl-N2-(3-cyclopropylaminocarbonylmethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R945393)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(N-cyclopropylaminocarbonylmethyleneoxy)aniline (100 mg) and 2-chloro-N4-cyclobutyl-5-fluoro-4-pyrimidineamine (50 mg) were reacted to give N4-cyclobutyl-N2-[3-(N-cyclopropylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 0.58 (m, 2H), 0.80-0.90 (m, 2H), 1.78-1.89 (m, 2H), 1.94-2.07 (m, 2H), 2.43-2.53 (m, 2H), 2.78 (m, J= 3.6 Hz, 1H), 4.49 (s, 2H), 4.56 (m, J= 7.8 Hz, 1H), 5.30 (br, 1H), 6.53 (ddd, J= 0.9 and 2.7 and 8.1 Hz, 1H), 6.66 (br, 1H), 7.01 (dd, J= 1.2 and 8.1 Hz, 1H), 7.21 (t, J= 8.1 Hz, 1H), 7.39 (br, 1H), 7.55 (t, J= 2.1 Hz, 1H), 7.76 (d, J= 3.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 168.10; LCMS: ret. time: 8.29 min.; purity: 86.71%; MS (m/e): 372.24 (MH^+).
7.4.286	N4-Cyclobutyl-N2-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R945394)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3,4-dichloroaniline (100 mg) and 2-chloro-N4-cyclobutyl-5-fluoro-4-pyrimidineamine (50 mg) were reacted to give N4-cyclobutyl-N2-(3,4-dichlorophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.65-1.77 (m, 2H), 2.07-2.20 (m, 2H), 2.24-2.33 (m, 2H), 4.42 (m, J= 7.8 Hz, 1H), 7.44 (dd, J= 2.4 and 8.7 Hz, 1H), 7.57 (d, J= 8.7 Hz, 1H), 8.12 (d, J= 5.1 Hz, 1H), 8.16 (d, J= 2.7 Hz, 1H), 8.99 (br, 1H), 10.49 (br, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 162.52; LCMS: ret. time: 13.61 min.; purity: 89.20%; MS (m/e): 327.10 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.287	N2-(3-Chloro-4-methoxyphenyl)-N4-cyclobutyl-5-fluoro-2,4-pyrimidinediamine (R945395)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-chloro-4-methoxyaniline (100 mg) and 2-chloro-N4-cyclobutyl-5-fluoro-4-pyrimidineamine (50 mg) were reacted to give N2-(3-chloro-4-methoxyphenyl)-N4-cyclobutyl-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.63-1.75 (m, 2H), 2.08-2.31 (m, 4H), 3.83 (s, 3H), 4.40 (m, J= 7 8 Hz, 1H), 7.15 (d, J= 9.0 Hz, 1H), 7.34 (dd, J= 2.4 and 8.7 Hz, 1H), 7.83 (d, J= 2.4 Hz, 1H), 8.10 (d, J= 5.4 Hz, 1H), 9.17 (br, 1H), 10.32 (br, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 162.93; LCMS: ret. time: 9.87 mın ; purity: 90.17%; MS (m/e): 323.15 (MH^+).
7.4.288	N4-Cyclobutyl-N2-[3-(N-cyclobutylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R945396)	In a manner similar to the preparatıon of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(N-cyclobutylaminocarbonylmethyleneoxy)aniline (100 mg) and 2-chloro-N4-cyclobutyl-5-fluoro-4-pyrimidineamine (50 mg) were reacted to give N4-cyclobutyl-N2-[3-(N-cyclobutylamino)carbonylmethyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 1.56-1.88 (m, 6H), 1.96-2.09 (m, 2H), 2.13-2.31 (m, 4H), 4.28 (m, J= 8.1 Hz, 1H), 4.32 (s, 2H), 4.40 (m, J= 8.1 Hz, 1H), 6.62 (ddd, J= 1.2 and 2.1 and 8.1 Hz, 1H), 7.09-7.20 (m, 3H), 7.59 (d, J= 4.8 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ - 162.52; LCMS: ret. time: 9.39 min.; purity: 94.65%; MS (m/e): 386.26 (MH^+).
7.4.289	N4-Cyclobutyl-N2-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamıne (R945397)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3,5-dichloro-4-methoxyaniline (100 mg) and 2-chloro-N4-cyclobutyl-5-fluoro-4-pyrimidineamine (50 mg) were reacted to gıve N4-cyclobutyl-N2-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-2,4-pyrımidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.63-1.76 (m, 2H), 2.07-2.33 (m, 4H), 3.78 (s, 3H), 4.41 (m, J= 7.8 Hz, 1H), 7.81 (s, 2H), 8.08 (d, J= 5.1 Hz, 1H), 8.82 (br, 1H), 10.21 (br, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 163.16; LCMS: ret. time: 13.63 min.; purity: 92.88%; MS (m/e): 357.10 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.290	N2-(3,4-Dichlorophenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945398)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3,4-dichloroaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-(3,4-dichlorophenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 4.63 (s, 2H), 7.39-7.42 (m, 3H), 7.52 (dd, J= 2.4 and 8.7 Hz, 1H), 8.06 (d, J= 2.1 Hz, 1H), 8.18 (d, J= 3.6 Hz, 1H), 9.46 (s, 1H), 9.59 (s, 1H), 11.17 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 162.48; LCMS: ret. time: 13.30 min.; purity: 90.24%; MS (m/e): 421.07 (MH^+).
7.4.291	N2-(3-Chloro-4-methoxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945399)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-chloro-4-methoxyaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-(3-chloro-4-methoxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 3.76 (s, 3H), 4.62 (s, 2H), 7.00 (d, J= 9.0 Hz, 1H), 7.40 (d, J= 8.7 Hz, 1H), 7.47 (m, 2H), 7.80 (d, J= 2.4 Hz, 1H), 8.12 (d, J= 3.3 Hz, 1H), 9.22 (s, 1H), 9.27 (s, 1H), 11.15 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 163.98; LCMS: ret. time: 10.38 min.; purity: 91.61%; MS (m/e): 417.14 (MH^+).
7.4.292	N2-(3,5-Dichloro-4-methoxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945400)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3,5-dichloro-4-methoxyaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 3.72 (s, 3H), 4.55 (s, 2H), 7.30 (d, J= 8.4 Hz, 1H), 7.35 (d, J= 8.4 Hz, 1H), 7.75 (s, 2H), 8.14 (d, J= 3.6 Hz, 1H), 9.48 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 162.65.

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Section Number	Name of compound and reference number	Experimental
7.4.293	N2-(3,5-Dimethoxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945401)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3,5-dimethoxyaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-(3,5-dimethoxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 3.64 (s, 6H), 4.62 (s, 2H), 6.06 (t, J= 2.4 Hz, 1H), 6.92 (d, J= 2.4 Hz, 2H), 7.32 (d, J= 8.7 Hz, 1H), 7.60 (d, J= 8.7 Hz, 1H), 8.13 (d, J= 3.6 Hz, 1H), 9.18 (s, 1H), 9.24 (s, 1H), 11.11 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 163.28; LCMS: ret. time: 10.41 min.; purity: 97.00%; MS (m/e): 413.19 (MH^+).
7.4.294	5-Fluoro-N2-(3-fluoro-4-methoxyphenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945402)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-fluoro-4-methoxyaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give 5-fluoro-N2-(3-fluoro-4-methoxyphenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 3.75 (s, 3H), 4.62 (s, 2H), 6 99 (t, J= 9.3 Hz, 1H), 7.26 (dd, J= 2.4 and 9.0 Hz, 1H), 7.36 (d, J= 8.4 Hz, 1H), 7.45 (d, J= 8.4 Hz, 1H), 7.66 (dd, J= 2.7 and 14.4 Hz, 1H), 8.11 (d, J= 3.3 Hz, 1H), 9.24 (s, 1H), 9.32 (s, 1H), 11.15 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 163.98, - 134.90; LCMS: ret. time: 9.84 min.; purity: 93.66%; MS (m/e): 401.18 (MH^+).
7.4.295	*cis/trans*-N4-[4-(4-Aminocyclohexyloxy)-3-chlorophenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945403)	*cis/trans*-N4-{4-[4-(tert-Butoxycarbonylamino)cyclohexyloxy]-3-chlorophenyl}-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine was deprotected under acidic condition (trifluoroacetic acid) to give *cis/trans*-N4-[4-(4-aminocyclohexyloxy)-3-chlorophenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 7.06 min.; purity: 92.49%; MS (m/e): 513.43 (M^-).

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Section Number	Name of compound and reference number	Experimental
7.4.296	5-Fluoro-N2-(4-methoxyphenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945404)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-methoxyaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give 5-fluoro-N2-(4-methoxyphenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 3.69 (s, 3H), 4.63 (s, 2H), 6.79 (d, J= 9.0 Hz, 2H), 7.35 (d, J= 8.4 Hz, 1H), 7.50 (d, J= 9.0 Hz, 2H), 7.53 (d, J= 9.0 Hz, 1H), 8.07 (d, J= 3.3 Hz, 1H), 9.05 (s, 1H), 9.18 (s, 1H), 11.13 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 175.00; LCMS: ret. time: 8.85 min.; purity: 100%; MS (m/e): 383.25 (MH^+).
7.4.297	N2-(3,4-Ethylenedioxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945405)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3,4-ethylenedioxyaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 4.16 (q, J= 2.1 Hz, 4H), 4.62 (s, 2H), 6.67 (d, J= 8.7 Hz, 1H), 6.98 (dd, J= 2.4 and 9.0 Hz, 1H), 7.27 (d, J= 2.4 Hz, 1H), 7.34 (d, J= 8.4 Hz, 1H), 7.53 (d, J= 9.0 Hz, 1H), 8.07 (d, J= 3.6 Hz, 1H), 9.05 (s, 1H), 9.21 (s, 1H), 11.11 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 174.73; LCMS: ret. time: 8.94 min.; purity: 97.69%; MS (m/e): 411.26 (MH^+).
7.4.298	5-Fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-N2-(4-trifluoromethoxyphenyl)-2,4-pyrimidinediamine (R945406)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-trifluoromethoxyaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give 5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-N2-(4-trifluoromethoxyphenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 4.64 (s, 2H), 7.18 (d, J= 8.1 Hz, 2H), 7.38 (d, J= 8.7 Hz, 1H), 7.47 (d, J= 8.7 Hz, 1H), 7.73 (d, J= 9.0 Hz, 2H), 8.14 (d, J= 3.3 Hz, 1H), 9.38 (s, 1H), 9.45 (s, 1H), 11.18 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 173.29, - 68.81; LCMS: ret. time: 12.95 min.; purity: 100%; MS (m/e): 437.25 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.299	N2-(4-Ethoxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945407)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-ethoxyaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-(4-ethoxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.30 (t, J= 6.9 Hz, 3H), 3.94 (q, J= 6.9 Hz, 2H), 4.63 (s, 2H), 6.77 (d, J= 8.7 Hz, 2H), 7.36 (d, J= 8.4 Hz, 1H), 7.48 (d, J= 9.0 Hz, 2H), 7.54 (d, J= 8.7 Hz, 1H), 8.06 (d, J= 3.6 Hz, 1H), 9.04 (s, 1H), 9.17 (s, 1H), 11.14 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 175.00; LCMS: ret. time: 9.87 min.; purity: 90.82%; MS (m/e): 397.28 (MH^+).
7.4.300	N2-(4-Butoxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945408)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-butoxyaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-(4-butoxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 0.93 (t, J= 7.5 Hz, 3H), 1.42 (hept, J= 7.5 Hz, 2H), 1.66 (p, J= 6.9 Hz, 2H), 3.89 (t, J= 6.3 Hz, 2H), 4.62 (s, 2H), 6.78 (d, J= 8.7 Hz, 2H), 7.35 (d, J= 8.4 Hz, 1H), 7.48 (d, J= 9.3 Hz, 2H), 7.54 (d, J= 8.7 Hz, 1H), 8.06 (d, J= 3.6 Hz, 1H), 9.04 (s, 1H), 9.17 (s, 1H), 11.14 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 175.02; LCMS: ret. time: 12.12 min.; purity: 95.36%; MS (m/e): 425.31 (MH^+).
7.4.301	5-Fluoro-N2-(4-phenoxyphenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945409)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-phenoxyaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give 5-fluoro-N2-(4-phenoxyphenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 4.60 (s, 2H), 6.91 (d, J= 9.0 Hz, 4H), 7.05 (t, J= 7.2 Hz, 1H), 7.32 (m, 3H), 7.52 (d, J= 8.4 Hz, 1H), 7.63 (d, J= 9.0 Hz, 2H), 8.10 (d, J= 3.6 Hz, 1H), 9.27 (s, 2H), 11.14 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 174.19; LCMS: ret. time: 12.69 min.; purity: 100%; MS (m/e): 445 27 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.302	N2-(4-Benzyloxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945410)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-benzyloxyaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-(4-benzyloxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 4.62 (s, 2H), 5.03 (s, 2H), 6.86 (d, J= 9.0 Hz, 2H), 7.31-7.51 (m, 9H), 8.06 (d, J= 3.3 Hz, 1H), 9.05 (s, 1H), 9.15 (s, 1H), 11.13 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 170.56; LCMS: ret. time: 12.02 min.; MS (m/e): 459.33 (MH^+).
7.4.303	*cis/trans*-N4-[3-Chloro-4-[4-(N-ethylamino)cyclohexyloxy]phenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (R945411)	*cis/trans*-4-[4-(tert-Butoxycarbonylamino)cyclohexyloxy]-3-chloronitrobenzene (5 g) was deprotected using TFA (10 mL) and dichloromethane (10 mL) to give *cis/trans*-4-[4-(amino)cyclohexyloxy]-3-chloronitrobenzene. It was capped with acetyl chloride in dichloromethane and triethylamine to give *cis/trans*-4-[4-(acetylamino)cyclohexyloxy]-3-chloronitrobenzene. It was then refluxed with boron hydride methyl sulfide complex in THF for 1 h to give *cis/trans*-3-chloro-4-[4-(N-ethylamino)cyclohexyloxy]nitrobenzene. It was reduced under hydrogenolysis conditions using 10% Pd-C in methanol at 60 psi for 1h. The catalyst was filtered off. The filtrate was evaporated to give *cis/trans*-3-chloro-4-[4-(N-ethylamino)cyclohexyloxy]aniline. In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and *cis/trans*-3-chloro-4-[4-(N-ethylamino)cyclohexyloxy]aniline were reacted to yield *cis/trans*-2-chloro-N4-[3-chloro-4-[4-(N-ethylamino)cyclohexyloxy]phenyl]-5-fluoro-4-pyrimidineamine. In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(methylaminocarbonylmethyleneoxy)aniline and *cis/trans*-2-chloro-N4-[3-chloro-4-[4-(N-ethylamino)cyclohexyloxy]phenyl]-5-fluoro-4-pyrimidineamine were reacted to give *cis/trans*-N4-{3-chloro-4-[4-(N-ethylamino)cyclohexyloxy]phenyl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine. LCMS: ret. time: 7.65 min.; purity: 78.88%; MS (m/e): 544 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.304	5-Fluoro-N2-(4-morpholinophenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945412)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-morpholinoaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give 5-fluoro-N2-(4-morpholinophenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 3.00 (t, J= 4.8 Hz, 4H), 3.71 (t, J= 4.8 Hz, 4H), 4.62 (s, 2H), 6.81 (d, J= 9.0 Hz, 2H), 7.35 (d, J= 8.4 Hz, 1H), 7.46 (d, J= 9.3 Hz, 2H), 7.56 (d, J= 8.4 Hz, 1H), 8.05 (d, J= 3.6 Hz, 1H), 9.00 (s, 1H), 9.13 (s, 1H), 11.13 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 175.15; LCMS: ret. time: 8.08 min.; purity: 92.97%; MS (m/e): 438.32 (MH^+).
7.4.305	5-Fluoro-N2-(4-isopropoxyphenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945413)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-isopropoxyaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give 5-fluoro-N2-(4-isopropoxyphenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.22 (d, J= 6.3 Hz, 6H), 4.48 (p, J= 6.0 Hz, 1H), 4.62 (s, 2H), 6.76 (d, J= 9.0 Hz, 2H), 7.34 (d, J= 8.7 Hz, 1H), 7.47 (d, J= 9.0 Hz, 2H), 7.53 (d, J= 8.4 Hz, 1H), 8.06 (d, J= 3.6 Hz, 1H), 9.02 (s, 1H), 9.15 (s, 1H), 11.12 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 175.03; LCMS: ret. time: 10.52 min.; purity: 100%; MS (m/e): 411.32 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.306	N4-(2,2-Difluoro-2H-3-oxo-4H-benz[1,4]oxazın-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine p-Toluenesulfonic Acid Salt (R945414)	N4-(2,2-Difluoro-2H-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine (118 mg, 0.25 mmol) was suspended in acetonitrile (4 mL) and methanol (4 mL). At 0 °C, the aq. solution (4 mL) of p-toluenesulfonic acid monohydrate (47.5 mg, 0.25 mmol) was added. The reaction solution was shaken at room temperature for 5 minutes and lyophilized to dryness. The resulting solid was recrystallized from methanol and ethyl acetate to give N4-(2,2-difluoro-2H-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine p-toluenesulfonic acid salt as a white solid. ^{1}H NMR (DMSO-d_6): δ 2.28 (s, 3H), 2.63 (d, J= 4.8 Hz, 3H), 4.33 (s, 2H), 6.58 (p, J= 3.0 Hz, 1H), 7.09 (d, J= 8.4 Hz, 2H), 7.14 (d, J= 8.1 Hz, 2H), 7.22 (s, 1H), 7.26 (d, J= 8.7 Hz, 1H), 7.36 (d, J= 2.7 Hz, 1H), 7.46 (d, J= 7.8 Hz, 2H), 7.53 (dd, J= 2.4 and 8.7 Hz, 1H), 7.95 (d, J= 4.8 Hz, 1H), 8.19 (d, J= 4.5 Hz, 1H), 9.60 (s, 1H), 10.11 (s, 1H), 11.98 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 162.01, - 76.80; LCMS: ret. time: 9.80 min.; purity: 100%; MS (m/e): 475.32 (MH^+).
7.4.307	N4-(2,2-Difluoro-2H-3-oxo-4H-benz[1.4]oxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimıdinediamıne Benzenesulfonic Acid Salt (R945415)	In a manner similar to the preparation of N4-(2,2-difluoro-2H-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimıdınediamine p-toluenesulfonic acid salt, N4-[2,2-difluoro-2H-3-oxo-4H-benz[1,4]oxazin-6-yl]-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrımidinedıamıne (118 mg, 0.25 mmol) and benzenesulfonic acid (60 mg) were reacted to give N4-(2,2-difluoro-2H-3-oxo-4H-benz[1.4]oxazin-6-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl)-2,4-pyrimidinediamine benzenesulfonic acid salt as a white solid. ^{1}H NMR (DMSO-d_6): δ 2.63 (d, J= 4.5 Hz, 3H), 4.33 (s, 2H), 6.56 (dt, J= 2.4 and 6.9 Hz, 1H), 7.10-7.37 (m, 8H), 7.52-7.59 (m, 3H), 7.96 (d, J= 4.5 Hz, 1H), 8.18 (d, J= 4.5 Hz, 1H), 9.53 (s, 1H), 10.03 (s, 1H), 11.98 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 162.30, - 76.83; LCMS: ret. time: 9 79 min.; purity: 100%; MS (m/e): 475.34 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.308	N4-(2,2-Dimethyl-2H-3-oxo-4H-5-pyrido[1,4]oxazin-6-yl]-5-fluoro-N2-[4-(4-methoxycarbonylpiperazino)phenyl]-2,4-pyrimidinediamine (R945416)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(4-methoxycarbonylpiperazino)aniline (100 mg) and 2-chloro-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine (50 mg) were reacted to give N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrido[1,4]oxazin-6-yl]-5-fluoro-N2-[4-(4-methoxycarbonylpiperazino)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.43 (s, 6H), 2.99 (t, J= 5.1 Hz, 4H), 3.49 (t, J= 5.1 Hz, 4H), 3.61 (s, 3H), 6.82 (d, J= 9.0 Hz, 2H), 7.37 (d, J= 8.4 Hz, 1H), 7.47 (d, J= 9.0 Hz, 2H), 7.55 (d, J= 8.1 Hz, 1H), 8.06 (d, J= 3.6 Hz, 1H), 9.02 (s, 1H), 9.14 (s, 1H), 11.08 (s, 1H), ^{19}F NMR (282 MHz, DMSO-d_6): δ - 164.38; LCMS: ret. time: 10.24 min.; purity: 100%; MS (m/e): 523.45 (MH^+).
7.4.309	N2-[4-(N-Acetyl-N-methylamino)phenyl]-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R945417)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(N-acetyl-N-methylamino)aniline (100 mg) and 2-chloro-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine (50 mg) were reacted to give N2-[4-(N-acetyl-N-methylamino)phenyl]-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.43 (s, 6H), 1.73 (s, 3H), 3.08 (s, 3H), 7.11 (d, J= 8.7 Hz, 2H), 7.41 (d, J= 8.4 Hz, 1H), 7.49 (d, J= 8.7 Hz, 1H), 7.68 (d, J= 8.7 Hz, 2H), 8.13 (d, J= 3.6 Hz, 1H), 9.35 (s, 1H), 9.40 (s, 1H), 11.12 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 162.87; LCMS: ret. time: 10.03 min.; purity: 100%; MS (m/e): 452.26 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.310	N2-[4-(N-Acetyl-N-ethylamino)phenyl]-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R945418)	In a manner similar to the preparation of 4-(4-methoxycarbonylpiperazino)nitrobenzene, N-ethyl-4-nitroaniline (1 g) and acetyl chloride (1 mL) were reacted to yield N-acetyl-N-ethyl-4-nitroaniline. ^{1}H NMR ($CDCl_3$): δ 1.15 (t, J= 7.2 Hz, 3H), 1.94 (s, 3H), 3.81 (q, J= 7.2 Hz, 2H), 7.36 (d, J= 9.0 Hz, 2H), 8.30 (d, J= 8.7 Hz, 2H). N-Acetyl-N-ethyl-4-nitroaniline was reduced under hydrogenolysis conditions using 10% Pd-C in methanol at 40 psi for 1h. The catalyst was filtered off. The filtrate was evaporated to give 4-(N-acetyl-N-ethylamino)aniline. ^{1}H NMR ($CDCl_3$): δ 1.09 (t, J= 7.2 Hz, 3H), 1.82 (s, 3H), 3.68 (q, J= 7.2 Hz, 2H), 6.79 (d, J= 8.4 Hz, 2H), 6.95 (d, J= 8.1 Hz, 2H). In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(N-acetyl-N-ethylamino)aniline (100 mg) and 2-chloro-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine (50 mg) were reacted to give N2-[4-(N-acetyl-N-ethylamino)phenyl]-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 0.97 (t, J= 7.2 Hz, 3H), 1.43 (s, 6H), 1.68 (s, 3H), 3.56 (q, J= 6.9 Hz, 2H), 7.06 (d, J= 8.7 Hz, 2H), 7.40 (d, J= 8.7 Hz, 1H), 7.48 (d, J= 8.1 Hz, 1H), 7.69 (d, J= 8.7 Hz, 2H), 8.13 (d, J= 3.3 Hz, 1H), 9.35 (s, 1H), 9.40 (s, 1H), 11.12 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 162.90; LCMS: ret. time: 10.51 min.; purity: 100%; MS (m/e): 466.25 (MH^+).
7.4.311	N2-[4-(4-Acetylpiperazino)phenyl]-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R945419)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(4-acetylpiperazino)aniline (100 mg) and 2-chloro-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine (50 mg) were reacted to give N2-[4-(4-acetylpiperazino)phenyl]-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.43 (s, 6H), 2.03 (s, 3H), 2.96 (t, J= 5.1 Hz, 2H), 3.03 (t, J= 4.8 Hz, 2H), 3.56 (m, 4H), 6.82 (d, J= 9.0 Hz, 2H), 7.37 (d, J= 8.4 Hz, 1H), 7.47 (d, J= 8.7 Hz, 2H), 7.56 (d, J= 8.1 Hz, 1H), 8.06 (d, J= 3.6 Hz, 1H), 9.02 (s, 1H), 9.13 (s, 1H), 11.08 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 164.40; LCMS: ret. time: 8.70 min.; purity: 97.70%; MS (m/e): 507.55 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.312	N2-[4-(N-Acetyl-N-methylamino)phenyl]-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945420)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(N-acetyl-N-methylamino)aniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-[4-(N-acetyl-N-methylamino)phenyl]-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.74 (s, 3H), 3.09 (s, 3H), 4.64 (s, 2H), 7.13 (d, J= 8.7 Hz, 2H), 7.40 (d, J= 8.7 Hz, 1H), 7.50 (d, J= 8.7 Hz, 1H), 7.69 (d, J= 8.7 Hz, 2H), 8.13 (d, J= 3.3 Hz, 1H), 9.34 (s, 1H), 9.39 (s, 1H), 11.16 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 171.37; LCMS: ret. time: 9.14 min.; purity: 91.43%; MS (m/e): 424.50 (MH^+).
7.4.313	N2-[4-(N-Acetyl-N-ethylamino)phenyl]-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945421)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(N-acetyl-N-ethylamino)aniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-[4-(N-acetyl-N-ethylamino)phenyl]-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 0.98 (t, J= 6.9 Hz, 3H), 1.69 (s, 3H), 3.57 (q, J= 6.9 Hz, 2H), 4.63 (s, 2H), 7.08 (d, J= 8.7 Hz, 2H), 7.39 (d, J= 8.4 Hz, 1H), 7.50 (d, J= 8.4 Hz, 1H), 7.69 (d, J= 9.0 Hz, 2H), 8.13 (d, J= 3.6 Hz, 1H), 9.34 (s, 1H), 9.40 (s, 1H), 11.16 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 171.36; LCMS: ret. time: 9.26 min.; purity: 91.13%; MS (m/e): 438.27 (MH^+).
7.4.314	N2-(3,4-Dimethoxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945422)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3,4-dimethoxyaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-(3,4-dimethoxyphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 3.64 (s, 3H), 3.68 (s, 3H), 4.63 (s, 2H), 6.79 (d, J= 9.0 Hz, 1H), 7.20-7.23 (m, 2H), 7.33 (d, J= 8.7 Hz, 1H), 7.59 (d, J= 8.7 Hz, 1H), 8.08 (d, J= 3.6 Hz, 1H), 9.03 (s, 1H), 9.16 (s, 1H), 11.13 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 172.45; LCMS: ret. time: 8.35 min.; purity: 94.21%; MS (m/e): 413.30 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.315	N4-(2,2-Dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-(4-morpholinophenyl)-2,4-pyrimidinediamine (R945423)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-morpholinoaniline (100 mg) and 2-chloro-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine (50 mg) were reacted to give N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-(4-morpholinophenyl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.43 (s, 6H), 2.99 (t, J= 4.8 Hz, 4H), 3.72 (t, J= 4.8 Hz, 4H), 6.80 (d, J= 8.7 Hz, 2H), 7.36 (d, J= 8.4 Hz, 1H), 7.46 (d, J= 9.0 Hz, 2H), 7.55 (d, J= 8.7 Hz, 1H), 8.06 (d, J= 3.6 Hz, 1H), 9.00 (s, 1H), 9.13 (s, 1H), 11.09 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 173.16; LCMS: ret. time: 9.59 min.; purity: 100%; MS (m/e): 466.28 (MH^+).
7.4.316	N2-[3-(N-Cyclobutylamino)carbonylmethyleneoxyphenyl]-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R945424)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-(cyclobutylaminocarbonylmethyleneoxy)aniline (100 mg) and 2-chloro-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine (50 mg) were reacted to give N2-[3-(N-cyclobutylamino)carbonylmethyleneoxyphenyl]-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.42 (s, 6H), 1.57-1.66 (m, 2H), 1.90-2.04 (m, 2H), 2.12 (m, 2H), 4.25 (q, J= 8.4 Hz, 1H), 4.33 (s, 2H), 6.46 (dd, J= 1.8 and 8.1 Hz, 1H), 7.08 (t, J= 8.1 Hz,1H), 7.25 (dd, J= 8.4 Hz, 1H), 7 35 (m, 1H), 7.36 (d, J= 9.0 Hz, 1H), 7.63 (d, J= 9.0 Hz, 1H), 8.12 (d, J= 3.6 Hz, 1H), 8.23 (d, J= 7.5 Hz, 1H), 9.22 (s, 1H), 9.26 (s, 1H), 11.06 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 171.41; LCMS: ret. time: 11.46 min.; purity: 97.65%; MS (m/e): 508.45 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.317	5-Fluoro-N2-[4-(4-methylpiperazino)phenyl]-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945426)	1-(4-Nitrophenyl)piperazine (1 g), iodomethane (0.3 mL) and sodium hydride(500 mg) in THF (10 mL) were reacted overnight at room temperature. The solution was diluted with water. The yellow precipitation was collected by filtration, washed with water to give 4-(4-methylpiperazino)nitrobenzene as yellow solid. ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H), 2.69 (t, J= 5.1 Hz, 4H), 3.52 (t, J= 5.1 Hz, 4H), 6.83 (d, J= 9.3 Hz, 2H), 8.12 (d, J= 9.3 Hz, 2H). 4-(4-Methylpiperazino)nitrobenzene was reduced under hydrogenolysis conditions using 10% Pd-C in methanol at 40 psi for 1h. The catalyst was filtered off. The filtrate was evaporated to give 4-(4-methylpiperazino)aniline. ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H), 2.75 (t, J= 5.1 Hz, 4H), 3.16 (t, J= 5.1 Hz, 4H), 6.65 (d, J= 9.0 Hz, 2H), 6.81 (d, J= 8.7 Hz, 2H). In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(4-methylpiperazino)aniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give 5-fluoro-N2-[4-(4-methylpiperazino)phenyl]-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 2.85 (s, 3H), 3.16 (m, 2H), 3.48 (m, 4H), 3.69 (m, 2H), 4.63 (s, 2H), 6.87 (d, J= 9.0 Hz, 2H), 7.36 (d, J= 8.7 Hz, 1H), 7.50 (d, J= 9.0 Hz, 2H), 7.54 (d, J= 8.1 Hz, 1H), 8.07 (d, J= 3.6 Hz, 1H), 9.08 (s, 1H), 9.21 (s, 1H), 11.16 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 172.68; LCMS: ret. time: 5.67 min.; purity: 100%; MS (m/e): 451 (MH^+).
7.4.318	N4-(2,2-Dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-[4-(4-methylpiperazino)phenyl]-2,4-pyrimidinediamine (R945427)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 4-(4-methylpiperazino)aniline (100 mg) and 2-chloro-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine (50 mg) were reacted to give N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-[4-(4-methylpiperazino)phenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.43 (s, 6H), 2.71 (s, 3H), 3.16 (br, 8H), 6.84 (d, J= 9.0 Hz, 2H), 7.37 (d, J= 8.4 Hz, 1H), 7.49 (d, J= 9.0 Hz, 2H), 7.54 (d, J= 8.4 Hz, 1H), 8.07 (d, J= 3.6 Hz, 1H), 9.05 (s, 1H), 9.18 (s, 1H), 11.10 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 172.96; LCMS: ret. time: 7.08 min.; purity: 91 96%; MS (m/e): 479.25 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.319	N2-(3,5-Dimethylphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945432)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3,5-dimethylaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-(3,5-dimethylphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 2.17 (s, 6H), 4.62 (s, 2H), 6.52 (s, 1H), 7.22 (s, 2H), 7.34 (d, J= 8.4 Hz, 1H), 7.57 (d, J= 8.4 Hz, 1H), 8.11 (d, J= 3.6 Hz, 1H), 9.10 (s, 1H), 9.19 (s, 1H), 11.14 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 172.16; LCMS: ret. time: 11.34 min.; purity: 90.04%; MS (m/e): 381.23 (MH^+).
7.4.320	N2-(3,5-Dimethylphenyl)-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R945433)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3,5-dimethylaniline (100 mg) and 2-chloro-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine (50 mg) were reacted to give N2-(3,5-dimethylphenyl)-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.42 (s, 6H), 2.16 (s, 6H), 6.51 (s, 1H), 7.23 (s, 2H), 7.35 (d, J= 8.4 Hz, 1H), 7.59 (d, J= 8.1 Hz, 1H), 8.11 (d, J= 3.6 Hz, 1H), 9.10 (s, 1H), 9.18 (s, 1H), 11.08 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 172.19; LCMS: ret. time: 13.05 min.; purity: 95.71%; MS (m/e): 409.30 (MH^+).
7.4.321	5-Fluoro-N2-(3-isopropylphenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945434)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-isopropylaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give 5-fluoro-N2-(3-isopropylphenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.15 (d, J= 6.9 Hz, 6H), 2.74 (p, J= 6.9 Hz, 1H), 4.63 (s, 2H), 6.76 (d, J= 7.8 Hz, 1H), 7.10 (t, J= 7.8 Hz, 1H), 7.34 (d, J= 8.7 Hz, 1H), 7.42 (s, 1H), 7.51 (d, J= 9.0 Hz, 1H), 7.57 (d, J= 8.4 Hz, 1H), 8.11 (d, J= 3.6 Hz, 1H), 9.15 (s, 1H), 9.21 (s, 1H), 11.15 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 172.02; LCMS: ret. time: 12.40 min.; purity: 92.20%; MS (m/e): 395.28 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.322	N2-(3-Chloro-4-methylphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945439)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-chloro-4-methylaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-(3-chloro-4-methylphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 2.22 (s, 3H), 4.63 (s, 2H), 7.13 (d, J= 8.7 Hz, 1H), 7.38 (m, 2H), 7.48 (d, J= 8.4 Hz, 1H), 7.83 (d, J= 2.1 Hz, 1H), 8.13 (d, J= 3.3 Hz, 1H), 9.31 (s, 1H), 9.33 (s, 1H), 11.13 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 171 47; LCMS: ret. time: 12.66 min.; purity: 94.85%; MS (m/e): 401.13 (MH^+).
7.4.323	5-Fluoro-N2-(3-methoxy-5-trifluoromethylphenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945440)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-methoxy-5-trifluoromethylaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give 5-fluoro-N2-(3-methoxy-5-trifluoromethylphenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 3.74 (s, 3H), 4.63 (s, 2H), 6.72 (s, 1H), 7.32 (d, J= 8.4 Hz, 1H), 7.51 (d, J= 8.7 Hz, 1H), 7.56 (s, 1H), 7.64 (s, 1H), 8.18 (d, J= 3.3 Hz, 1H), 9.36 (s, 1H), 9.55 (s, 1H), 11.12 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 170.42; LCMS: ret. time: 13.14 min.; purity: 86.65%; MS (m/e): 451.30 (MH^+).
7.4.324	5-Fluoro-N2-(indol-6-yl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945443)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 6-aminoindol (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give 5-fluoro-N2-(indol-6-yl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 4.62 (s, 2H), 6.30 (s, 1H), 7.17 (m, 2H), 7.29 (d, J= 8.7 Hz, 1H), 7.35 (d, J= 8.7 Hz, 1H), 7.75 (d, J= 8.7 Hz, 1H), 7.82 (s, 1H), 8.10 (d, J= 3.6 Hz, 1H), 9.08 (s, 1H), 9.11 (s, 1H), 10.84 (s, 1H), 11.11 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 172.73; LCMS: ret. time: 8.52 min.; purity: 81.74%; MS (m/e): 392.30 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.325	N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-(indol-6-yl)-2,4-pyrimidinediamine (R945444)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 6-aminoindol (100 mg) and 2-chloro-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine (50 mg) were reacted to give N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-(indol-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 1.42 (s, 6H), 6.30 (s, 1H), 7.18 (m, 2H), 7.29 (d, J= 8.4 Hz, 1H), 7.35 (d, J= 8.7 Hz, 1H), 7.77 (d, J= 8.7 Hz, 1H), 7.80 (s, 1H), 8.10 (d, J= 3.6 Hz, 1H), 9.02 (s, 1H), 9.09 (s, 1H), 10.84 (s, 1H), 11.04 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 172.86; LCMS: ret. time: 9.91 min.; purity: 98.01%; MS (m/e): 420.18 (MH^+).
7.4.326	N2-(3,5-Dichlorophenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945454)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3,5-dichloroaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-(3,5-dichlorophenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 4.62 (s, 2H), 6.99 (t, J= 1.8 Hz, 1H), 7.38 (s, 2H), 7.70 (d, J= 2.1 Hz, 2H), 8.19 (d, J= 3.6 Hz, 1H), 9.52 (s, 1H), 9.66 (s, 1H), 11.17 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 170.19; LCMS: ret. time: 14.05 min.; purity: 85.53%; MS (m/e): 421.21 (MH^+).
7.4.327	N2-(3-Bromophenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945455)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-bromoaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-(3-bromophenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 4.63 (s, 2H), 7.02 (ddd, J= 0.9 and 1.8 and 7.8 Hz, 1H), 7.13 (t, J= 8.1 Hz, 1H), 7.39 (d, J= 8.7 Hz, 1H), 7.47 (d, J= 8.1 Hz, 1H), 7.52 (dd, J= 0.9 and 8.1 Hz, 1H), 7.99 (t, J= 1.8 Hz, 1H), 8.16 (d, J= 3.6 Hz, 1H), 9.40 (s, 1H), 9.47 (s, 1H), 11.17 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 170.91; LCMS: ret. time: 12.31 min.; purity: 100%; MS (m/e): 431.20 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.328	N2-(3-tert-Butylphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazın-6-yl)-2,4-pyrimidinediamine (R945456)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3-tert-butylanıline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to gıve N2-(3-tert-butylphenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidınediamine. ^{1}H NMR (DMSO-d_6): δ 1.23 (s, 9H), 4.62 (s, 2H), 6.91 (d, J= 8.1 Hz, 1H), 7.11 (t, J= 8.1 Hz, 1H), 7.34 (d, J= 8.4 Hz, 1H), 7.48 (s, 1H), 7.58 (s, 1H), 7.63 (d, J= 9.9 Hz, 1H), 8 11 (d, J= 3.6 Hz, 1H), 9.12 (s, 1H), 9.16 (s, 1H), 11.12 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 171.99; LCMS: ret. tıme: 13.16 min.; purity: 93.03%; MS (m/e): 409.29 (MH^+).
7.4.329	N2-(3,4-Difluorophenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R945458)	In a manner similar to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 3,4-difluoroaniline (100 mg) and 2-chloro-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-4-pyrimidineamine (50 mg) were reacted to give N2-(3,4-difluorophenyl)-5-fluoro-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 4.63 (s, 2H), 7.27 (m, 2H), 7.38 (s, 2H), 7.88 (ddd, J= 2.7 and 8.1 and 14.1 Hz, 1H), 8.15 (d, J= 3.6 Hz, 1H), 9.46 (s, 1H), 9.48 (s, 1H), 11.17 (s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 162.44, - 148.50, - 138.13; LCMS: ret. time: 11.63 min.; purity: 84.89%; MS (m/e): 389.25 (MH^+).
	Synthesis of Anilines	
7.4.330	(S)-2-Methyl-6-nitro-3-oxo-4H-benz[1,4]oxazine	To solution of 2-amino-4-nitrophenol (6.6 g) in DMF (100 mL) at 0 °C was added 95% NaH (1 g) solid all at once. The solution was stirred at 0 °Cfor 20 minutes then at room temperature for 1 hour. (S)-(-)-Methyl-2-chloropropionate (5 g) was added all at once and the reaction was heated with a reflux condenser attached at 85 °C overnight. The reaction mixture was concentrated and the residue was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed three times with water and then once with brine, dried over MgSO4, filtered and the volume was minimized on the rotary evaporater to about 15 mL. The residue was chromatographed EtOAc/hexanes 1:4 isocratically. The pure fractions were combined and evaporated and the crude product recrystallized from EtOAc/hexanes to yield (S)-2-methyl-6-nitro-3-oxo-4H-benz[1,4]oxazine. ^{1}H NMR (DMSO-d6): δ 7.82 (dd, 1H), 7.76 (d, 1H), 7.12 (d, 1H), 4.90 (q, 1H), 1.42 (d, 3H); LCMS: purity: 100 %; MS (m/e): 209 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.331	(S)-6-Amino-2-methyl-3-oxo-4H-benz[1,4]oxazine	To a solution of (S)-2-methyl-6-nitro-3-oxo-4H-benz[1,4]oxazine (2.5 g) in 250 mL EtOH/EtOAc (1:1; v/v) was added 500 mg of 10% Pd/C (Degussa) and the reaction was hydrogenated in the Parr apparatus at 50 PSI for 1 hour. The reaction was filtered through a bed of celite, evaporated and dried in vacuo to yield the 2.3 g of (S)-6-Amino-2-methyl-3-oxo-4H-benz[1,4]oxazine. ^{1}H NMR (DMSO-d6): δ 6.60 (d, 1H), 6.12 (m, 2H), 4.40 (q, 1H), 1.32 (d, 3H); LCMS: purity: 100 %; MS (m/e): 179 (MH^+).
7.4.332	(R)-2-Methyl-6-nitro-3-oxo-4H-benz[1,4]oxazine	In like manner to the synthesis of (S)-2-methyl-6-nitro-3-oxo-4H-benz[1,4]oxazine, the reaction of (R)-(+)-methyl-2-chloropropionate with 2-amino-4-nitrophenol gave (R)-2-methyl-6-nitro-3-oxo-4H-benz[1,4]oxazine. ^{1}H NMR (DMSO-d6): δ 7.82 (dd, 1H), 7.76 (d, 1H), 7.12 (d, 1H), 4.90 (q, 1H), 1.42 (d, 3H); LCMS: purity: 100 %; MS (m/e): 209 (MH^+).
7.4.333	(R)-6-Amino-2-methyl-3-oxo-4H-benz[1,4]oxazine	In like manner to the synthesis of (S)-6-amino-2-methyl-3-oxo-4H-benz[1,4]oxazine, the hydrogenation of (R)-2-methyl-6-nitro-3-oxo-4H-benz[1,4]oxazine gave (R)-6-amino-2-methyl-3-oxo-4H-benz[1,4]oxazine. ^{1}H NMR (DMSO-d6): δ 6.60 (d, 1H), 6.12 (m, 2H), 4.40 (q, 1H), 1.32 (d, 3H); LCMS: purity: 100 %; MS (m/e): 179 (MH^+).
7.4.334	7-Amino-4,4-dimethyl-1,3-dioxo-2H,4H-isoquinoline	The material was prepared according to the procedure outlined in *J. Med Chem*, 2002, 45(16), 3394-3405.
7.4.335	(±)-2-(2-Hydroxyethyl)-6-nitro-3-oxo-4H-benz[1,4]oxazine	To solution of 2-Amino-4-nitrophenol (16.5 g) in DMF (100 mL) at 0 °C was added 95% NaH (3 g) solid all at once. The reaction mixture was stirred at 0 °C for 20 minutes then at room temperature for 1 hour. 2-Bromobutyrolactone (13.8 mL) was added to the reaction mixture and it was then heated at 85 °C for overnight period with a reflux condenser attached. The reaction mixturewas concentrated to approximately 25 mL and diluted with 25 mL of MeOH. 400 mL of DI water was added with stirring and the precipitated product was collected filtration and dried on the funnel for 4 h to yield (±)-2-(2-hydroxyethyl)-6-nitro-3-oxo-4H-benz[1,4]oxazine. ^{1}H NMR (DMSO-d6): δ 7.82 (dd, 1H), 7.75 (d, 1H), 7.18 (d, 1H), 4.90 (m, 1H), 4.70 (t, 1H), 3.8 (m, 2H), 1.96 (m, 2H); LCMS: purity: 100 %; MS (m/e): 239 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.336	(±)-6-Amino-2-(2-hydroxyethyl)-3-oxo-4H-benz[1,4]oxazine	To a solution of (±)-2-(2-hydroxyethyl)-6-nitro-3-oxo-4H-benz[1,4]oxazine (1 g) in EtOH/EtOAc (100 mL; 1:1 v/v) was hydrogenated at 50 PSI in the presence of 200 mg of 10% Pd/C (Degussa) to give (±)-6-amino-2-(2-hydroxyethyl)-3-oxo-4H-benz[1,4]oxazine. ^{1}H NMR (DMSO-d6): δ 6.60 (d, 1H), 6.12 (m,, 2H), 4.58 (t, 1H), 4.40 (m, 1H), 3.57 (m, 2H), 1.76 (m, 2H); LCMS: purity: 98 %; MS (m/e): 209 (MH^+)
7.4.337	(S)-2-Chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, the reaction of 2,4-dichloro-5-fluoropyrimidine and (S)-6-amino-2-methyl-3-oxo-4H-benz[1,4]oxazine yielded (S)-2-Chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 8.2 (d, 1H), 7.21 (m, 2H), 6.95 (d, 1H), 4.62 (q, 1H), 1.41 (d, 3H); LCMS: purity: 96 %; MS (m/e): 309 (MH^+).
7.4.338	N2-chloro-5-fluoro-N4-(2-(R)-methyl -1,4-benzoxazin-3-on-6-yl)-pyrimidineamine	
7.4.339	(R)-2-Chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, the reaction of 2,4-dichloro-5-fluoropyrimidine and (R)-6-amino-2-methyl-3-oxo-4H-benz[1,4]oxazine yielded (R)-2-Chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 8.2 (d, 1H), 7.21 (m, 2H), 6.95 (d, 1H), 4.62 (q, 1H), 1.41 (d, 3H); LCMS: purity: 96 %; MS (m/e): 309 (MH^+).
7.4.340	(±)-2-Chloro-5-fluoro-N4-[2-(2-hydroxyethyl)-3-oxo-4H-benz[1,4]oxazin-6-yl]-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, the reaction of 2,4-dichloro-5-fluoropyrimidine and (±)-6-amino-2-(2-hydroxyethyl)-3-oxo-4H-benz[1,4]oxazine yielded (±)-2-Chloro-5-fluoro-N4-[2-(2-hydroxyethyl)-3-oxo-4H-benz[1,4]oxazin-6-yl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 8.2 (d, 1H), 7.22 (m, 2H), 6.95 (d, 1H), 4.60 (m, 1H), 3.56 (m, 2H), 1.87 (m, 2H); LCMS: purity: 94 %; MS (m/e): 339 (MH^+).
7.4.341	2-Chloro-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-Amino-4,4-dimethyl-2H,4H-1,3-dioxo-isoquinoline were reacted to yield 2-chloro-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 8.38 (d, 1H), 8.05 (m, 2H), 7.78 (d, 1H), 1.47 (s, 6H;); LCMS: purity: 94 %; MS (m/e): 335 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.342	(S)-5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R909317)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, (S)-2-Chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield (S)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.04 (d, 1H), 7.23 (m, 4H), 7.04 (t, 1H), 6.92 (d, 1H), 6.53 (dd, 1H), 4.61 (q, 2H), 4.37 (s, 2H), 2.61 (d, 3H), 1.40 (d, 3H); LCMS: purity: 96 %; MS (m/e): 453 (MH^+)
7.4.343	N4-(4,4-Dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylenedioxyphenyl]-2,4-pyrimidinediamine (R909318)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-4-pyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-N2-[3-(N-methylamino)carbonylmethylenedioxyphenyl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.30 (dd, 1H), 8.18 (m, 2H), 7.98 (m, 1H), 7.62 (d, 1H), 7.38 (s, 1H), 7.22 (d, 1H), 7.04 (t, 1H), 6.43 (dd, 1H), 4.24 (s, 2H), 2.61 (s, 3H), 1.44 (s, 6H); LCMS: purity: 92%; MS (m/e): 479 (MH^+).
7.4.344	(R)-5-Fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R909317)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, (R)-2-Chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and 3-(N-methylaminocarbonylmethyleneoxy)aniline were reacted to yield (R)-5-fluoro-N2-[3-(N-methylamino)carbonylmethyleneoxyphenyl]-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.04 (d, 1H), 7.23 (m, 4H), 7.04 (t, 1H), 6.92 (d, 1H), 6.53 (dd, 1H), 4.61 (q, 2H), 4.37 (s, 2H), 2.61 (d, 3H), 1.40 (d, 3H); LCMS: purity: 96 %; MS (m/e): 453 (MH^+).
7.4.345	N2-(3-Chloro-4-hydrox-5-methylyphenyl)-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-2,4-pyrimidinediamine (R909320)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-4-pyrimidineamine and 3-chloro-4-hydroxy-5-methylaniline were reacted to yield N2-(3-chloro-4-hydrox-5-methylyphenyl)-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.22 (d, 1H), 8.19 (d, 1H), 8.02 (dd, 1H), 7.62 (m, 3H), 1.50 (s, 6H); LCMS: purity: 92%; MS (m/e): 456 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.346	(S)-N2-(3-Chloro-4-methoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R909321)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, (S)-2-chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and 3-chloro-4-methoxyaniline were reacted to yield (S)-N2-(3-chloro-4-methoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.12 (d, 1H), 7.41 (dd, 1H), 7.22 (m, 3H), 6.97 (m, 1H), 4.61 (q, 1H), 3.78 (s, 3H), 1.40 (d, 3H); LCMS: purity: 97%; MS (m/e): 430 (MH^+).
7.4.347	(R)-N2-(3-Chloro-4-methoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R909322)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, (R)-2-chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and 3-chloro-4-methoxyaniline were reacted to yield (R)-N2-(3-chloro-4-methoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.12 (d, 1H), 7.41 (dd, 1H), 7.22 (m, 3H), 6.97 (m, 1H), 4.61 (q, 1H), 3.78 (s, 3H), 1.40 (d, 3H); LCMS: purity: 97%; MS (m/e): 430 (MH^+).
7.4.348	N2-(3,5-Dimethoxyphenyl)-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)- 5-fluoro-2,4-pyrimidinediamine (R909323)	In like manner to the synthesis of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro- N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-4-pyrimidineamine and 3,5-dimethoxyaniline were reacted to yield N2-(3,5-dimethoxyphenyl)-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)- 5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.18 (d, 1H), 8.05 (m, 3H), 7.75 (m,, 3H), 3.30 (s, 6H), 1.52 (s, 6H); LCMS: purity: 91%; MS (m/e): 452 (MH^+).
7.4.349	(S)-N2-(3,5-Dichloro-4-methoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]-oxazin-6-yl)-2,4-pyrimidinediamine (R908946)	In like manner to the synthesis of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, (S)-N2-chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and 3,5-dichloro-4-methoxyaniline were reacted to yield (S)-N2-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]-oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.07 (d, 1H), 7.78 (s, 2H), 7.09 (m, 2H), 6.95 (d, 1H), 4.61 (q, 1H), 3.75 (s, 3H), 1.21 (d, 3H); LCMS: purity: 98%; MS (m/e): 465 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.350	(R)-N2-(3,5-Dichloro-4-methoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]-oxazin-6-yl)-2,4-pyrimidinediamine (R908947)	In like manner to the synthesis of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, (R)-N2-chloro-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and 3,5-dichloro-4-methoxyaniline were reacted to yield (R)-N2-(3,5-dichloro-4-methoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]-oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.07 (d, 1H), 7.78 (s, 2H), 7.09 (m, 2H), 6.95 (d, 1H), 4.61 (q, 1H), 3.75 (s, 3H), 1.21 (d, 3H); LCMS: purity: 98%; MS (m/e): 465 (MH^+).
7.4.351	(±)-N2-(3,5-Dimethoxyphenyl)-5-fluoro-N4-[2-(2-hydroxyethyl)-3-oxo-4H-benz[1,4]oxazin-6-yl]-2,4-pyrimidinediamine (R908950)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-chloro-5-fluoro-N4-[2-(2-hydroxyethyl)-3-oxo-4H-benz[1,4]oxazin-6-yl]-4-pyrimidineamine and 3,5-dimethoxyaniline were reacted to yield (±)-N2-(3,5-Dimethoxyphenyl)-5-fluoro-N4-[2-(2-hydroxyethyl)-3-oxo-4H-benz[1,4]oxazin-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.04 (d, 1H), 7.23 (m, 2H), 6.95 (m, 3H), 6.02 (m, 1H), 4.58 (m, 1H), 3.60 (m, 7H), 1.90 (m, 2H); LCMS: purity: 95%; MS (m/e): 456 (MH^+).
7.4.352	(±)-N2-(3-Chloro-4-methoxyphenyl)-5-fluoro-N4-[2-(2-hydroxyethyl)-3-oxo-4H-benz[1,4]oxazin-6-yl]-2,4-pyrimidinediamine (R908951)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-chloro-5-fluoro-N4-[2-(2-hydroxyethyl)-3-oxo-4H-benz[1,4]oxazin-6-yl]-4-pyrimidineamine and 3-chloro-4-methoxyaniline were reacted to yield (±)-N2-(3-chloro-4-methoxyphenyl)-5-fluoro-N4-[2-(2-hydroxyethyl)-3-oxo-4H-benz[1,4]oxazin-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.04 (d, 1H), 7.80 (m, 1H), 7.41 (m, 1H), 7.20 (m, 2H), 6.97 (m, 2H), 4.61 (m, 1H), 3.73 (s, 3H), 3.50 (m, 2H), 1.90 (m, 2H); LCMS: purity: 93%; MS (m/e): 460 (MH^+).
7.4.353	(S,S)-N2,N4-Bis-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R908952)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, (S)-2-chloro-5-fluoro-N4-(2-methyl3-oxo-4H-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and (S)-6-amino-2-methyl-4H-benz[1,4]oxazine were reacted to yield (S,S)-N2,N4-bis-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.04 (d, 1H), 7.23 (m, 2H), 7.15 (m, 1H), 7.04 (m, 1H), 6.92 (m, 2H), 4.58 (m, 2H), 1.38 (m, 6H); LCMS: purity: 95%; MS (m/e): 451 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.354	(S)-N2-(3,5-Dimethoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R908953)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, (S)-N2-chloro-5-fluoro-N4-(2-methyl-3-oxo-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and 3,5-dimethoxyaniline were reacted to yield (S)-N2-(3,5-dimethoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.04 (d, 1H), 7.23 (m, 1H), 7.19 (m, 1H), 6.95 (m, 3H), 6.05 (m, 1H), 4.61 (q, 1H), 3.60 (s, 6H), 1.40 (d, 3H); LCMS: purity: 98%; MS (m/e): 426 (MH^+).
7.4.355	(R)-N2-(3,5-Dimethoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine (R908954)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, (R)-N2-chloro-5-fluoro-N4-(2-methyl-3-oxo-benz[1,4]oxazin-6-yl)-4-pyrimidineamine and 3,5-dimethoxyaniline were reacted to yield (R)-N2-(3,5-dimethoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine ^{1}H NMR (DMSO-d6): δ 8.04 (d, 1H), 7.23 (m, 1H), 7.19 (m, 1H), 6.95 (m, 3H), 6.05 (m, 1H), 4.61 (q, 1H), 3.60 (s, 6H), 1.40 (d, 3H); LCMS: purity: 98%; MS (m/e): 426 (MH^+).
7.4.356	N2-(3,5-Dichloro-4-methoxyphenyl)-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-2,4-pyrimidinediamine (R908955)	In like manner to the synthesis of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-chloro-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-4-pyrimidineamine and 3,5-dichloro-4-methoxyaniline were reacted to yield N2-(3,5-Dichloro-4-methoxyphenyl)-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.22 (d, 1H), 8.20 (d, 1H), 8.02 (dd, 1H), 7.62 (m, 3H), 3.75 (s, 3H), 1.50 (s, 6H); LCMS: purity: 92%; MS (m/e): 491 (MH^+).
7.4.357	N4-(4,4-Dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-N2-(indazol-6-yl)- 5-fluoro-2,4-pyrimidinediamine (R908956)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-chloro-N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-5-fluoro-4-pyrimidineamine and 6-aminoindazole were reacted to yield N4-(4,4-dimethyl-1,3-dioxo-2H,4H-isoquinolin-7-yl)-N2-(indazol-6-yl)- 5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.28 (m, 2H), 8.17 (m, 2H), 8.05 (m, 2H), 7.95 (s, 1H), 7.62 (m, 3H), 7.23 (m, 1H), 1.48 (s, 6H); LCMS: purity: 95%; MS (m/e): 432 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.358	N4-(3,3-Dimethyl-4H-benz[1,4]oxazin-6-yl)-N2-(3,5-dimethylphenyl)--5-fluoro-2,4-pyrimidinediamine (R908586)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-chloro-N4-(3,3-dimethyl-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3,5-dimethylaniline were reacted to yield N4-(3,3-dimethyl-4H-benz[1,4]oxazin-6-yl)-N2-(3,5-dimethylphenyl)--5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.02 (d, 1H), 7.21 (m, 2H), 6.80 (m, 1H), 6.77 (m, 1H), 6.60 (m, 1H), 6.50 (m, 1H), 3.75 (s, 2H), 2.15 (s, 6H), 1.15 (s, 6H); LCMS: purity: 95%; MS (m/e): 394 (MH^+).
7.4.359	N2-(3-Chloro-4-methoxyphenyl)-N4-(3,3-dimethyl-4H-benzo[1,4]xazin-6-yl)-5-fluoro-2,4-pyrimidinediamine (R908587)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-chloro-N4-(3,3-dimethyl-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 3-chloro-4-methoxyaniline were reacted to yield N2-(3-chloro-4-methoxyphenyl)-N4-(3,3-dimethyl-4H-benzo[1,4]xazin-6-yl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.01 (d, 1H), 7.81 (m, 1H), 7.58 (m, 1H), 6.97 (m, 1H), 6.80 (m, 2H), 6.60 (m, 1H), 3.77 (s, 3H), 3.74 (s, 2H), 1.15 (s, 6H); LCMS: purity: 94%; MS (m/e): 430 (MH^+).
7.4.360	N4-(3,3-Dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-N2-(indazol-6-yl)-2,4-pyrimidinediamine (R908591)	In like manner to preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-chloro-N4-(3,3-dimethyl-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 6-aminoindazole were reacted to yield N4-(3,3-dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-N2-(indazol-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.19 (s, 1H), 8.03 (d, 1H), 7.91 (s, 1H), 7.58 (m, 1H), 7.22 (m, 1H), 6.97 (m, 1H), 6.84 (m, 1H), 6.64 (m, 1H), 3.77 (s, 2H), 1.15 (s, 6H); LCMS: purity: 92%; MS (m/e): 406 (MH^+).
7.4.361	N4-(3,3-Dimethyl-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(N1-methylindazol-6-yl)-2,4-pyrimidinediamine (R908592)	In like manner to the preparartion of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, N2-chloro-N4-(3,3-dimethyl-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 6-amino-N1-methylindazole were reacted to yield N4-(3,3-dimethyl-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(N1-methylindazol-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 8.16 (s, 1H), 8.08 (d, 1H), 7.90 (s, 1H), 7.22 (m, 1H), 7.22 (m, 1H), 6.97 (m, 2H), 6.64 (m, 1H), 3.80 (s, 3H), 3.77 (s, 2H), 1.15 (s, 6H); LCMS: purity: 93%; MS (m/e): 420 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.362	(R)-N2-(3-Chloro-4-methoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine Toluenesulfonic Acid Salt (R908580)	In like manner to the preparation of N2-(3,5-dimethoxyphenyl)-N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine p-Toluenesulfonic Acid Salt, the reaction of (R)-N2-(3-chloro-4-methoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine with p-Toluenesulfonic acid monohydrate gave (R)-N2-(3-chloro-4-methoxyphenyl)-5-fluoro-N4-(2-methyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-2,4-pyrimidinediamine Toluenesulfonic Acid Salt.
	Preparation of Aminoindazolines	
7.4.363	1-(2-Ethoxycarbonylethyl)-5-nitroindazoline and 2-(2-ethoxycarbonylethyl)-5-nitroindazoline	In like manner to the preparation of 1-(methoxycarbonyl)methyl-5-nitroindazoline, 1-(2-ethoxycarbonylethyl)-5-nitroindazoline was prepared by alkylation of 5-nitroindazoline with ethyl 3-bromopropionate in presence of K_2CO_3. The 1-(2-ethoxycarbonylethyl)-5-nitroindazoline (43%) with high Rf value on the TLC in 30% EtOAcn-hexanes was collected by silica gel column chromatographic purification. ^{1}H NMR ($CDCl_3$): δ 8.70 (d, 1H, J= 1.7 Hz), 8.27 (dd, 1H, J= 2.3 and 8.8 Hz), 8.20 (d, 1H, J= 1.7 Hz), 7.59 (d, 1H, J= 8.8 Hz), 4.70 (t, 2H, J= 6.4 Hz), 4.07 (qt, 2H, J= 7.0 Hz), 3.01 (t, 2H, J= 6.4 Hz), 1.16 (t, 3H, J= 7.0 Hz). The lower Rf value by-product, 2-(2-ethoxycarbonylethyl)-5-nitroindazoline was also collected by eluting the column with 50% EtOAcn-hexanes. ^{1}H NMR ($CDCl_3$): δ 8.71 (d. 1H. J= 2.0 Hz), 8.32 (s, 1H), 8.08 (app dd, 1H, J= 2.0 and 9.7 Hz), 7.73 (dd, 1H, J= 0.8 and 9.7 Hz), 4.77 (t, 2H, J= 6.4 Hz), 4.12 (qt, 2H, J= 7.0 Hz), 3.08 (t, 2H, J= 6.4 Hz), 1.22 (t, 3H, J= 7.0 Hz).
7.4.364	5-Amino-1-(2-ethoxycarbonylethyl)indazoline	In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 1-(2-ethoxycarbonylethyl)-5-nitroindazoline was reduced to provide 5-amino-1-(2-ethoxycarbonylethyl)indazoline. ^{1}H NMR ($CDCl_3$): δ 7.78 (s, 1H), 7.30 (d, 1H; J= 8.8 Hz), 6.91 (d, 1H, J= 2.3 Hz), 6.87 (dd, 1H, J= 2.3 and 8.8 Hz), 4.59 (t, 2H, J= 6.4 Hz), 4.08 (qt, 2H, J= 7.0 Hz), 3.02 (br s, 2H), 2.92 (t, 2H, J= 7.0 Hz), 1.16 (t, 3H, J= 7.0 Hz).
7.4.365	5-Amino-2-(2-ethoxycarbonylethyl)indazoline	In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, the reduction of 2-(2-ethoxycarbonylethyl)-5-nitroindazoline provided 5-amino-2-(2-ethoxycarbonylethyl)indazoline. ^{1}H NMR ($CDCl_3$): δ 7.64 (s, 1H), 7.45 (dd, 1H, J= 0.9 and 9.1 Hz), 6.74 (dd, 1H, J= 2.0 and 9.1 Hz), 6.67(d, 1H, J= 2.0 Hz), 4.57 (t, 2H, J= 6.7 Hz), 4.05 (qt, 2H, J= 7.0 Hz), 3.28 (br s, 2H), 2.93 (t, 2H, J= 6.7 Hz), 1.16 (t, 3H, J= 7.0 Hz).

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Section Number	Name of compound and reference number	Experimental
7.4.366	1-methyl-6-nitroindazoline and 2-methyl-6-nitroindazoline	In like manner to the preparation of 1-(methoxycarbonylmethyl)-5-nitroindazoline, 6-nitroindazole was alkylated with methyl iodide in presence of K_2CO_3. The reaction mixture was diluted with water upon completion of the reaction. The solid formed was filtered, dried and chromatographed with 15% EtOAc:n-n-hexanes on silica gel to provide high Rf value product 1-methyl-6-nitroindazoline . ^{1}H NMR ($CDCl_3$): δ 8.32 (s, 1H), 8.10 (s, 1H), 8.01 (dd, 1H, J= 2.7 and 8.8 Hz), 7.83 (d, 1H, J= 8.8 Hz), 4.18 (s, 3H). The lower Rf value by-product 2-methyl-6-nitroindazoline was also collected by eluting the column with 30% EtOAc:n-hexanes. ^{1}H NMR ($CDCl_3$): δ 8.69 (d, 1H, J= 2.0 Hz), 8.03 (s, 1H), 7.90 (dd, 1H, J= 2.0 and 9.1 Hz), 7.75 (d, 1H, J= 9.1 Hz), 4.31 (s, 13H).
7.4.367	6-Amino-1-methylindazoline	In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 1-methyl-6-nitroindazoline was reduced to give 6-amino-1-methylindazoline. ^{1}H NMR ($CDCl_3$): δ 7.80 (s, 1H), 7.48 (dd, 1H, J= 0.6 and 8.2 Hz), 6.58 (dd, 1H, J= 1.8 and 8.2 Hz), 6.54 (d, 1H, J= 0.6 Hz), 3.94 (s, 3H), 3.5 (br s, 2H).
7.4.368	6-Amino-2-methylindazoline	In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 2-methyl-6-nitroindazoline was reduced to give 6-amino-2-methylindazoline. ^{1}H NMR ($CDCl_3$): δ 7.71 (s, 1H), 7.43 (d, 1H, J= 8.8 Hz), 6.79 (app d, 1H, J= 1.7 Hz), 6.58 (dd, 1H, J= 1.7 and 8.8 Hz), 4.11 (s, 3H), 3.31 (br s, 2H).
7.4.369	2-Chloro-5-fluoro-N4-(4-fluoro-3-methoxyphenyl)-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-fluoro-3-methoxyaniline were reacted to provide 2-chloro-5-fluoro-N4-(4-fluoro-3-methoxyphenyl)-4-pyrimidineamine . ^{1}H NMR (DMSO-d6): δ 9.99 (s, 1H), 8.31 (d, 1H, J= 3.5 Hz), 7.54 (dd, 1H, J= 8.2 Hz), 7.30-7.17 (m, 2H), 3.81 (s, 3H). LCMS: ret. time: 12.11 min.; purity: 98%; MS (m/e): 272 (MH^+).
7.4.370	2-Chloro-N4-(4-chloro-3-fluorophenyl)-5-fluoro-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-chloro-3-fluoroaniline were reacted to provide 2-chloro-N4-(4-chloro-3-fluorophenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.25 (s, 1H), 8.39 (d, 1H, J= 3.5 Hz), 7.87 (dd, 1H, J= 1.8 and 11.4 Hz), 7.59 (m, 1H), 7.09-6.38 (m, 1H). LCMS: ret. time: 13.74 min.; purity: 93%; MS (m/e): 277 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.371	2-Chloro-N4-(3-chloro-4-fluorophenyl)-5-fluoro-4-pyrimidineamine	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloro-4-fluoroaniline were reacted to provide 2-chloro-N4-(3-chloro-4-fluorophenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.12 (s, 1H), 8.35 (s, 1H), 7.93 (dd, 1H, J= 2.6 and 7.6 Hz), 7.69-7.64 (m, 1H), 7.43 (t, 1H, J= 9.2 Hz). LCMS: ret. time: 13.38 min.; purity: 91%; MS (m/e): 277 (MH^+).
7.4.372	N4-(2,6-Dimethoxypyrid-3-yl)- N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935381)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(2,6-dimethoxypyrid-3-yl)-5-fluoro-4-pyrimidineamine and 5-amino-1-(2-ethoxycarbonylethyl)indazoline were reacted to give N4-(2,6-dimethoxypyrid-3-yl)- N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.08 (s, 1H), 8.68 (s, 1H), 8.00 (d, 1H, J= 4.1 Hz), 7.93 (s, 1H), 7.74 (d, 1H, J= 8.2 Hz), 7.67 (s, 1H), 7.42 (d, 1H, J= 9.4 Hz), 7.34 (d, 1H, J= 9.4 Hz), 6.46 (d, 1H, J= 8.2 Hz), 4.51 (t, 2H, J= 6.4 Hz), 3.96 (qt, 2H, J= 7.0 Hz), 3.91 (s, 1H), 3.83 (s, 1H), 2.85 (t, 2H, J= 6.4 Hz), 1.05 (t, 3H, J= 7.0 Hz). LCMS: ret. time: 10.94 min.; purity: 90%; MS (m/e): 482 (MH^+).
7.4.373	N4-(4-Chlorophenyl)-5-fluoro-N2-{1-[2-(N-methylamino)carbonylethyl]indazolin-5-yl}-2,4-pyrimidinediamine (R935382)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(4-chlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride salt were reacted to provide N4-(4-chlorophenyl)-5-fluoro-N2-{1-[2-(*N*-methylaminocarbonyl)ethyl]indazolin-5-yl}-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.44 (s, 1H), 9.21 (s, 1H), 8.11 (d, 1H, J= 4.1 Hz), 8.07 (s, 1H), 7.85 (d, 2H, J= 9.4 Hz), 7.82 (dd, 2H, J= 2.9 and 8.8 Hz), 7.52 (d, 1H, J= 9.4 Hz), 7.46 (d, 1H, J= 8.2 Hz), 7.34 (d, 1H, J= 8.8 Hz), 4.53 (t, 2H, J= 7.0 Hz), 2.63 (t, 2H, J= 7.0 Hz), 2.49 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 8.58 min.; purity: 97%; MS (m/e): 440 (MH^+).
7.4.374	N4-(4-Chlorophenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-5-yl]-2,4-pyrimidinediamine (R935383)	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(4-chlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with diisobutyl lithiumaluminum hydride to produce N4-(4-chlorophenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.44 (s, 1H), 9.20 (s, 1H), 8.11 (d, 1H, J= 4.2 Hz), 8.07 (s, 1H), 7.85 (d, 1H, J= 9.4 Hz), 7.82 (dd, 2H, J= 2.9 and 8.8 Hz), 7.52 (d, 1H, J= 9.4 Hz), 7.46 (d, 1H, J= 9.4 Hz), 7.32 (d, 1H, J= 8.8 Hz), 4.56 (t, 1H, J= 5.2 Hz), 4.39 (t, 2H, J= 6.4 Hz), 3.35 (app q, 2H, J= 6.4 Hz), 1.93 (q, 2H, J= 6.4 Hz). LCMS: ret. time: 8.85 min.; purity: 96%; MS (m/e): 413 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.375	N4-(3,4-Difluorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935384)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3,4-difluorophenyl)-5-fluoro-4-pyrimidineamine and 5-amino-1-(2-ethoxycarbonylethyl)indazoline were reacted to give N4-(3,4-difluorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.30 (s, 1H), 10.09 (s, 1H), 8.26 (d, 1H, J= 4.7 Hz), 7.95 (s, 1H), 7.89 (s, 2H), 7.66 (d, 1H, J= 8.8 Hz), 7.47-7.32 (m, 3H), 4.60 (t, 2H, J= 6.4 Hz), 3.97 (qt, 2H, J= 7.0 Hz), 2.90 (t, 2H, J= 6.4 Hz), 1.06 (t, 3H, J= 7.0 Hz). LCMS: ret. time: 11.45 min.; purity: 96%; MS (m/e): 457 (MH^+).
7.4.376	N4-(3,4-Difluorophenyl)-5-fluoro-N2-{1-[2-(*N*-methylaminocarbonyl)ethyl]indazolin-5-yl}-2,4-pyrimidinediamine (R935385)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-difluorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride salt were reacted to provide N4-(3,4-difluorophenyl)-5-fluoro-N2-{1-[2(*N*-methylaminocarbonyl)ethyl]indazolin-5-yl}-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.49 (s, 1H), 9.27 (s, 1H), 8.13 (d, 1H, J= 3.5 Hz), 8.08-8.00 (app s, 2H), 2.87 (s, 1H), 7.83 (qt, 1H, J= 4.7 Hz), 7.56-7.49 (m, 3H), 7.36 (dd, 1H, J= 8.8 and 20.1 Hz), 4.52 (t, 2H, J= 6.4 Hz), 2.63 (t, 2H, J= 6.4 Hz), 2.59 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 8.44 min.; purity: 96%; MS (m/e): 442 (MH^+).
7.4.377	N4-(3,4-Difluorophenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-5-yl]-2,4-pyrimidinediamine (R935386)	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3,4-difluorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with diisobutyl lithiumaluminum hydride to produce N4-(3,4-difluorophenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.49 (s, 1H), 9.26 (s, 1H), 8.13 (d, 1H, J= 3.5 Hz), 8.07-8.03 (app s, 2H), 7.86 (s, 1H), 7.54-7.45 (m, 3H), 7.33 (dd, 1H, J= 8.8 and 19.3 Hz), 4.56 (t, 1H, J= 4.7 Hz), 4.39 (t, 2H, J= 6.5 Hz), 3.35 (qt, 2H, J= 6.5 Hz), 1.93 (q, 2H, J= 6.5 Hz). LCMS: ret. time: 8.86 min.; purity: 96%; MS (m/e): 415 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.378	N4-(3,4-Dichlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935389)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine and 5-amino-1-(2-ethoxycarbonylethyl)indazoline were reacted to give N4-(3,4-dichlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.25 (s, 1H), 10.00 (s, 1H), 8.27 (d, 1H, J= 4.7 Hz), 8.02 (s, 1H), 7.95 (s, 1H), 7.87 (s, 1H), 7.72 (d, 1H, J= 8.8 Hz), 7.65 (d, 1H, J= 8.8 Hz), 7.52 (d, 1H, J= 8.8 Hz), 7.35 (d, 1H, J= 8.8 Hz), 4.59 (t, 2H, J= 6.4 Hz), 3.97 (qt, 2H, J= 7.0 Hz), 2.90 (t, 2H, J= 6.4 Hz), 1.06 (t, 3H, J= 7.0 Hz). LCMS: ret. time: 13.10 min.; purity. 95%; MS (m/e): 490 (MH^+).
7.4.379	N4-(3,4-Dichlorophenyl)-5-fluoro-N2-{1-[2(*N*-methylaminocarbonyl)ethyl]indazolin-5-yl}-2,4-pyrimidinediamine (R935390)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-dichlororophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride salt were reacted to provide N4-(3,4-dichlorophenyl)-5-fluoro-N2-{1-[2(*N*-methylaminocarbonyl)ethyl]indazolin-5-yl}-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.55 (s, 1H), 9.28 (s, 1H), 8.15 (d, 1H, J= 3.5 Hz), 8.08 (d, 1H, J= 2.3 Hz), 8.00 (s, 1H), 7.86 (s, 1H), 7.80 (m, 2H), 7.55-7.44 (m, 3H), 4.52 (t, 2H, J= 7.0 Hz), 2.63 (t, 2H, J= 7.0 Hz), 2.50 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 9.83 min.; purity: 96%; MS (m/e): 475 (MH^+).
7.4.380	N4-(3,4-Dichlorophenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-5-yl]-2,4-pyrimidinediamine (R935391)	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3,4-dichlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with diisobutyl lithiumaluminum hydride to produce N4-(3,4-dichlorophenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.67 (s, 1H), 9.38 (s, 1H), 8.23 (d, 1H, J= 3.5 Hz), 8.17 (app t, 1H, J= 2.3 Hz), 8.08 (s, 1H), 7.95 (s, 1H), 7.87 (d, 1H, J= 8.8 Hz), 7.62 (d, 1H, J= 8.8 Hz), 7.59 –7.53 (m, 2H), 4.47 (t, 2H, J= 6.4 Hz), 3.44 (app t , 2H, J= 6.4 Hz), 2.02 (q, 2H, J= 6.4 Hz). LCMS: ret. time: 10.31 min.; purity: 95%; MS (m/e): 448 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.381	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935392)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine and 1-methyl-6-aminoindazole were reacted to give N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.40 (s, 1H), 10.27 (s, 1H), 8.27 (d, 1H, J= 4.7 Hz), 7.95 (s, 1H), 7.81 (s, 1H), 7.66 (d, 1H, J= 8.8 Hz), 7.25-7.23 (m, 1H), 7.15-7.09 (m, 2H), 6.77 (d, 1H, J= 8.8 Hz), 4.24-4.15 (m, 4H), 3.81 (s, 3H). LCMS: ret. time: 9.19 min.; purity: 97%; MS (m/e): 393 (MH^+).
7.4.382	N4-(3,4-Dichlorophenyl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935393)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine and 1-methyl-6-aminoindazole were reacted to give N4-(3,4-dichlorophenyl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.68 (s, 1H), 9.56 (s, 1H), 8.23 (d, 1H, J= 4.1 Hz), 8.13 (d, 1H, J= 2.3 Hz), 7.98 (s, 1H), 7.86 (s, 1H), 7.79 (dd, 1H, J= 2.3 and 8,8 Hz), 7.58 (d, 1H, J= 8.8 Hz), 7.53 (d, 1H, J= 8.8 Hz), 7.22 (dd, 1H, J= 2.3 and 8.8 Hz), 3.77 (s, 3H). LCMS: ret. time: 13.48 min.; purity: 97%; MS (m/e): 404 (MH^+).
7.4.383	2-Chloro-5-fluoro-N-(1-methylindazolin-6-yl)-4-pyrimidineamine (R935394)	In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-1-methyl-indazoline were reacted to provide 2-chloro-5-fluoro-N-(1-methylindazolin-6-yl)-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.15 (s, 1H), 8.34 (d, 1H, J= 3.5 Hz), 8.00 (s, 1H), 7.98 (app s, 1H), 7.72 (d, 1H, J= 8.2 Hz), 7.39 (d, 1H, J= 8.2 Hz), 3.81 (s, 3H). LCMS: ret. time: 10.45 min.; purity: 95%; MS (m/e): 278 (MH^+).
7.4.384	N2-(3-Chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935395)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1-methylindazolin-6-yl)-4-pyrimidineamine was reacted with 4-amino-2-chloro-6-methylphenol to give N2-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-N4-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.48 (s, 1H), 9.06 (s, 1H), 8.58 (s, 1H), 8.11 (d, 1H, J= 3.5 Hz), 8.07 (s, 1H), 7.93 (s, 1H), 7.65 (d, 1H, J= 8.8 Hz), 7.56 (s, 1H), 7.36 (dd, 1H, J= 2.3 and 8.8 Hz), 7.21 (d, 1H, J= 2.3 Hz), 3.87 (s, 3H), 1.99 (s, 3H). LCMS: ret. time: 9.13 min.; purity: 95%; MS (m/e): 399 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.385	N4-(3,4-Dichlorophenyl)-5-fluoro-N2-[2-(2-methoxy-4-methoxycarbonylbenzyl)indazolin-6-yl]-2,4-pyrimidinediamine (R935396)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-2-(2-methoxy-4-methoxycarbonylbenzyl)indazoline to provide N4-(3,4-dichlorophenyl)-5-fluoro-N2-[2-(2-methoxy-4-methoxycarbonylbenzyl)indazolin-6-yl]-2,4-pyrimidinediamine. LCMS: ret. time: 14.80 min.; purity: 94%; MS (m/e): 568 (MH^+).
7.4.386	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[2-(2-methoxy-4-methoxycarbonylbenzyl)indazolin-6-yl]-2,4-pyrimidinediamine (R935398)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-2-(2-methoxy-3-methoxycarbonylbenzyl)indazoline to provide N4-(3,4-dichlorophenyl)-5-fluoro-N2-[2-(2-methoxy-4-methoxycarbonylbenzyl)indazolin-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.80 (s, 1H), 9.66 (s, 1H), 8.32 (s, 1H), 8.16 (d, 1H, J= 4.4 Hz), 7.90 (s, 1H), 7.71 (d, 2H, J= 3.5 Hz), 7.61 (d, 1H, J= 8.2 Hz), 7.52 (s, 1H), 7.49 (d, 1H, J= 8.2 Hz), 7.15 (d, 1H, J= 8.5 Hz), 7.09 (d, 1H, J= 8.5 Hz), 6.89 (d, 1H, J= 8.5 Hz), 5.59 (s, 2H), 3.91 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H). LCMS: ret. time: 12.16 min.; purity: 94%; MS (m/e): 563 (MH^+).
7.4.387	N4-(3,4-Ethylenedioxyphenyl)-5-fluoro-N2-{1-[2-methoxy-4-(*N*-methylaminocarbonyl)benzyl]indazolin-6-yl}-2,4-pyrimidinediamine (R935399)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[1-(2-methoxy-4-methoxycarbonylbenzyl)indazolin-6-yl]-2,4-pyrimidinediamine and methylamine hydrochloride salt were reacted to provide N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-{1-[2-methoxy-4-(*N*-methylaminocarbonyl)benzyl]indazolin-6-yl}-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.15 (s, 1H), 8.42 (qt, 1H, J= 3.5 Hz), 8.20 (s, 1H), 8.06 (d, 1H, J= 3.3 Hz), 8.05 (s, 1H), 7.50 (d, 1H, J= 8.8 Hz), 7.45 (s, 1H), 7.34 (dd, 1H, J= 1.2 and 7.6 Hz), 7.28-7.26 (m, 2H), 7.18 (dd, 1H, J= 2.3 and 8.3 Hz), 6.93 (d, 1H, J= 7.6 Hz), 6.77 (dd, 1H, J= 2.3 and 8.8 Hz), 5.52 (s, 2H), 4.18 (s, 4H), 3.88 (s, 3H), 2.76 (d, 3H, J= 3.5 Hz). LCMS: ret. time: 9.03 min.; purity: 91%; MS (m/e): 556 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.388	N4-(3, 4-Difluorophenyl)-5-fluoro-N2-(indazolin-6-yl)-2,4-pyrimidinediamine (R935400)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3,4-difluorophenyl)-5-fluoro 4-pyrimidineamine and 6-aminoindazoline were reacted to give N4-(3,4-difluorophenyl)-5-fluoro-N2-(indazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.66 (s, 1H), 9.56 (s, 1H), 8.20 (d, 1H, J= 4.1 Hz), 8.16-8.05 (m, 2H), 7.91 (s, 1H), 7.59 (d, 2H, J= 8.8 Hz), 7.36 (dd, 1H, J= 19.9 and 8.8 Hz), 7.24 (dd, 1H, J= 1.7 and 8.8 Hz). LCMS: ret. time: 10.39 min.; purity: 94%; MS (m/e): 357 (MH^+).
7.4.389	N4-(3,4-Difluorophenyl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935401)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3,4-difluorophenyl)-5-fluoro-4-pyrimidineamine and 1-methyl-6-aminoindazole were reacted to give N4-(3,4-difluorophenyl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.15 (s, 1H), 10.09 (s, 1H), 8.29 (d, 1H, J= 4.1 Hz), 8.03-7.97 (m, 1H), 7.93 (s, 1H), 7.88 (s, 1H), 7.65 (d, 1H, J= 8.8 Hz), 7.50-7.52 (m, 1H), 7.37 (dd, 1H, J= 8.3 and 19.4 Hz), 7.21 (d, 1H, J= 8.3 Hz), 3.84 (s, 3H). LCMS: ret. time: 11.78 min.; purity: 98%; MS (m/e): 371 (MH^+).
7.4.390	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935402)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 1-methyl-6-aminoindazole were reacted to give N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.43 (s, 1H), 9.37 (s, 1H), 8.14 (d, 1H, J= 3.5 Hz), 7.99 (s, 1H), 7.83-7.81 (m, 2H), 7.69-7.65 (m, 1H), 7.54 (d, 1H, J= 8.8 Hz), 7.21 (d, 1H, J= 8.2Hz), 7.11 (d, 1H, J= 8.8 Hz), 3.82 (s, 3H), 3.72 (s, 3H). LCMS: ret. time: 10.60 min.; purity: 94%; MS (m/e): 399 (MH^+).
7.4.391	N4-(3,4-Dichlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-6-yl]-5-fluoro-2,4-pyrimidinediamine (R935403)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine and 6-amino-1-(2-ethoxycarbonylethyl)indazoline were reacted to give N4-(3,4-dichlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-6-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.65 (s, 1H), 9.53 (s, 1H), 8.22 (d, 1H, J= 3.5 Hz), 8.12 (t, 1H, J= 2.9 Hz), 8.00 (s, 1H), 7.90 (s, 1H), 7.82 (app dd, 1H, J= 2.9 and 8.8 Hz), 7.57 (d, 1H, J= 8.8 Hz), 7.53 (d, 1H, J= 8.8 Hz), 7.28 (d, 1H, J= 8.8 Hz), 4.34 (t, 2H, J= 6.4 Hz), 3.94 (qt, 2H, J= 7.0 Hz), 2.83 (t, 2H, J= 6.4 Hz), 1.04 (t, 3H, J= 7.0 Hz). LCMS: ret. time: 14.36 min.; purity: 99%; MS (m/e): 490 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.392	N4-(3,4-Dichlorophenyl)-5-fluoro-N2-{1-[2(*N*-methylamino)carbonylethyl]indazolin-6-yl}-2,4-pyrimidinediamine (R935404)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-dichlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-6-yl]-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride salt were reacted to provide N4-(3,4-dichlorophenyl)-5-fluoro-N2-{1-[2(*N*-methylamino)carbonylethyl]indazolin-6-yl}-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.64 (s, 1H), 9.51 (s, 1H), 8.22 (d, 1H, J= 3.5 Hz), 8.13 (t, 1H, J= 2.9 Hz), 7.95 (s, 1H), 7.89 (s, 1H), 7.85-7.79 (m, 2H), 7.58 (d, 1H, J= 8.8 Hz), 7.55 (d, 1H, J= 8.8 Hz), 7.29 (d, 1H, J= 8.8 Hz), 4.33 (t, 2H, J= 6.4 Hz), 2.60 (t, 2H, J= 6.4 Hz), 2.48 (d, 3H, J= 3.5 Hz). LCMS: ret. time: 11.09 min.; purity: 95%; MS (m/e): 475 (MH^+).
7.4.393	N4-(3,4-Dichlorophenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-6-yl]-2,4-pyrimidinediamine (R935405)	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3,4-dichlorophenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-6-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with diisobutyl lithiumaluminum hydride to produce N4-(3,4-dichlorophenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.72 (s, 1H), 9.59 (s, 1H), 8.29 (d, 1H, J =3.5 Hz), 8.20 (t, 1H, J= 2.9 Hz), 8.02 (s, 1H), 7.96 (s, 1H), 7.90 (d, 1H, J= 8.8 Hz), 7.66 (d, 1H, J= 8.8 Hz), 7.61 (d, 1H, J= 8.8 Hz), 7.38 (d, 1H, J= 8.8 Hz), 4.58 (t, 1H, J= 4.7 Hz), 4.26 (app t, 2H, J= 6.4 Hz), 3.36 (app t, 2H, J= 7.0 Hz), 1.94 (q, 2H, J= 6.4 Hz). LCMS: ret. time: 11.84 min.; purity: 94%; MS (m/e): 448 (MH^+).
7.4.394	N4-(3-Chloro-4-methoxyphenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-6-yl]-5-fluoro-2,4-pyrimidinediamine (R935406)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 6-amino-1-(2-ethoxycarbonylethyl)indazoline were reacted to give N4-(3-chloro-4-methoxyphenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-6-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.41 (s, 1H), 9.36 (s, 1H), 8.14 (d, 1H, J= 3.5 Hz), 8.01 (s, 1H), 7.87 (s, 1H), 7.83 (t, 1H, J= 2.9 Hz), 7.71-7.66 (m, 1H), 7.54 (d, 1H, J= 8.8 Hz), 7.27 (d, 1H, J= 8.8 Hz), 7.10 (d, 1H, J= 8.8 Hz), 4.28 (t, 2H, J= 6.4 Hz), 3.93 (qt, 2H, J= 7.0 Hz), 3.82 (s, 3H), 2.80 (t, 2H, J= 6.4 Hz), 1.03 (t, 3H, J= 7.0 Hz). LCMS: ret. time: 11.77 min.; purity: 98%; MS (m/e): 486 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.395	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-6-yl]-2,4-pyrimidinediamine (R935407)	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-methoxyphenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-6-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with diisobutyl lithiumaluminum hydride to produce N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-6-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.38 (s, 1H), 9.35 (s, 1H), 8.13 (d, 1H, J= 3.5 Hz), 7.95 (s, 1H), 7.85 (s, 1H), 7.84 (app t, 1H, J= 2.9 Hz), 7.70-7.65 (m, 1H), 7.55 (d, 1H, J= 8.8 Hz), 7.29 (d, 1H, J= 8.8 Hz), 7.10 (d, 1H, J= 8.8 Hz), 4.48 (t, 1H, J= 5.3 Hz), 4.13 (t, 2H, J= 7.0 Hz), 3.82 (s, 3H), 3.26 (t, 2H, J= 7.0 Hz), 1.83 (app q, 2H, J= 7.0 Hz). LCMS: ret. time: 9.34 min.; purity: 97%; MS (m/e): 443 (MH^+).
7.4.396	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-(indazolin-6-yl)-2,4-pyrimidinediamine (R935408)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 6-aminoindazoline were reacted to give N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(indazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 12.64 (s, 1H), 9.27 (s, 2H), 8.08 (d, 1H, J= 3.5 Hz), 7.98 (s, 1H), 7.83 (s, 1H), 7.80 (d, 1H, J= 2.9 Hz), 7.73 (dd, 1H, J= 2.9 and 8.8 Hz), 7.51 (d, 1H, J= 8.8 Hz), 7.25 (d, 1H, J= 8.8 Hz), 7.04 (d, 1H, J= 8.8 Hz), 3.78 (s, 3H). LCMS: ret. time: 9.46 min.; purity: 92%; MS (m/e): 385 (MH^+).
7.4.397	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-{1-[2-(*N*-methylaminocarbonyl)ethyl]indazolin-6-yl}-2,4-pyrimidinediamine (R935409)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-methoxyphenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-6-yl]-5-fluoro-2,4-pyrimidinediamine and hydrogen chloride salt were reacted to provide N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-{1-[2(*N*-methylaminocarbonyl)ethyl]indazolin-6-yl}-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.39 (s, 1H), 9.35 (s, 1H), 8.14 (d, 1H, J= 3.5 Hz), 7.96 (s, 1H), 7.86 (d, 1H, J= 1.2 Hz), 7.83 (d, 1H, J= 2.3 Hz), 7.79 (qt, 1H, J= 4.7 Hz), 7.68 (dd, 1H, J= 2.3 and 8.8 Hz), 7.54 (d, 1H, J= 8.8 Hz), 4.28 (t, 2H, J= 7.0 Hz), 3.82 (s, 3H), 3.30 (d, 3H, J= 4.7 Hz), 2.56 (t, 2H, J= 7.0 Hz). LCMS: ret. time: 8.98 min.; purity: 93%; MS (m/e): 471 (MH^+).
7.4.398	5-Fluoro-N4-(4-fluoro-3-methoxyphenyl)-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine (R935410)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-fluoro-3-methoxyphenyl)-4-pyrimidineamine and 1-methyl-5-aminoindazoline were reacted to give 5-fluoro-N4-(4-fluoro-3-methoxyphenyl)-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.32 (s, 1H), 9.18 (s, 1H), 8.12-8.11 (m, 1H), 8.09 (d, 1H, J= 3.5 Hz), 7.79 (app d, 1H, J= 1.8 Hz), 7.51-7.47 (m, 3H), 7.37-7.32 (m, 1H), 7.13 (dd, 1H, J= 8.8 and 11.1 Hz), 3.98 (s, 3H), 3.68 (s, 3H). LCMS: ret. time: 9.18 min.; purity: 98%; MS (m/e): 383 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.399	N4-(4-Chloro-3-fluorophenyl)-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine (R935411)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chloro-3-fluorophenyl)-5-fluoro-4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give N4-(4-chloro-3-fluorophenyl)-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.60 (s, 1H), 9.31 (s, 1H), 8.16 (d, 1H, J= 3.5 Hz), 8.13-8.11 (m, 1H), 8.08 (s, 1H), 7.86 (s, 1H), 7.60-7.54 (m, 1H), 7.51-7.42 (m, 3H), 3.99 (s, 3H). LCMS: ret. time: 9.87 min.; purity: 100%; MS (m/e): 387 (MH^+).
7.4.400	N4-(3,4-Dimethoxyphenyl)-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine (R935412)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3, 4-dimethoxyphenyl)-5-fluoro 4-pyrimidineamime and 1-methyl-5-aminoindazoline were reacted to give N4-(3,4-dimethoxyphenyl)-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.21 (s, 1H), 10.12 (s, 1H), 8.18 (d, 1H, J= 5.3 Hz), 7.96 (s, 1H), 7.85 (s, 1H), 7.57 (d, 1H, J= 8.8 Hz), 7.36 (d, 1H, J= 8.8 Hz), 7.23-7.17 (m, 2H), 6.89 (d, 1H. J= 8.8 Hz), 4.00 (s, 3H), 3.75 (s, 3H), 3.57 (s, 3H). LCMS: ret. time: 7.80 min.; purity: 99%; MS (m/e): 395 (MH^+).
7.4.401	N2-(3-Chloro-4-methoxy-5-methylphenyl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine (R93413)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazolin-6-yl)-4-pyrimidineamine was reacted with 3-chloro-4-methoxy-5-methylaniline to produce N2-(3-chloro-4-methoxy-5-methylphenyl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 12.88 (s, 1H), 9.48 (s, 1H), 9.25 (s, 1H), 8.13 (d, 1H, J= 3.5 Hz), 7.98 (s, 1H), 7.79 (s, 1H), 7.69 (d, 1H, J= 8.8 Hz), 7.63 (d, 1H, J= 2.3 Hz), 7.45 (dd, 1H, J= 1.9 and 8.8 Hz), 7.42 (d, 1H, J= 2.3 Hz), 3.63 (s, 3H), 2.01 (s, 3H). LCMS: ret. time: 10.87 min.; purity: 95%; MS (m/e): 399 (MH^+).
7.4.402	N4-(4-Chloro-3-fluorophenyl)-5-fluoro-N2-(indazolin-6-yl)-2,4-pyrimidinediamine (R935414)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chloro-3-fluorophenyl)-5-fluoro 4-pyrimidineamine and 6-aminoindazoline were reacted to give N4-(4-chloro-3-fluorophenyl)-5-fluoro-N2-(indazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.71 (s, 1H), 9.55 (s, 1H), 8.20 (t, 1H, J= 2.3 Hz), 8.22 (d, 1H, J= 3.5 Hz), 8.16 (app d, 1H, J= 2.3 Hz), 8.07 (s, 1H), 7.91 (s, 1H), 7.65 (d, 1H, J= 8.8 Hz), 7.59 (d, 1H, J= 8.8 Hz), 7.47 (t, 1H, J= 8.8 Hz), 7.25 (dd, 1H, J= 1.8 and 8.8 Hz). LCMS: ret. time: 9.02 min.; purity: 100%; MS (m/e): 373 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.403	N4-(4-Chloro-3-fluorophenyl)-5-fluoro-N2-(indazolin-5-yl)-2,4-pyrimidinediamine (R935415)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(4-chloro-3-fluorophenyl)-5-fluoro 4-pyrimidineamine and 5-aminoindazoline were reacted to give N4-(4-chloro-3-fluorophenyl)-5-fluoro-N2-(indazolin-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.36 (s, 1H), 10.09 (s, 1H), 8.27 (d, 1H, J= 4.7 Hz), 7.97 (s, 1H), 7.95 (s, 1H), 7.90 (s, 1H), 7.52 (d, 1H, J= 8.8 Hz), 7.50 (d, 1H, J= 8.8 Hz), 7.46 (d, 1H, J= 8.8 Hz), 7.39 (dd, 1H, J= 1.8 and 8.8 Hz). LCMS: ret. time: 9.87 min.; purity: 100%; MS (m/e): 387 (MH^+).
7.4.404	5-Fluoro-N4-(4-fluoro-3-methoxyphenyl)-N2-(indazolin-6-yl)-2,4-pyrimidinediamine (R935416)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-fluoro-3-methoxyphenyl)-4-pyrimidineamine and 6-aminoindazoline were reacted to give 5-fluoro-N4-(4-fluoro-3-methoxyphenyl)-N2-(indazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 12.70 (s, 1H), 9.35 (s, 1H), 9.32 (s, 1H), 8.14 (d, 1H, J= 4.1 Hz), 8.07 (s, 1H), 7.88 (s, 1H), 7.54 (dd, 1H, J= 3.5 and 8.8 Hz), 7.50-7.46 (m, 2H), 7.26 (dd, 1H, J= 1.2 and 8.2 Hz), 7.11 (dd, 1H, J= 8.8 and 11.8 Hz), 3.72 (s, 3H). LCMS: ret. time: 9.34 min.; purity: 93%; MS (m/e): 369 (MH^+).
7.4.405	5-Fluoro-N4-(4-fluoro-3-methoxyphenyl)-N2-(indazolin-5-yl)-2,4-pyrimidinediamine (R935417)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-fluoro-3-methoxyphenyl)-4-pyrimidineamine and 5-aminoindazoline were reacted to give 5-fluoro-N4-(4-fluoro-3-methoxyphenyl)-N2-(indazolin-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 12.84 (s, 1H), 9.33 (s, 1H), 9.16 (s, 1H), 8.09 (d, 1H, J= 3.5 Hz), 7.83 (s, 1H), 7.49 (dd, 1H, J= 2.3 and 8.3 Hz), 7.43 (dd, 1H, J= 2.3 and 8.3 Hz), 7.37 (d, 1H, J= 8.8 Hz), 7.35-7.30 (m, 2H), 7.11 (dd, 1H, J= 8.8 and 11.1 Hz), 3.67 (s, 3H). LCMS: ret. time: 8.09 min.; purity: 97%; MS (m/e): 369 (MH^+).
7.4.406	N2-(3-Chloro-4-methoxy-5-methylphenyl)-5-fluoro-N4-{4H-imidazo[2,1-*c*]-benz[1,4]oxazin-8-yl}-2,4-pyrimidinediamine (R935418)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-{4H-imidazo[2,1-*c*]-benz[1,4]oxazin-8-yl}-4-pyrimidineamine was reacted with 3-chloro-4-methoxy-5-methylaniline to produce N2-(3-chloro-4-methoxy-5-methylphenyl)-5-fluoro-N4-{4H-imidazo[2,1-*c*]-benz[1,4]oxazin-8-yl}-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.48 (s, 1H), 9.27 (s, 1H), 8.11 (d, 1H, J= 3.5 Hz), 7.99 (d, 1H, J= 2.3 Hz), 7.71 (s, 1H), 7.64 (d, 1H, J= 2.3 Hz), 7.35 (dd, 1H, J= 2.3 and 8.8 Hz), 7.31 (d, 1H, J= 2.3 Hz), 7.13 (d, 2H, J= 8.8 Hz), 5.26 (s, 2H), 3.58 (s, 3H), 2.01 (s, 3H). LCMS: ret. time: 10.68 min.; purity: 95%; MS (m/e): 453 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.407	N2-(3-Chloro-4-methoxy-5-methylphenyl)-5-fluoro-N4-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935419)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1-methylindazolin-6-yl)-4-pyrimidineamine was reacted with 3-chloro-4-methoxy-5-methylaniline to give N2-(3-chloro-4-methoxy-5-methylphenyl)-5-fluoro-N4-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.17 (s, 1H), 9.87 (s, 1H), 8.25 (d, 1H, J= 3.7 Hz), 7.99 (s, 1H), 7.96 (s, 1H), 7.71 (d, 1H, J= 8.2 Hz), 7.58 (t, 1H, J= 2.3 Hz), 7.37 –7.33 (m, 1H), 7.26 (s, 1H), 3.89 (s, 3H), 3.64 (s, 3H), 2.02 (s, 3H); LCMS: ret. time: 12.15 min.; purity: 98%; MS (m/e): 413 (MH^+).
7.4.408	N2-(3, 5-Dimethoxyphenyl)-5-fluoro-N4-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935420)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1-methylindazolin-6-yl)-4-pyrimidineamine was reacted with 3,5-dimethoxyaniline to give N2-(3,5-dimethoxyphenyl)-5-fluoro-N4-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.67 (s, 1H), 10.44 (s, 1H), 8.36 (d, 1H, J= 4.9 Hz), 8.01 (s, 2H), 7.72 (d, 1H, J= 8.8 Hz), 7.32 (d, 1H, J= 8.8 Hz), 6.70 (s, 2H), 6.21 (s, 1H), 3.87 (s, 3H), 3.52 (s, 6H). LCMS: ret. time: 10.75 min.; purity: 100%; MS (m/e): 395 (MH^+).
7.4.409	N2-(4-Chloro-2,5-dimethoxyphenyl)-5-fluoro-N4-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935421)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1-methylindazolin-6-yl)-4-pyrimidineamine was reacted with 4-chloro-2,5-dimethoxyaniline to give N2-(4-chloro-2,5-dimethoxyphenyl)-5-fluoro-N4-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.56 (s, 2H), 8.13 (d, 1H, J= 4.5 Hz), 8.05 (s, 1H), 7.92 (s, 1H), 7.81 (d, 1H, J= 5.0 Hz), 7.62 (d, 1H, J= 8.8 Hz), 7.31 (dd, 1H, J= 5.0 and 8.8 Hz), 7.06 (s, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.30 (s, 3H). LCMS: ret. time: 12.81 min.; purity: 100%; MS (m/e): 429 (MH^+).
7.4.410	N2-(3,5-Dimethoxyphenyl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine (R935423)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazolin-6-yl)-4-pyrimidineamine was reacted with 3,5-dimethoxyaniline to produce N2-(3,5-dimethoxyphenyl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.52 (s, 1H), 10.26 (s, 1H), 8.30 (d, 1H, J= 5.3 Hz), 8.03 (s, 1H), 7.57 (s, 1H), 7.69 (d, 1H, J= 8.8 Hz), 7.42-7.37 (m, 1H), 6.68 (d, 2H, J= 2.3 Hz), 6.15 (d, 1H, J= 2.3 Hz), 3.49 (s, 6H). LCMS: ret. time: 9.23 min.; purity: 100%; MS (m/e): 381 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.411	N2-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazine-6-yl)-5-fluoro-N4-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935424)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1-methylindazolin-6-yl)-4-pyrimidineamine was reacted with 6-amine-2,2-dimethyl-3-oxo-4H-benz[1,4]oxazine to give N2-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl]-5-fluoro-N4-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.65 (s, 1H), 8.20 (d, 1H, J= 4.7 Hz), 8.06 (s, 1H), 7.97 (s, 1H), 7.67 (d, 1H, J= 8.5 Hz), 7.43-7.38 (m, 1H), 7.13 (d, 1H, J= 8.8 Hz), 7.00 (s, 1H), 6.78 (d, 1H, J= 8.8 Hz), 3.91 (s, 3H), 1.36 (s, 6H). LCMS: ret. time: 9.20 min.; purity: 100%; MS (m/e): 434 (MH^+).
7.4.412	N4-(3-Chloro-4-fluorophenyl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935425)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-fluorophenyl)-5-fluoro-4-pyrimidineamine and 1-methyl-6-aminoindazoline were reacted to give N4-(3-chloro-4-fluorophenyl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 9.57 (s, 1H), 9.51 (s, 1H), 8.21 (d, 1H, J= 3.5 Hz), 8.06 (d, 1H, J= 4.1 Hz), 7.98 (s, 1H), 7.86 (d, 1H, J= 0.7 Hz), 7.78-7.75 (m, 1H), 7.57 (d, 1H, J= 8.8 Hz), 7.36 (dd, 1H, J= 9.0 and 8.8 Hz), 7.24 (td, 1H, J= 1.4, 9.0 and 8.8 Hz), 3.79 (s, 3H). LCMS: ret. time: 12.34 min.; purity: 97%; MS (*m/e*): 387 (MH^+).
7.4.413	N4-(3-Chloro-4-fluorophenyl)-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine (R935426)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-fluorophenyl)-5-fluoro-4-pyrimidineamine and 1-methyl-5-aminoindazoline were reacted to give N4-(3-chloro-4-fluorophenyl)-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.47 (s, 1H), 9.25 (s, 1H), 8.13 (d, 1H, J= 3.5 Hz), 8.01-7.98 (m, 2H), 7.84 (s,1H), 7.77-7.74 (m, 1H), 7.50 (s, 2H), 7.34 (app t, 1H, J= 9.0 Hz), 3.99 (s, 3H). LCMS: ret. time: 10.80 min.; purity: 98%; MS (m/e): 386 (MH^+).
7.4.414	N4-(3-Chloro-4-fluorophenyl)-5-fluoro-N2-(indazolin-6-yl)-2,4-pyrimidinediamine (R935427)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-fluorophenyl)-5-fluoro-4-pyrimidineamine and 6-aminoindazoline were reacted to give N4-(3-chloro-4-fluorophenyl)-5-fluoro-N2-(indazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 12.72 (s, 1H), 9.52 (s, 1H), 9.43 (s, 1H), 8.19 (d, 1H, J= 3.5 Hz), 8.08-8.04 (m, 2H), 7.89-7.83 (m, 2H), 7.58 (d, 1H, J= 8.8 Hz), 7.35 (t, 1H, J= 9.0 Hz), 7.26 (d, 1H, J= 8.8 Hz). LCMS: ret. time: 10.26 min.; purity: 94%; MS (m/e): 373 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.415	N4-(3-Chloro-4-fluorophenyl)-5-fluoro-N2-(indazolin-5-yl)-2,4-pyrimidinediamine (R935428)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-fluorophenyl)-5-fluoro-4-pyrimidineamine and 5-aminoindazoline were reacted to give N4-(3-chloro-4-fluorophenyl)-5-fluoro-N2-(indazolin-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.14 (s, 1H), 9.92 (s, 1H), 8.24 (d, 1H, J= 4.9 Hz), 7.97-7.89 (m, 3H), 7.69-7.65 (m, 1H), 7.49 (d, 1H, J= 8.8 Hz), 7.40 (d, 1H, J= 10.8 Hz), 7.34 (d, 1H, J= 10.8 Hz). LCMS: ret. time: 9.42 min.; purity: 96%; MS (*m/e*): 373 (MH^+).
7.4.416	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine Benzenesulfonic Acid Salt (R935429)	N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazine-6-yl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine (1.5 g, 3.57 mmol) in MeOH (20 mL) was cooled to 0 °C. To the above contents, benzenesulfonic acid (0.594 g, 3.75 mmol, 98%) dissolved in CH_3CN (20 ml) was added dropwise for 5 min. The clear solution formed was stirred (15 min) at the same temperature and allowed to warm to room temperature (60 min). The clear solution turned into precipitated form. The reaction mixture was concentrated, dissolved in MeOH (4 mL) and triturated with EtOAC:n-hexanes. The solid obtained was filtered and dried under high vacuum to provide N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine Benzenesulfonic Acid Salt. ^{1}H NMR (DMSO-d6): δ 10.70 (s, 1H), 10.34 (s, 1H), 9.99 (s, 1H), 8.21 (d, 1H, J= 5.3 Hz), 8.00 (d, 1H, J= 1.8 Hz), 7.67 (d, 2H, J= 8.5 Hz), 7.60-7.57 (m, 2H), 7.34-7.28 (m, 4H), 7.19 (dd, 1H, J= 8.8 and 1.8 Hz), 7.10 (d, 1H, J= 2.3 Hz), 6.87 (d, 1H, J= 8.0 Hz), 1.36 (s, 6H). LCMS: ret. time: 8.39 min.; purity: 100%; MS (m/e): 420 (MH^+).
7.4.417	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine *p*-Toluenesulfonic Acid Salt (R935430)	In like manner to the preparation of N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine benzenesulfonic acid salt, N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine was reacted with *p*-toluenesulfonic acid monohydrate to give N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine *p*-toluenesulfonic acid Salt. ^{1}H NMR (DMSO-d6): δ 10.70 (s, 1H), 10.22 (s, 1H), 9.88 (s, 1H), 8.19 (d, 1H, J= 5.3 Hz), 7.99 (d, 1H, J= 0.9 Hz), 7.72 (s, 1H), 7.64 (d, 1H, J= 8.5 Hz), 7.46 (d, 2H, J= 8.0 Hz), 7.34 (dd, 1H, J= 2.3 and 8.5 Hz), 7.19 (dd, 1H, J= 2.3 and 8.5 Hz), 7.12 (s, 1H), 7.10 (d, 2H, J= 8.0 Hz), 6.87 (d, 1H, J= 8.5 Hz), 2.27 (s, 3H), 1.36 (s, 6H). LCMS: ret. time: 8.39 min.; purity: 100%; MS (m/e): 420 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.418	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935431)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 5-amino-1-(2-ethoxycarbonylethyl)indazoline were reacted to give N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazine-6-yl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.79 (s, 1H), 10.48 (s, 1H), 10.36 (s, 1H), 8.25 (d, 1H, J= 4.9 Hz), 7.91 (s, 1H), 7.87 (s, 1H), 7.63 (d, 1H, J= 8.8 Hz), 7.38 (dd, 1H, J= 1.7 and 8.8 Hz), 7.21 (d, 1H, J= 8.8 Hz), 7.19 (s, 1H), 6.89 (d, 1H, J= 8.8 Hz), 4.58 (t, 2H, J= 6.4 Hz), 3.97 (qt, 2H, J= 7.0 Hz), 2.89 (t, 2H, J= 6.4 Hz), 1.36 (s, 6H), 1.06 (t, 3H, J= 7.0 Hz). LCMS: ret. time: 9.52 min.; purity: 100%; MS (m/e): 520 (MH^+).
7.4.419	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-5-yl]-2,4-pyrimidinediamine (R935432)	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with diisobutyl lithiumaluminum hydride. Usual workup followed by silica gel column chromatographic purification with 2% MeOH:EtOAc provided N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-5-yl]-2,4-pyrimidinediamine as a white solid. LCMS: ret. time: 7.75 min.; purity: 95%; MS (*m/e*): 478 (MH^+).
7.4.420	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-{1-[2(*N*-methylaminocarbonyl)ethyl]indazolin-5-yl}-2,4-pyrimidinediamine (R935433)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride salt were reacted to provide N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-{1-[2(*N*-methylaminocarbonyl)ethyl]indazolin-5-yl}-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.64 (s, 1H), 9.32 (s, 1H), 9.09 (s, 1H), 8.09 (s, 1H), 8.06 (d, 1H, J= 3.8 Hz), 7.82 (qt, 1H, J= 4.4 Hz), 7.78 (s, 1H), 7.45 (app d, 2H, J= 8.4 Hz), 7.32-7.27 (m, 1H), 7.21 (s, 1H), 6.89 (d, 1H, J= 8.8 Hz), 4.50 (t, 2H, J= 7.0 Hz), 2.62 (t, 2H, J= 7.0 Hz), 2.50 (d, 3H, J= 4.4 Hz), 1.40 (s, 6H). LCMS: ret. time: 7.45 min.; purity: 97%; MS (m/e): 505 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.421	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-6-yl]-5-fluoro-2,4-pyrimidinediamine (R935434)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 6-amino-1-(2-ethoxycarbonylethyl)indazoline were reacted to give N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-6-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.73 (s, 1H), 10.11 (br s, 1H), 8.24 (d, 1H, J= 4.7 Hz), 7.94 (s, 1H), 7.85 (s, 1H), 7.61 (d, 1H, J= 8.5 Hz), 7.29-7.24 (m, 3H), 6.86 (d, 1H, J= 8.8 Hz), 4.35 (t, 2H, J= 6.4 Hz), 3.94 (qt, 2H, J= 7.0 Hz), 2.83 (t, 2H, J= 6.4 Hz), 1.38 (s, 6H), 1.03 (s, 3H). LCMS: ret. time: 10.64 min.; purity: 96%; MS (m/e): 520 (MH^+).
7.4.422	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-{1-[2-(*N*-methylaminocarbonyl)ethyl]indazolin-6-yl}-2,4-pyrimidinediamine (R935435)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-6-yl]-5-fluoro-2,4-pyrimidinediamine and $Me_2NH.HCl$ were reacted to provide N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-{1-[2(*N*-methylaminocarbonyl)ethyl]indazolin-6-yl}-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.61 (s, 1H), 9.41 (s, 1H), 9.29 (s, 1H), 8.13 (d, 1H, J= 3.8 Hz), 7.86 (s, 1H), 7.81 (qt, 1H, J= 4.7 Hz), 7.52 (d, 1H, J= 8.8 Hz), 7.40-7.30 (m, 2H), 7.27-7.25 (app m, 1H), 6.86 (d, 1H, J= 8.5 Hz), 4.33 (t, 2H, J= 6.8 Hz), 2.49 (d, 3H, J= 3.8 Hz), 1.39 (s, 6H). LCMS: ret. time: 8.32 min.; purity: 92%; MS (m/e): 505 (MH^+).
7.4.423	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[1-(methoxycarbonyl)methyl-indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935436)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 5-amino-1-(methoxycarbonyl)methyl-indazoline were reacted to give N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[1-(methoxycarbonyl)methyl-indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.79 (s, 1H), 10.40 (s, 1H), 10.27 (s, 1H), 8.23 (d, 1H, J= 5.0 Hz), 7.95 (s, 1H), 7.92 (s, 1H), 7.59 (d, 1H, J= 8.8 Hz), 7.38 (dd, 1H, J= 1.7 and 8.8 Hz), 7.23 (dd, 1H, J= 1.7 and 8.8 Hz), 7.19 (s, 1H), 6.89 (d, 1H, J= 8.8 Hz), 5.36 (s, 2H), 3.66 (s, 3H), 1.36 (s, 6H). LCMS: ret. time: 8.58 min.; purity: 95%; MS (m/e): 492 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.424	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-[1-(*N*-methylaminocarbonyl)methylindazolin-5-yl}-2,4-pyrimidinediamine (R935437)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[1-(methoxycarbonyl)methyl-indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride were reacted to provide N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-[1-(*N*-methylaminocarbonyl)methylindazolin-5-yl}-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.64 (s, 1H), 9.29 (s, 1H), 9.07 (s, 1H), 8.12 (s, 1H), 8.06 (d, 1H, J= 3.8 Hz), 7.98 (qt, 1H, J= 4.7 Hz), 7.80 (s, 1H), 7.46 (dd, 1H, J= 2.3 and 8.8 Hz), 7.41 (d, 1H, J= 8.8 Hz), 7.31 (dd, 1H, J= 2.3 and 8.8 Hz), 7.22 (app s, 1H), 6.89 (d, 1H, J= 8.8 Hz), 4.96 (s, 2H), 2.59 (d, 3H, J= 4.7 Hz), 1.40 (s, 6H). LCMS: ret. time: 7.44 min.; purity: 100%; MS (m/e): 491 (MH^+).
7.4.425	N2-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N4-(indazolin-5-yl)-2,4-pyrimidinediamine (R935438)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazolin-5-yl)-4-pyrimidineamine was reacted with 6-amine-2,2-dimethyl-4H-benz(1,4)oxazine-3-one to produce N2-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N4-(indazolin-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 12.97 (s, 1H), 10.55 (s, 1H), 9.30 (s, 1H), 9.04 (s, 1H), 8.19 (s, 1H), 8.02 (d, 1H, J= 3.8 Hz), 7.94 (s, 1H), 7.59 (dd, 1H, J= 2.0 and 8.8 Hz), 7.45 (d, 1H, J= 9.1 Hz), 7.17 (d, 1H, J= 2.0 Hz), 7.14 (s, 1H), 6.72 (d, 1H, J= 9.1 Hz), 1.35 (s, 6H). LCMS: ret. time: 7.46 min.; purity: 93%; MS (m/e): 420 (MH^+).
7.4.426	N2-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N4-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine (R935439)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(1-methylindazolin-6-yl)-4-pyrimidineamine was reacted with 6-amine-2,2-dimethyl-4H-benz(1,4)oxazine-3-one to give N2-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N4-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.67 (s, 1H), 10.41 (s, 1H), 10.09 (s, 1H), 8.22 (d, 1H, J= 4.9 Hz), 8.05 (s, 1H), 7.93 (s, 1H), 7.51 (d, 2H, J= 8.8 Hz), 7.05 (dd, 1H, J= 2.3 and 8.5 Hz), 6.95 (s, 1H), 6.81 (d, 1H, J= 8.5 Hz), 4.01 (s, 3H), 1.34 (s, 6H). LCMS: ret. time: 8.45 min.; purity: 100%; MS (m/e): 434 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.427	N2-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine (R935440)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(indazolin-6-yl)-4-pyrimidineamine was reacted with 6-amine-2,2-dimethyl-4H-benz(1,4)oxazine-3-one to produce N2-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.57 (s, 1H), 9.80 (s, 1H), 9.44 (s, 1H), 8.12 (d, 1H, J= 4.4 Hz), 7.99 (s, 1H), 7.82 (s, 1H), 7.66 (d, 1H, J= 8.5 Hz), 7.50-7.47 (dd, 1H, J= 2.5 and 8.5 Hz), 7.20 (dd, 1H, J= 2.5 and 8.5 Hz), 7.06 (s, 1H), 6.76 (d, 1H, J= 8.5 Hz), 1.34 (s, 6H). LCMS: ret. time: 8.26 min.; purity: 95%; MS (m/e): 420 (MH^+).
7.4.428	N4-(3,4-Dimethoxyphenyl)-5-fluoro-N2-(indazolin-5-yl)-2,4-pyrimidinediamine (R935441)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3,4-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine was reacted with 5-aminoindazoline to produce N4-(3,4-dimethoxyphenyl)-5-fluoro-N2-(indazolin-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 12.82 (s, 1H), 9.17 (s, 1H), 9.11 (s, 1H), 8.16 (s, 1H), 8.04 (d, 1H, J= 3.8 Hz), 7.79 (s, 1H), 7.43 (d, 1H, J= 8.8 Hz), 7.35 (d, 1H, J= 8.8 Hz), 7.28-7.23 (m, 2H), 6.90 (d, 1H, J= 8.5 Hz), 3.76 (s, 3H), 3.62 (s, 3H). LCMS: ret. time: 7.06 min.; purity: 100%; MS (m/e): 381 (MH^+).
7.4.429	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-[1-(2-methoxy-4-methoxycarbonylbenzyl)indazolin-6-yl]- 2,4-pyrimidinediamine (R935442)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine was reacted with 6-amino-1-(2-methoxy-4-methoxycarbonylbenzyl)indazoline to provide N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-[1-(2-methoxy-4-methoxycarbonylbenzyl)indazolin-6-yl]- 2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.72 (s, 1H), 10.19 (br s, 2H), 8.24 (d, 1H, J= 4.7 Hz), 8.00 (d, 1H, J= 0.9 Hz), 7.85 (s, 1H), 7.64 (d, 1H, J= 8.5 Hz), 7.44 (d, 1H, J= 1.8 Hz), 7.40 (dd, 1H, J= 1.7 and 8.0 Hz), 7.26 (dd, 2H, J= 1.7 and 8.8 Hz), 7.21 (d, 1H, J= 1.8 Hz), 6.81 (d, 1H, J= 8.5 Hz), 6.76 (d, 1H, J= 8.0 Hz), 5.39 (s, 2H), 3.8 (s, 3H), 3.80 (s, 3H), 1.34 (s, 6H). LCMS: ret. time: 12.04 min.; purity: 100%; MS (m/e): 598 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.430	N4-(3,4-Dichlorophenyl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine *p*-Toluenesulfonic Acid Salt (R935443)	In like manner to the preparation of N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine benzenesulfonic acid salt, N4-(3,4-dichlorophenyl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine was reacted with *p*-toluenesulfonic acid to give N4-(3,4-dichlorophenyl)-5-fluoro-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine *p*-toluenesulfonic acid salt ^{1}H NMR (DMSO-d6): δ 10.12 (s, 1H), 9.92 (s, 1H), 8.29 (d, 1H, J= 4.1 Hz), 8.09 (s, 1H), 7.93 (s, 1H), 7.88 (s, 1H), 7.74 (d, 1H, J= 8.5 Hz), 7.66 (d, 1H, J= 8.5 Hz), 7.55 (d, 1H, J= 8.8 Hz), 7.46 (d, 2H, J= 7.9 Hz), 7.20 (d, 1H, J= 8.5 Hz), 3.82 (s, 3H), 2.27 (s, 3H). LCMS: ret. time: 8.39 min.; purity: 100%; MS (*m/e*): 420 (MH^+). LCMS: ret. time. 13.48 min.; purity: 97%; MS (m/e): 404 (MH^+)
7.4.431	N4-(3,4-Dichlorophenyl)-5-fluoro-N2-(2-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935444)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine and 2-methyl-6-aminoindazole were reacted to give N4-(3,4-dichlorophenyl)-5-fluoro-N2-(2-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.59 (s, 1H), 9.33 (s, 1H), 8.20 (d, 1H, J= 3.8 Hz), 8.16 (s, 1H), 8.10 (t, 1H, J= 2.3 Hz), 7.97 (s, 1H), 7.94 (dt, 1H, J= 2.3 and 8.8 Hz), 7.53 (d, 1H, J= 8.5 Hz), 7.51 (d, 1H, J= 8.8 Hz), 7.19 (dd, 1H, J= 1.2 and 8.8 Hz), 4.08 (s, 3H). LCMS: ret. time: 12.08 min.; purity: 100%; MS (m/e): 404 (MH^+).
7.4.432	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(2-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935445)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 2-methyl-6-aminoindazole were reacted to give N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-(2-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.77 (s, 1H), 10.69 (s, 1H), 10.65 (s, 1H), 8.35 (d, 1H, J= 5.3 Hz), 8.31 (s, 1H), 7.86 (s, 1H), 7.64 (d, 1H, J= 8.8 Hz), 7.40 (s, 1H), 7.19-7.15 (m, 1H), 7.05 (dd, 1H, J= 1.5 and 8.8 Hz), 6.90 (d, 1H, J= 8.5 Hz), 4.12 (s, 3H), 1.40 (s, 6H). LCMS: ret. time: 8.93 min.; purity: 100%; MS (m/e): 434 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.433	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-(2-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935446)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 2-methyl-6-aminoindazole were reacted to give N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(2-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.34 (s, 1H), 9.22 (s, 1H), 8.14 (s, 1H), 8.11 (d, 1H, J= 3.8 Hz), 8.03 (s, 1H), 7.84-7.79 (m, 1H), 7.73 (t, 1H, J= 2.5 Hz), 7.50 (d, 1H, J= 9.1 Hz), 7.17 (d, 1H, J= 8.9 Hz), 7.15 (d, 1H, J= 9.0 Hz), 4.06 (s, 3H), 3.88 (s, 3H), 3.88 (s, 3H). LCMS: ret. time: 9.29 min.; purity: 97%; MS (m/e): 399 (MH^+).
7.4.434	N4-(3,4-Dichlorophenyl)-N2-[2-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935447)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine and 5-amino-2-(2-ethoxycarbonylethyl)indazoline were reacted to give N4-(3,4-dichlorophenyl)-N2-[2-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.18 (s, 1H), 9.82 (s, 1H), 8.25 (d, 1H, J= 4.7 Hz), 8.23 (s, 1H), 8.07 (s, 1H), 7.84 (s, 1H), 7.72 (d, 1H, J= 8.8 Hz), 7.57 (d, 1H, J= 9.4 Hz), 7.52 (d, 1H, J= 8.8 Hz), 7.29 (d, 1H, J= 9.4 Hz), 4.63 (t, 2H, J= 6.4 Hz), 4.03 (qt, 2H, J= 7.0 Hz), 3.00 (t, 2H, J= 6.4 Hz), 1.12 (t, 3H, J= 7.0 Hz). LCMS: ret. time: 12.53 min.; purity: 95%; MS (m/e): 490 (MH^+).
7.4.435	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[2-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935448)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-4-pyrimidineamine and 5-amino-2-(2-ethoxycarbonylethyl)indazoline were reacted to give N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[2-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.80 (s, 1H), 10.46 (s, 1H), 10.25 (s, 1H), 8.24 (d, 1H, J= 5.0 Hz), 8.19 (s, 1H), 7.79 (s, 1H), 7.54 (d, 1H, J= 9.1 Hz), 7.23 (d, 2H, J= 9.1 Hz), 7.19 (s, 1H), 6.88 (d, 1H, J= 9.1 Hz), 4.61 (t, 2H, J= 6.4 Hz), 4.03 (qt, 2H, J= 7.0 Hz), 3.00 (t, 2H, J= 6.4 Hz), 1.36 (s, 6H), 1.11 (t, 3H, = 7.0 Hz). LCMS: ret. time: 8.96 min.; purity: 95%; MS (m/e): 520 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.436	5-Fluoro-N4-(4-fluoro-3-methoxyphenyl)-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935449)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-fluoro-3-methoxyphenyl)-4-pyrimidineamine and 1-methyl-6-aminoindazoline were reacted to give 5-fluoro-N4-(4-fluoro-3-methoxyphenyl)-N2-(1-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d_6): δ 10.61 (s, 1H), 10.52 (s, 1H), 8.37 (d, 1H, J= 5.2 Hz), 7.96 (s, 1H), 7.79 (s, 1H), 7.66 (d, 1H, J= 8.5 Hz), 7.46 (dd, 1H, J= 2.3 and 8.0 Hz), 7.27-7.12 (m, 3H), 3.75 (s, 3H), 3.55 (s, 3H). LCMS: ret. time: 10.86 min.; purity: 97%; MS (*m/e*): 383 (MH^+).
7.4.437	5-Fluoro-N4-(4-fluoro-3-methoxyphenyl)-N2-(2-methylindazolin-6-yl)-2,4-pyrimidinediamine (R935450)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N-(4-fluoro-3-methoxyphenyl)-4-pyrimidineamine and 2-methyl-6-aminoindazoline were reacted to give 5-fluoro-N4-(4-fluoro-3-methoxyphenyl)-5-fluoro-N2-(2-methylindazolin-6-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.18 (s, 1H), 10.08 (s, 1H), 8.28 (s, 1H), 8.26 (d, 1H, J= 4.8 Hz), 7.84 (s, 1H), 7.61 (d, 1H, J= 9.1 Hz), 7.48 (dd, 1H, J= 2.3 and 8.0 Hz), 7.38-7.34 (m, 1H), 7.18-7.10 (m, 2H), 4.11 (s, 3H), 3.65 (s, 3H). LCMS: ret. time: 9.23 min.; purity: 97%; MS (m/e): 383 (MH^+).
7.4.438	N4-(3,4-Dichlorophenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-5-yl]-2,4-pyrimidinediamine Bis(*p*-Toluenesulfonic Acid Salt (R935451)	In like manner to the preparation of N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N4-(indazolin-6-yl)-2,4-pyrimidinediamine benzenesulfonic acid salt, N4-(3,4-dichlorophenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-5-yl]-2,4-pyrimidinediamine was reacted with 2 eq. of *p*-toluenesulfonic acid monohydrate. The clear reaction mixture was concentrated, triturated with ether and stirred overnight under N_2. The white precipitate formed was collected by filtration to give N4-(3,4-dichlorophenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-5-yl]-2,4-pyrimidinediamine bis*p*-toluenesulfonic acid salt. ^{1}H NMR (DMSO-d6): δ 10.67 (s, 1H), 10.24 (s, 1H), 8.31 9d, 1H, J= 5.0 Hz), 8.00 (s, 1H), 7.98 (s, 1H), 7.79 (s, 1H), 7.69 (d, 1H, J= 9.1 Hz), 7.63 (s, 1H), 7.53 (d, 1H, J= 8.8 Hz), 7.46 (d, 4H, J= 8.2 Hz), 7.38 (dd, 1H, J= 1.4 and 8.8 Hz), 7.10 (d, 4H, J= 8.2 Hz), 4.45 (t, 2H, J= 6,7 Hz), 3.39 (t, 2H, J= 6.7 Hz), 2.27 (s, 6H), 1.96 (q, 2H, J= 6.7 Hz). LCMS: ret. time: 13.52 min.; purity: 100%; MS (m/e): 404 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.439	N4-(3,4-Dichlorophenyl)-5-fluoro-N2-{2-[2-(*N*-methylaminocarbonyl)ethyl]indazolin-5-yl}-2,4-pyrimidinediamine (R935452)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3,4-dichlororophenyl)-N2-[2-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride salt were reacted to provide N4-(3,4-dichlorophenyl)-5-fluoro-N2-{2-[2-(*N*-methylaminocarbonyl)ethyl]indazolin-5-yl}-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.50 (s, 1H), 9.18 (s, 1H), 8.11 (d, 1H, J= 3.5 Hz), 8.07 (t, 1H, J= 2.6 Hz), 8.02 (s, 1H), 7.89 (s, 1H), 7.83 (qt, 1H, J= 4.4 Hz), 7.80-7.77 (m, 2H), 7.45 (d, 1H, J= 8.8 Hz), 7.43 (d, 1H, J= 8.8 Hz), 7.29 (dd, 1H, J= 2.3 and 8.8 hz), 4.51 (t, 2H, J= 6.7 Hz), 2.69 (t, 2H, J= 6.7 Hz), 2.47 (d, 3H, J= 4.4 Hz). LCMS: ret. time: 9.50 min.; purity: 93%; MS (m/e): 475 (MH^+).
7.4.440	N4-(2,2-Dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-{2-[2(*N*-methylaminocarbonyl)ethyl]indazolin-5-yl}-2,4-pyrimidinediamine (R935453)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-N2-[2-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride salt were reacted to provide N4-(2,2-dimethyl-3-oxo-4H-benz[1,4]oxazin-6-yl)-5-fluoro-N2-{2-[2(*N*-methylaminocarbonyl)ethyl]indazolin-5-yl}-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.63 (s, 1H), 9.31 (s, 1H), 9.01 (s, 1H), 8.06 (d, 1H, J= 3.5 Hz), 8.02 (s, 1H), 7.96 (s, 1H), 7.87 (t, 1H, J= 4.4 Hz), 7.43 (d, 1H, J= 8.8 Hz), 7.33-7.25 (m, 3H), 6.88 (d, 1H, J= 8.5 Hz), 4.53 (t, 2H, J= 6.7 Hz), 2.73 (t, 2H, J= 6.7 Hz), 2.53 (d, 3H, J= 4.4 Hz), 1.41 (s, 6H). LCMS: ret. time: 7.19 min.; purity: 100%; MS (m/e): 505 (MH^+).
7.4.441	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine (R935458)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 1-methyl-5-aminoindazole were reacted to give N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(1-methylindazolin-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.29 (s, 1H), 10.18 (s, 1H), 8.24 (d, 1H, J= 5.0 Hz), 7.89 (s, 1H), 7.86 (s, 1H), 7.74 (d, 1H, J= 2.3 Hz), 7.60 (d, 1H, J= 9.1 Hz), 7.54 (dd, 1H, J= 2.3 and 8.8 Hz), 7.39 (dd, 1H, J= 2.0 and 9.1 Hz), 7.09 (d, 1H, J= 9.1 Hz), 4.00 (s, 3H), 3.83 (s, 3H). LCMS: ret. time: 9.92 min.; purity: 98%; MS (m/e): 401 (MH^+).

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Section Number	Name of compound and reference number	Experimental
7.4.442	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-(indazolin-5-yl)-2,4-pyrimidinediamine (R935459)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 5-aminoindazoline were reacted to give N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-(indazolin-5-yl)-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.59 (s, 1H), 9.40 (s, 1H), 8.10 (d, 1H, J= 4.1 Hz), 7.97 (s, 1H), 7.87 (s, 1H), 7.79 (d, 1H, J= 2.3 Hz), 7.60 (dd, 1H, J= 2.3 and 8.8 Hz), 7.42 (s, 2H), 7.08 (d, 1H, J= 8.8 Hz), 3.84 (s, 3H). LCMS: ret. time: 8.84 min.; purity: 94%; MS (m/e): 388 (MH^+).
7.4.443	N4-(3-Chloro-4-methoxyphenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine (R935460)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-chloro-N-(3-chloro-4-methoxyphenyl)-5-fluoro-4-pyrimidineamine and 5-amino-1-(2-ethoxycarbonylethyl)indazoline were reacted to give N4-(3-chloro-4-methoxyphenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 10.41 (s, 1H), 10.30 (s, 1H), 8.27 (d, 1H, J= 5.3 Hz), 7.93 (s, 1H), 7.83 (s, 1H), 7.73 (d, 1H, J= 2.3 Hz), 7.67 (d, 1H, J= 8.8 Hz), 7.55 (dd, 1H, J= 2.3 and 8.8 Hz), 7.39 (dd, 1H, J= 2.3 and 8.8 Hz), 7.10 (d, 1H, J= 8.8 Hz), 4.59 (t, 2H, J= 6.4 Hz), 3.97 (qt, 2H, J= 7.0 Hz), 3.83 (s, 3H), 2.90 (t, 2H, J= 6.4 Hz), 1.06 (t, 3H, J= 7.0 Hz). LCMS: ret. time: 11.20 min.; purity: 96%; MS (m/e): 488 (MH^+).
7.4.444	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-5-yl]-2,4-pyrimidinediamine (R935461)	In like manner to the preparation of N2-(3,4-ethylenedioxyphenyl)-5-fluoro-N4-[4(2-hydroxy-1,1-dimethylethyl)phenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-methoxyphenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine was reacted with diisobutyl lithiumaluminum hydride to produce N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-[1-(3-hydroxypropyl)indazolin-5-yl]-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.29 (s, 1H), 9.18 (s, 1H), 8.07 (d, 1H, J= 3.8 Hz), 8.02 (s, 1H), 7.81 (s, 1H), 7.80 (d, 1H, J= 2.3 Hz), 7.65 (dd, 1H, J= 2.3 and 8.8 Hz), 7.48 (app d, 2H, J= 8.8 Hz), 7.10 (d, 1H, J= 8.8 Hz), 4.58 (t, 1H, J= 4.7 Hz), 4.37 (t, 2H, J= 6.7 Hz), 3.84 (s, 3H), 3.34 (t, 1H, J= 6.7 Hz), 1.92 (q, 2H, J= 6.7 Hz). LCMS: ret. time: 9.00 min.; purity: 98%; MS (m/e): 445 (MH^+).

Section Number	Name of compound and reference number	Experimental
7.4.445	N4-(3-Chloro-4-methoxyphenyl)-5-fluoro-N2-{1-[2-(*N*-methylaminocarbonyl)ethyl]indazolin-5-yl}-2,4-pyrimidinediamine (R935462)	In like manner to the preparation of N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-[3-(*N*-methylamino)carbonylmethyleneoxyphenyl]-2,4-pyrimidinediamine, N4-(3-chloro-4-methoxyphenyl)-N2-[1-(2-ethoxycarbonylethyl)indazolin-5-yl]-5-fluoro-2,4-pyrimidinediamine and methylamine hydrochloride salt were reacted to provide N4-(3-chloro-4-methoxyphenyl)-5-fluoro-N2-{1-[2-(*N*-methylaminocarbonyl)ethyl]indazolin-5-yl}-2,4-pyrimidinediamine. ^{1}H NMR (DMSO-d6): δ 9.31 (s, 1H), 9.20 (s, 1H), 8.08 (d, 1H, J= 4.8 Hz), 8.02 (s, 1H), 7.84 (qt, 1H, J= 4.7 Hz), 7.81 (s, 1H), 7.78 (d, 1H, J= 2.6 Hz), 7.66 (dd, 1H, J= 2.6 and 9.1 Hz), 7.49 (d, 1H, J= 9.1 Hz), 7.46 (d, 1H, J= 9.1 Hz), 7.11 (d, 1H, J= 9.1 Hz), 4.51 (t, 2H, J= 6.7 Hz), 3.85 (s, 3H), 2.63 (t, 2H, J= 6.7 Hz), 2.50 (d, 3H, J= 4.7 Hz). LCMS: ret. time: 8.60 min.; purity: 93%; MS (m/e): 472 (MH^+).

7.5 The 2,4-Pyrimidinediamine Compounds of the Invention Inhibit FcεRI Receptor-Mediated Degranulation

The ability of the 2,4-pyrimidinediamine compounds of the invention to inhibit IgE-induced degranulation was demonstrated in a variety of cellular assays with cultured human mast cells (CHMC) and/or mouse bone marrow derived cells (BMMC). Inhibition of degranulation was measured at both low and high cell density by quantifying the release of the granule specific factors tryptase, histamine and hexosaminidase. Inhibition of release and/or synthesis of lipid mediators was assessed by measuring the release of leukotriene LTC4 and inhibition of release and/or synthesis of cytokines was monitored by quantifying TNF-α, IL-6 and IL-13. Tryptase and hexosaminidase were quantified using fluorogenic substrates as described in their respective examples. Histamine, TNFα, IL-6, IL-13 and LTC4 were quantified using the following commercial ELISA kits: histamine (Immunotech #2015, Beckman Coulter), TNFα (Biosource #KHC3011), IL-6 (Biosource #KMC0061), IL-13 (Biosource #KHC0132) and LTC4 (Cayman Chemical #520211). The protocols of the various assays are provided below.

7.5.1 Culturing of Human Mast and Basophil Cells

Human mast and basophil cells were cultured from CD34-negative progenitor cells as described below (see also the methods described in copending U.S. application Serial No. 10/053,355, filed November 8, 2001, the disclosure of which is incorporated herein by reference).

7.5.1.1 Preparation of STEMPRO-34 Complete Medium

To prepare STEMPRO-34 complete medium ("CM"), 250 mL STEMPRO-34™ serum free medium ("SFM"; GibcoBRL, Catalog No. 10640) was added to a filter flask. To this was added 13 mL STEMPRO-34 Nutrient Supplement ("NS"; GibcoBRL, Catalog No. 10641) (prepared as described in more detail, below). The NS container was rinsed with approximately 10 mL SFM and the rinse added to the filter flask. Following addition of 5 mL L-glutamine (200 mM; Mediatech, Catalog No. MT 25-005-CI and 5 mL 100X penicillin/streptomycin ("pen-strep"; HyClone, Catalog No. SV30010), the volume was brought to 500 mL with SFM and the solution was filtered.

The most variable aspect of preparing the CM is the method by which the NS is thawed and mixed prior to addition to the SFM. The NS should be thawed in a 37° C water bath and swirled, not vortexed or shaken, until it is completely in solution. While swirling, take note whether there are any lipids that are not yet in solution. If lipids are present and the NS is not uniform in appearance, return it to the water bath and repeat the swirling process until it is uniform in appearance. Sometimes this component goes into solution immediately, sometimes after a couple of swirling cycles, and sometimes not at all. If, after a couple of hours, the NS is still not in solution, discard it and thaw a fresh unit. NS that appears non-uniform after thaw should not be used.

7.5.1.2 Expansion of CD34+ Cells

A starting population of CD34-positive (CD34+) cells of relatively small number (1-5 x 10^6 cells) was expanded to a relatively large number of CD34-negative progenitor cells (about 2-4 x 10^9 cells) using the culture media and methods described below. The CD34+ cells (from a single donor) were obtained from Allcells (Berkeley, CA). Because there is a degree of variation in the quality and number of CD34+ cells that Allcells typically provides, the newly delivered cells were transferred to a 15 mL conical tube and brought up to 10 mL in CM prior to use.

On day 0, a cell count was performed on the viable (phase-bright) cells and the cells were spun at 1200 rpm to pellet. The cells were resuspended to a density of 275,000 cells/mL with CM containing 200 ng/mL recombinant human Stem Cell Factor ("SCF"; Peprotech, Catalog No. 300-07) and 20 ng/mL human flt-3 ligand (Peprotech, Catalog No. 300-19) ("CM/SCF/flt-3 medium"). On about day 4 or 5, the density of the culture was checked by performing a cell count and the culture was diluted to a density of 275,000 cells/mL with fresh CM/SCF/flt-3 medium. On about day 7, the culture was transferred to a sterile tube and a cell count was performed. The cells were spun at 1200 rpm and resuspended to a density of 275,000 cells/mL with fresh CM/SCF/flt-3 medium.

This cycle was repeated, starting from day 0, a total of 3-5 times over the expansion period.

When the culture is large and being maintained in multiple flasks and is to be resuspended, the contents of all of the flasks are combined into a single container prior to performing a cell count. This ensures that an accurate cell count is achieved and provides for a degree of uniformity of treatment for the entire population. Each flask is checked

separately for contamination under the microscope prior to combining to prevent contamination of the entire population.

Between days 17-24, the culture can begin to go into decline (*i.e.*, approximately 5-10% of the total number of cells die) and fail to expand as rapidly as before. The cells are then monitored on a daily basis during this time, as complete failure of the culture can take place in as little as 24 hours. Once the decline has begun, the cells are counted, spun down at 850 rpm for 15 minutes, and resuspended at a density of 350,000 cells/mL in CM/SCF/flt-3 medium to induce one or two more divisions out of the culture. The cells are monitored daily to avoid failure of the culture.

When greater than 15% cell death is evident in the progenitor cell culture and some debris is present in the culture, the CD34-negative progenitor cells are ready to be differentiated.

7.5.1.3 Differentiation of CD34-Negative Progenitor Cells into Mucosal Mast Cells

A second phase is performed to convert the expanded CD34-negative progenitor cells into differentiated mucosal mast cells. These mucosal cultured human mast cells ("CHMC") are derived from CD34+ cells isolated from umbilical cord blood and treated to form a proliferated population of CD34-negative progenitor cells, as described above. To produce the CD43-negative progenitor cells, the resuspension cycle for the culture was the same as that described above, except that the culture was seeded at a density of 425,000 cells/mL and 15% additional media was added on about day four or five without performing a cell count. Also, the cytokine composition of the medium was modified such that it contained SCF (200 ng/mL) and recombinant human IL-6 (200 ng/mL; Peprotech, Catalog No. 200-06 reconstituted to 100 ug/mL in sterile 10 mM acetic acid) ("CM/SCF/IL-6 medium").

Phases I and II together span approximately 5 weeks. Some death and debris in the culture is evident during weeks 1-3 and there is a period during weeks 2-5 during which a small percentage of the culture is no longer in suspension, but is instead attached to the surface of the culture vessel.

As during Phase I, when the culture is to be resuspended on day seven of each cycle, the contents of all flasks are combined into a single container prior to performing a cell count to ensure uniformity of the entire population. Each flask is checked separately for

contamination under the microscope prior to combining to prevent contamination of the entire population.

When the flasks are combined, approximately 75% of the volume is transferred to the communal container, leaving behind about 10 mL or so in the flask. The flask containing the remaining volume was rapped sharply and laterally to dislodge the attached cells. The rapping was repeated at a right angle to the first rap to completely dislodge the cells.

The flask was leaned at a 45 degree angle for a couple of minutes before the remaining volume was transferred to the counting vessel. The cells were spun at 950 rpm for 15 min prior to seeding at 35-50 mL per flask (at a density of 425,000 cells/mL).

7.5.1.4 Differentiation of CD34-Negative Progenitor Cells into Connective Tissue-Type Mast Cells

A proliferated population of CD34-negative progenitor cells is prepared as above and treated to form a tryptase/chymase positive (connective tissue) phenotype. The methods are performed as described above for mucosal mast cells, but with the substitution of IL-4 for IL-6 in the culture medium. The cells obtained are typical of connective tissue mast cells.

7.5.1.5 Differentiation of CD34-Negative Progenitor Cells into Basophil Cells

A proliferated population of CD34-negative progenitor cells is prepared as described in Section 7.5.1.3, above, and used to form a proliferated population of basophil cells. The CD34-negative cells are treated as described for mucosal mast cells, but with the substitution of IL-3 (at 20-50 ng/mL) for IL-6 in the culture medium.

7.5.2 CHMC Low Cell Density IgE Activation: Tryptase and LTC4 Assays

To duplicate 96-well U-bottom plates (Costar 3799) add 65 ul of compound dilutions or control samples that have been prepared in MT [137 mM NaCl, 2.7 mM KCl, 1.8 mM $CaCl_2$, 1.0 mM $MgCl_2$, 5.6 mM Glucose, 20 mM Hepes (pH 7.4), 0.1% Bovine Serum Albumin, (Sigma A4503)] containing 2% MeOH and 1% DMSO. Pellet CHMC cells (980 rpm, 10 min) and resuspend in pre-warmed MT. Add 65 ul of cells to each 96-well plate. Depending on the degranulation activity for each particular CHMC donor, load 1000-1500 cells/well. Mix four times followed by a 1 hr incubation at 37°C. During the 1

hr incubation, prepare 6X anti-IgE solution [rabbit anti-human IgE (1 mg/ml, Bethyl Laboratories A80-109A) diluted 1:167 in MT buffer]. Stimulate cells by adding 25 ul of 6X anti-IgE solution to the appropriate plates. Add 25 ul MT to un-stimulated control wells. Mix twice following addition of the anti-IgE. Incubate at 37°C for 30 minutes. During the 30 minute incubation, dilute the 20 mM tryptase substrate stock solution [(Z-Ala-Lys-Arg-AMC·2TFA; Enzyme Systems Products, #AMC-246)] 1:2000 in tryptase assay buffer [0.1 M Hepes (pH 7.5), 10 % w/v Glycerol, 10 uM Heparin (Sigma H-4898) 0.01% NaN_3]. Spin plates at 1000 rpm for 10 min to pellet cells. Transfer 25 ul of supernatant to a 96-well black bottom plate and add 100 ul of freshly diluted tryptase substrate solution to each well. Incubate plates at room temperature for 30 min. Read the optical density of the plates at 355nm/460nm on a spectrophotometric plate reader.

Leukotriene C4 (LTC4) is also quantified using an ELISA kit on appropriately diluted supernatant samples (determined empirically for each donor cell population so that the sample measurement falls within the standard curve) following the supplier's instructions.

7.5.3 CHMC High Cell Density IgE Activation: Degranulation (Tryptase, Histamine), Leukotriene (LTC4), and Cytokine (TNFalpha, IL-13) Assays

Cultured human mast cells (CHMC) are sensitized for 5 days with IL-4 (20 ng/ml), SCF (200 ng/ml), IL-6 (200 ng/ml), and Human IgE (CP 1035K from Cortx Biochem, 100-500ng/ml depending on generation) in CM medium. After sensitizing, cells are counted, pelleted (1000 rpm, 5-10 minutes), and resuspended at 1-2 $x10^6$ cells/ml in MT buffer. Add 100 ul of cell suspension to each well and 100 ul of compound dilutions. The final vehicle concentration is 0.5% DMSO. Incubate at 37°C (5% CO_2) for 1 hour. After 1hour of compound treatment, stimulate cells with 6X anti-IgE. Mix wells with the cells and allow plates to incubate at 37°C (5% CO_2) for one hour. After 1 hour incubation, pellet cells (10 minutes, 1000 RPM) and collect 200 ul per well of the supernatant, being careful not to disturb pellet. Place the supernatant plate on ice. During the 7-hour step (see next) perform tryptase assay on supernatant that had been diluted 1:500. Resuspend cell pellet in 240 ul of CM media containing 0.5% DMSO and corresponding concentration of compound. Incubate CHMC cells for 7 hours at 37°C (5% CO_2). After incubation, pellet cells (1000 RPM, 10 minutes) and collect 225 ul per well and place in -80°C until ready to perform ELISAS. ELISAS are performed on appropriately diluted samples (determined

empirically for each donor cell population so that the sample measurement falls within the standard curve) following the supplier's instructions.

7.5.4 BMMC High Cell Density IgE Activation: Degranulation (Hexosiminidase, Histamine), Leukotriene (LTC4), and Cytokine (TNFalpha, IL-6) Assays

7.5.4.1 Preparation of WEHI-Conditioned Medium

WEHI-conditioned medium was obtained by growing murine myelomonocytic WEHI-3B cells (American Type Culture Collection, Rockville, MD) in Iscove's Modified Eagles Media (Mediatech, Hernandon, VA) supplemented with 10% heat-inactivated fetal bovine serum (FBS; JRH Biosciences, Kansas City, MO), 50 μM 2-mercaptoethanol (Sigma, St. Louis, MO) and 100 IU/mL penicillin-steptomycin (Mediatech) in a humidified 37°C, 5% CO_2/95% air incubator. An initial cell suspension was seeded at 200,000 cells/mL and then split 1:4 every 3-4 days over a period of two weeks. Cell-free supernatants were harvested, aliquoted and stored at -80°C until needed.

7.5.4.2 Preparation of BMMC Medium

BMMC media consists of 20% WEHI-conditioned media, 10% heat-inactivated FBS (JHR Biosciences), 25 mM HEPES, pH7.4 (Sigma), 2mM L-glutamine (Mediatech), 0.1 mM non-essential amino acids (Mediatech), 1mM sodium pyruvate (Mediatech), 50 μM 2-mercaptoethanol (Sigma) and 100 IU/mL penicillin-streptomycin (Mediatech) in RPMI 1640 media (Mediatech). To prepare the BMMC Media, all components are added to a sterile IL filter unit and filtered through a 0.2 μm filter prior to use.

7.5.4.3 Protocol

Bone marrow derived mast cells (BMMC) are sensitized overnight with murine SCF (20 ng/ml) and monoclonal anti-DNP (10 ng/ml, Clone SPE-7, Sigma # D-8406) in BMMC media at a cell density of 666 $x10^3$ cells/ml. After sensitizing, cells are counted, pelleted (1000 rpm, 5-10 minutes), and resuspended at 1-3 $x10^6$ cells/ml in MT buffer. Add 100 ul of cell suspension to each well and 100 ul of compound dilutions. The final vehicle concentration is 0.5% DMSO. Incubate at 37°C (5% CO_2) for 1 hour. After 1hour of compound treatment, stimulate cells with 6X stimulus (60 ng/ml DNP-BSA). Mix

wells with the cells and allow plates to incubate at 37°C (5% CO_2) for one hour. After 1hour incubation, pellet cells (10 minutes, 1000 RPM) and collect 200 ul per well of the supernatant, being careful not to disturb pellet, and transfer to a clean tube or 96-well plate. Place the supernatant plate on ice. During the 4-5 hour step (see next) perform the hexosiminidase assay. Resuspend cell pellet in 240 ul WEI-conditioned media containing 0.5% DMSO and corresponding concentration of compound. Incubate BMMC cells for 4-5 hours at 37°C (5% CO_2). After incubation, pellet cells (1000 RPM, 10 minutes) and collect 225 ul per well and place in -80°C until ready to perform ELISAS. ELISAS are performed on appropriately diluted samples (determined empirically for each donor cell population so that the sample measurement falls within the standard curve) following the supplier's instructions.

Hexosaminidase assay: In a solid black 96-well assay plate, add 50 uL hexosaminidase substrate (4-methylumbelliferyl-N-acetyl-β-D-glucosaminide; 2mM) to each well. Add 50 uL of BMMC cell supernatant (see above) to the hexoseaminidase substrate, place at 37°C for 30 minutes and read the plate at 5, 10, 15, and 30 minutes on a spectrophotometer.

7.5.5 Basophil IgE or Dustmite Activation: Histamine Release Assay

The basophil activation assay was carried out using whole human peripheral blood from donors allergic to dust mites with the majority of the red blood cells removed by dextran sedimentation. Human peripheral blood was mixed 1:1 with 3% dextran T500 and RBCs were allowed to settle for 20-25min. The upper fraction was diluted with 3 volumes of D-PBS and cells were spun down for 10 min at 1500 rpm, RT. Supernatant was aspirated and cells were washed in an equal volume MT-buffer. Finally, cells were resuspended in MT-buffer containing 0.5% DMSO in the original blood volume. 80 uL cells were mixed with 20 uL compound in the presence of 0.5% DMSO, in triplicate, in a V-bottom 96-well tissue culture plate. A dose range of 8 compound concentrations was tested resulting in a 10-point dose response curve including maximum (stimulated) and minimum (unstimulated) response. Cells were incubated with compound for 1 hour at 37°C, 5% CO_2 after which 20 uL of 6x stimulus [1 ug/mL anti-IgE (Bethyl Laboratories) 667 au/mL house dustmite (Antigen Laboratories)] was added. The cells were stimulated for 30 minutes at 37°C, 5% CO_2. The plate was spun for 10 min at 1500 rpm at room temperature

and 80 uL the supernatant was harvested for histamine content analysis using the histamine ELISA kit supplied by Immunotech. The ELISA was performed according to supplier's instructions.

7.5.6 Results

The results of low density CHMC assays (Section 7.5.2), the high density BMMC assays (Section 7.5.4) and the basophil assays (Section 7.5.5) are provided in TABLE 1. The results of the high density CHMC assays (Section 7.5.3) are provided in TABLE 2. In TABLES 1 and 2, all reported values are IC_{50}s (in μM). A value of "9999" indicates an IC_{50}> 10μM, with no measurable activity at a 10μM concentration. Most compounds tested had IC_{50}s of less than 10μM, with many exhibiting IC_{50}s in the sub-micromolar range.

7.6 The 2,4-Pyrimidinediamine Compounds Inhibit FcγRI Receptor-Mediated Degranulation

The ability of the 2,4-pyrimidinediamine compounds of the invention to inhibit FcγRI-mediated degranulation was demonstrated with Compounds R921218, R921302, R921303, R940347, R920410, R927050, R940350, R935372, R920323, R926971 and R940352 in assays similar to those described in Section 7.5, with the exception that the cells were not primed with IgE and were activated with rabbit anti-human IgG Fab fragment (Bethyl Laboratories, Catalog No. A80-105).

All of the compounds tested exhibited IC_{50}s in the sub micromolar range.

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R008951														
R008952														
R008953														
R008955														
R008956														
R008958														
R067934														
R067963														
R070153														
R070790	1.665	9999												
R070791														
R081166														
R088814														
R088815														
R091880														
R092788														
R908696	3 553													
R908697	9999	9999												
R909236	0.996	9999												
R909237	9999	9999												
R909238	0 174	9999							<0.22		<0.22	0 521	0.432	<0 22

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R909239	0.264	9999												
R909240	0.262	9999												
R909241	0.181	9999							<0 22		<0.22	1.021	0.253	<0.22
R909242	0.567	9999												
R909243	0.263	>10												
R909245	0.255	6.242												
R909246	0.169	9999												
R909247	2.393	9999												
R909248	3.582	9999												
R909249	9999	9999												
R909250	8.025	9999												
R909251	0.138	9999												
R909252	0.248	9999												
R909253	7.955	9999												
R909254	0.136	9999												
R920664	9999	9999												
R920665	1.1	9999												
R920666	2.53	9999												
R920668	3.2	9999												
R920669	0.42	9999												
R920670	2.18	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R920671	9999	9999												
R920672	9999	9999												
R920818	9999	9999												
R920819	10	9999												
R920820	9999	9999												
R920846	9999	9999												
R920860	1.009	9999												
R920861	0.598	>10												
R920893	1.239	9999												
R920894	0.888	5.566												
R920910	0.751	7.922												
R920917	1 579	9.729												
R921218	0.499	9999	0.55	0.6	9999	0 24	9999	0.302	0.133	9999	0 203	0.766	0.274	0.100
R921219	0.059	9999				0.025	9999	0.020	0.069		0 058	0.040	0 039	0.009
R925734				9.2	>10				9999	9999				
R925747	1.021	3.1							3 1					
R925755	0.898	9999												
R925757	2.8	9999												
R925758	1.175	9999												
R925760	4.85	9999												
R925765	6.8	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R925766	8.9	9999												
R925767	10													
R925768	9999													
R925769	9999													
R925770	9999													
R925771	0.5	2.8	0.22											
R925772	9999	9999												
R925773	0.673	9999												
R925774	0.435	9999												
R925775	0 225	9999	0.2											
R925776	2.1	9999												
R925778	0 225	9999	0.18											
R925779	0.265	9999	0.19											
R925783	2.9	9999												
R925784	3.2	9999												
R925785	2.5	9999												
R925786	1.85	9999												
R925787	9	9999												
R925788	2.4	9999												
R925790	9999	9999												
R925791	9999	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R925792	6.25	9999												
R925794	9999	9999												
R925795	9999	9999												
R925796	2	9999												
R925797	0 85	9999	0.28											
R925798	9999	9999												
R925799	9999	9999												
R925800	9999	9999												
R925801	9999	9999												
R925802	9999	9999												
R925803	9999	9999												
R925804	9999	9999												
R925805	9999	9999												
R925806	9999	9999												
R925807	9999	9999												
R925808	9999	9999												
R925810	9999	9999												
R925811	3.3	9999												
R925812	5 8	9999												
R925813	9999	9999												
R925814	9999	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R925815	9999	9999												
R925816	6	9999												
R925819	9999	9999												
R925820	9999	9999												
R925821	9999	9999												
R925822	9999	9999												
R925823	9999	9999												
R925824	9999	9999												
R925837	9999	9999												
R925838	9999	9999												
R925839	9999	9999												
R925840	9999	9999												
R925841	9999	9999												
R925842	7.3	9999												
R925843	9999	9999												
R925844	5.1	9999												
R925845	2.3	9999												
R925846	9999	9999												
R925849	8.2	9999												
R925851	0 925	9999												
R925852	3	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R925853	9999	9999												
R925854	9999	9999												
R925855	4 2	9999												
R925856	9.85	9999												
R925857	5.95	9999												
R925858	8.05	7.3												
R925859	9999	9999												
R925860	9999	9999												
R925861	9999	9999												
R925862	0.7	9999												
R925863	0.274	9999												
R925864	9999	9999												
R925865	9999	9999												
R926016						9999	9999		9999	9999				
R926017				1.43	9999	0.53	9999		1.4	9.6				
R926018						9999	10		8.5	9999				
R926037						9999	9999		9999	9999				
R926038						9999	9999		9999	9999				
R926039						9999	9999		9999	9999				
R926058						9999	9999		9999	9999				
R926064				6.2					5.9	7.3				

TABLE 1

Test Compound	Low Density					High Density								
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926065				3.5					9999	9999				
R926068				>10					7.4	8.2				
R926069				9.1					4.5	4.4				
R926072				>10					9999	9999				
R926086						2.5	9999		2.8	7.3				
R926108			0.76	0.787	6.4	0.95	9999		0.9	9999				
R926109	0.538	5.5	0.73	0.55	>10	0.15	9999		0.6	3.2				
R926110	1.071	9999	1.42	1.2	>10	0.3	9999		1	4.5				
R926113	0.413		0.49	0.413	9999	0.27	9999		0.65	9999				
R926114				3.427	8.1	1.7	10		9999	9999				
R926145				4.764	>10				2 4	8.8				
R926146			1.59	0.761	6.7				1.35	5				
R926147				1 899	>10				2	7.1				
R926206						>10	>10		6.6	8.6				
R926209						>10	9999		10	9.1				
R926210	0.926	9999	0.8	700	9999	0.37	>10		0.6	>10				
R926211	1.299	9.8		2.7	9999	1.55	>10		3.9	>10				
R926212	0.654	9999	0.45			0 5	>10		0.5	5				
R926213	1.639	5.5				1.75	>10							
R926218				>10					9999	9999				
R926219				1.102	6.7				2.5	3 2				

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926220				>10					9999	9999				
R926221				8.5					9.9	9999				
R926222				>10					9999	9999				
R926223				>10					9999	9999				
R926224				>10					9999	9999				
R926225				>10					9999	9999				
R926228				>10					9999					
R926229				>10										
R926230				>10										
R926234				>10					9999					
R926237	1.207	6.2							1.9					
R926240	0.381	1.7	0.145											
R926241	7	9999												
R926242	4.2	9999												
R926243	3.1	9999												
R926245	3.1	9.4												
R926248	0.9	9999	0.76											
R926249	0.5	9999	0.25											
R926252	2.8													
R926253	0.8		0.675											
R926254	1.3	4												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926255	1.4	4.5												
R926256	0.275	5.1	0.23											
R926257	1.5	7.5												
R926258	0 9	9999	0.59											
R926259	2 5	6.2												
R926319	9999	9999												
R926320	9999	9999												
R926321	9999	9999												
R926325	9999	9999												
R926331	9999	9999												
R926339	0.66	9999												
R926340	3 23	9999												
R926341	0.875	9999												
R926342	10	9999												
R926376	9999													
R926386	9999	9999												
R926387	0.65	9999	0.7											
R926394	9999	9999												
R926395	0.875	6.4	0.29											
R926396	0.7	2.6	0.16											
R926397	9999	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926398	9999	9999												
R926399	9999	9999												
R926400	9999	9999												
R926401	9999	9999												
R926402	9999	9999												
R926403	9999	9999												
R926404	9999	9999												
R926405	3.4	9999												
R926406	9999	9999												
R926408	9.6	9999												
R926409	3.15	9999												
R926411	0.69	2.5												
R926412	0.62	9999												
R926461	0.725	9999												
R926467	1.175	8.8												
R926469	9999													
R926474	2.5	9999												
R926475	2.15	>10												
R926476	0 6	7.7												
R926477	0.27	9999												
R926478	9999													

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926479	9999													
R926480	1.9	9999												
R926481	1.445	9999												
R926482	1.037	>10												
R926483	9999													
R926484	1.523	9999												
R926485	4.012	9999												
R926486	0.647	7.403												
R926487	0.554	8.867	1.25											
R926488	0.331	>10	0 752											
R926489	1.414	>10												
R926490	1.571	9999												
R926491	1.158	>10												
R926492	0.645	9999												
R926493	0.25	9 181	0.078											
R926494	0.313	9999	0.078											
R926495	0.121	>10	0.078			0.04	9999	0.038	0.056		0.089	0.24	0 077	0.028
R926496	0.571	>10												
R926497	0.138	9999				0.27	9999	0.205						
R926498	0.209	>10							<0.22		0.515	0.995	0.614	<0 22
R926499	0 29	>10												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926500	0.418	>10												
R926501	0.298	>10				0 609	9999	0.645						
R926502	0 483	>10				0.405	9999	0 491						
R926503	0.452	>10												
R926504	0.569	>10												
R926505	0.145	9999							<0 22		<0 22	<0 22	<0.22	<0 22
R926506	0.343	9999												
R926508	0 127	9999				0.065	9999	0.054	0.086		0.107	0 162	0 054	0 026
R926509	1.16	9999												
R926510	0.44	>10												
R926511	0.786	>10												
R926514	9999	9999												
R926516	1	9999												
R926526	9999	9999												
R926527	9999	9999												
R926528	8.75	9999												
R926535	9999	9999												
R926536	9999	9999												
R926555	9999	9999												
R926559	7.7	9999												
R926560	9999	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926562	9999	9999												
R926563	9999	9999												
R926564	3.75	9999												
R926565	0.625	3.3												
R926566	2.73	9999												
R926567	9.3	9999												
R926569	0.61	3.07												
R926571	9999	9999												
R926572	1.8	6.08												
R926574	1.96	2.63												
R926576	9999	9999												
R926579	9999	9999												
R926580	10	9999												
R926582	1.3	9999												
R926583	9999	9999												
R926584	9999	9999												
R926585	9999	9999												
R926586	2.75	9999												
R926587	9999	9999												
R926588	7.85	9999												
R926589	0.325	10												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926591	2.62	9999												
R926593	0.68	8.3	0.495											
R926594	9999	9999												
R926595	4.85	9999												
R926604	2.85	9999												
R926605	2.45	9999												
R926614	0.228	9999												
R926615	0.445	9999												
R926616	0 625	3.25												
R926617	9.45	9999												
R926620	8.35	9999												
R926623	9999	9999												
R926662	9999	9999												
R926663	9999	9999												
R926675	0.63	9999												
R926676	0.76	9999												
R926680	1.71	9999												
R926681	0.775	9999												
R926682	8 41	9999												
R926683	10	9999												
R926688	2.25	>10												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926690	0.146	>10												
R926696	0 309	>10												
R926698	9999													
R926699	0.76	9999												
R926700	0.157	>10												
R926701	2.2	9999												
R926702	0.886	9999												
R926703	0.525	9999												
R926704	0.564	9999												
R926705	0.263	9999	0.533											
R926706	0.07	2 406	0.078											
R926707	0.214	9999							<0.056		<0.056	0.39	0.088	<0.056
R926708	0.472	9999												
R926709	0.858	9999												
R926710	1.763	9999												
R926711	1.245	9999												
R926712	1.084	9999												
R926713	0.446	8.741												
R926714	0.428	>10												
R926715	0.588	>10												
R926716	1.06	9999												

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TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926717	7.874	9999												
R926718	1 826	9999												
R926719	0.1335	4.024												
R926720	1 555	9999												
R926721	4.441	9999												
R926722	5.96	9999												
R926723	2.591	9999												
R926724	2 059	9999												
R926725	0.431	9999												
R926726	9999	9999												
R926727	0.387	9999												
R926728	0.482	>10												
R926730	0.251	9999												
R926731	9999	9999												
R926732	0.444	9999												
R926733	1.496	9999												
R926734	4.493	9999												
R926735	3.712	9999												
R926736	0 288	9999												
R926737	0 059	9999							0.075		0.073	0.046	0.068	0 017
R926738	0.342	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926739	0.508	9999												
R926740	4 422	9999												
R926741	2.908	9999							0.961		1 025	9999	0.772	0 537
R926742	0.127					0.043	9999	0.055	0.041		0.055	0.105	0.053	0.022
R926743	9999													
R926744	9999													
R926745	0.083	9999												
R926746	0.989	9999												
R926747	0.213	>10												
R926748	0.345	>10												
R926749	0.472	9999												
R926750	0.361	>10												
R926751	0.598	9999												
R926764	0.252	5.64												
R926765	0.324	4.39												
R926766	0.756	9999												
R926767	0.387	>10												
R926768	0.443	>10												
R926769	1.067	9999												
R926770	0.583	9999												
R926771	2.049	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926772	0.337	7.501												
R926773	0.548	7.849												
R926774	1.934	7.935												
R926775	3.47	>10												
R926776	0.81	9999												
R926777	0 378	9999												
R926778	0.414	9999												
R926779	9999	9999												
R926780	0.152	>10							<0.22		<0 22	0.461	<0.22	<0.22
R926781	0 573	9999												
R926782	0.173	>10							<0.22		<0.22	1.461	0 276	<0 22
R926783	0.304	>10												
R926784	0.252	9999												
R926785	0.222	>10							0.989		0.561	1.411	1.312	0 513
R926786	0.504	9999												
R926787	5.422	9999												
R926788	0.336	6.341												
R926789	2.315	9999												
R926790	0.462	7.412												
R926791	0.233	>10							0.064		<0.056	0.896	0.205	<0 056
R926792	3.197	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926793	3.073	9999												
R926795	2.041	>10												
R926796	0.914	9999												
R926797	2.235	9999												
R926798	2.347	5.87												
R926799	9999	9999												
R926800	4.581	9999												
R926801	10	9999												
R926802	1.251	>10												
R926803	1.541	>10												
R926804	1.578	7.109												
R926805	0.764	9999												
R926806	0.374	9999												
R926807	0.291	9999												
R926808	0.368	9999												
R926809	0.78	3.052												
R926810	1.221	9999												
R926811	3.662	9999												
R926812	0 185	>10												
R926813	0.152	9999												
R926814	1.101	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926815	1 181	9999												
R926816	0.084	9999												
R935000	9999	9999												
R935001	9999	9999												
R935002	9999	9999												
R935003	9999	9999												
R935004	9999	9999												
R935005	9999	9999												
R935006	10	9.8												
R935016	9999	9999												
R935019	8.8	9999												
R935020	9999	9999												
R935021	9999	9999												
R935023	9999	9999												
R935025	1.04	9999												
R935029	2 83	9999												
R935075	0.93	9999												
R935076	4 15	9999												
R935077	9999	9999												
R935114	1.725	9999												
R935117	9999													

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935134	0.909	1.799												
R935135	10	9999												
R935136	0.952	2.129												
R935137	10	9999												
R935138	0.096	0.552							<0.22		<0.22	0.373	0.409	<0.22
R935139	0.846	9999												
R935140	0.275	0.959												
R935141	0.727	>10												
R935142	0 873	>10												
R935143	0 573	>10												
R935144	0 63	9999												
R935145	0 548	>10												
R935146	3.802	9999												
R935147	1.404	9999												
R935148	2.218	9.423												
R935149	0.708	>10												
R935150	1.926	9.738												
R935151	0.479	>10												
R935152	0.505	9.316												
R935153	0.238	>10												
R935154	0.127	>10							0.104		0.085	0.547	0.131	0.041

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935155	0.401	9999												
R935156	0.149	>10							<0.22		<0 22	0.433	0 22	<0.22
R935157	0.256	4.656												
R935158	0 551	>10												
R935159	0.232	4.135												
R935160	0.202	>10							<0.22		0.317	0.876	0.484	<0 22
R935161	0.277	9999												
R935162	0 269	>10												
R935163	9999	9999												
R935164	0.204	9999												
R935165	4.988	9999												
R935166	0.568	9999												
R935167	2.132	>10												
R935168	0.488	9.484												
R935169	0.999	8.007												
R935170	0.673	9999												
R935171	0.536	9999												
R935172	1.385	6.808												
R935173	0.454	>10												
R935174	1.384	9999												
R935175	0.885	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935176	1.169	9999												
R935177	0.889	>10												
R935178	0.515	9999												
R935179	0.557	9999												
R935180	1.22	9999												
R935181	1.76	9999												
R935182	0.124	2.469												
R935183	0.729	9999												
R935184	0 605	9999												
R935185	0 351	6.642												
R935186	0.211	9999												
R935187	9.059	>10												
R935188	0.239	9999												
R935189	0.619	9999												
R935190	0.156	9999												
R935191	0.151	9999							0.068		0.043	0.213	0 071	0.027
R935192	0.337	9999												
R935193	0.136	9999							0.08		0.048	0.312	0 092	0.037
R935194	0.11	9999							0.125		0.054	0 493	0 118	0 034
R935196	0.117	9999												
R935197	0.174	>10												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935198	0.126	>10												
R935199	0.45	>10												
R935202	0.181	9.765												
R935203	0.562	>10												
R935204	0.554	9999												
R935205	2.959	9999												
R935206	4.711	9999												
R935207	9999	9999												
R935208	1.274	9999												
R935209	0 526	1.035												
R935211	1.238	9999												
R935212	1.427	9999												
R935213	0 619	10												
R935214	0.453	5.499												
R935218	4.712	9999												
R935219	5.409	9999												
R935220	3 789	9999												
R940089	9999	9999												
R940090	9999	9999												
R940095	9999	9999												
R940100	9999	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R940215	0.845	9999												
R940216	0.2675	7.3												
R940217	9999	9999												
R940222	9999	9999												
R940233	0.132	>10												
R940235	0.8	>10												
R940250														
R940251														
R940253	1.006	>10												
R940254	0.986	9999												
R940255	1 033	9999												
R940256	1.104	9999												
R940257	0.667	9999												
R940258	0.473	5.72												
R940260	1.126	9999												
R940261	9999	9999												
R940262	9999	9999												
R940263	9999	9999												
R940264	10	9999												
R940265	0.239	>10							0.981		0.306	1.211	1.131	0.486
R940266	9999	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R940267	3.151	9999												
R940269	1.654	9999												
R940270	2.144	8.739												
R940271	0.401	6.821												
R940275	0.862	9999												
R940276	0.211	9999							0.136		0.073	0 332	0 251	<0 056
R940277	0.141	9999							0.279		0.315	0.625	0.262	0.181
R940280	6.999	9999												
R940281	0.525	5.529												
R940282	0.401	3.015												
R940283	0.553	4.982												
R940284	0.465	3.744												
R940285	3.499	9999												
R940286	0.337	7.082												
R940287	0.288	7.684												
R940288	0.208	9999												
R940289	0.272	9999												
R940290	0.116	9999							0.255		0 545	0.59	0 246	0.1
R940291	0.396	9999												
R940292	0.683	9999												
R940293	9999	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R940294	1.366	9999												
R940295	0.126	8.812												
R940296	0.41	>10												
R940297	3.465	10												
R945025	9999	9999												
R945032	0.37	9999												
R945033	9999	9999												
R945034	1.85	9999												
R945035	9999	9999												
R945036	9999	9999												
R945037	9999	9999												
R945038	9999	9999												
R945040	9999	9999												
R945041	9999	9999												
R945042	9999	9999												
R945043	9999	9999												
R945045	9999	9999												
R945046	0.82	>10												
R945047	0.845	9999												
R945048	0.76	9999												
R945051	0.95	>10												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R945052	0.425	2.48												
R945053	0.1185	1.48												
R945056	10	9999												
R945057	10	9999												
R945060	0.9375	>10												
R945061	10	9999												
R945062	0.625	>10												
R945063	1.55	>10												
R945064	0.53	>10												
R945065	1.425	>10												
R945066	5 2	nd												
R945067	9999	nd												
R945068	9999	nd												
R945070	0.45	>10												
R945071	0.205	>10												
R945096	1.75	>10												
R945097	10	9999												
R945109	1.025	>10												
R945110	0.602	9999												
R945117	4.077	9999												
R945118	0.668	9999												

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TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R945124	0 69	7 852												
R945125	0.896	>10												
R945126	9999	9999												
R945127	0 704	8.955												
R945128	0 685	8.8												
R945129	1.003	>10												
R945130	1.874	9999												
R945131	0.77	9999												
R945132	0.571	8.77												
R945133	1.064	>10												
R945134	9999	9999												
R945135	0 986	8.245												
R945137	1.649	>10												
R945138	1.058	6 733												
R945139	1 016	>10												
R945140	0.573	>10												
R945142	1.049	>10												
R945144	0.244	9999												
R945145	9999	>10												
R945146	3.756	9999												
R945147	3.546	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R945148	0 307	9999												
R945149	0.391	>10												
R945150	0.467	>10							>2		>2	9999	0.709	0.634
R945151	4 07	9999												
R945152	6.94	9999												
R945153	0.688	6.561												
R945155	1.878	>10												
R945156	0.787	9999												
R945157	1.477	9999												
R945162	9999	9999												
R945163	0.922	4.251												
R945164	10	9999												
R945165	9999	9999												
R945166	9999	9999												
R945167	0.761	9999												
R945168	10	9999												
R945169	10	9999												
R945170	0 661	>10												
R945171	1.327	9999												
R945172	1.179	9999												
R945173	1.419	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R945175	1.648	9999												
R950082	9999	9999												
R950083	9999	9999												
R950090	9999	9999												
R921302	0.37	9999				0.19	9999	0.282						
R950092	9999	9999												
R950093	0.64	5.55												
R950100	0 71	>10												
R950107	0.46	>10												
R950108	2.075	>10												
R950109	7.95													
R950120	3	9999												
R950121	4.25	>10												
R950122	3.025	9999												
R950123	3.25	8.45												
R950125	1.375	6.3												
R950129	0.665	>10												
R950130	4.9													
R950131	9999													
R950132	9													
R950133	2.2	>10												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950134	1.875	9999												
R950135	0.85	>10												
R950137	2.23	9999												
R950138	9.5													
R950139	1 375	9999												
R950140	2.825	9999												
R950141	0 31	>10												
R950142	10													
R950143	8.23													
R950144	10													
R950145	9999													
R950146	9999													
R950147	9999													
R950148	2.275	9999												
R950149	10	9999												
R950150	9999	9999												
R950151	9999													
R950152	10													
R950153	9999													
R950154	2.075	9999												
R950155	9999													

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950156	9999													
R950157	9999													
R950158	9.98													
R950159	0.61	9999												
R950160	1	9999												
R950162	0.434	>10												
R950163	0.874	9999												
R950164	1.893	9999												
R950165	1.288	9999												
R950166	1.889	9999												
R950167	9999	9999												
R950168	6.496	8.653												
R950169	1.273	9.518												
R950170	9999	9999												
R950171	0.585	>10												
R950172	0.983	9999												
R950173	2.368	>10												
R950174	4.618	9999												
R950175	1.688	9999												
R950176	1.342	9999												
R950177	2.361	8.434												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950178	0.688	>10												
R950179	0.955	>10												
R950180	0.278	9999												
R950181	0.254	9999												
R950182	0.627	9999												
R950183	4.797	9999												
R950184	2 222	9999												
R950185	1.03	8.81												
R950186	0.558	>10												
R950187	0 724	>10												
R950188	2.327	9999												
R950189	10	9999												
R950190	1 573	9999												
R950191	0.178	9999							<0.22		>2	0 401	<0.22	<0 22
R950192	0 244	9999												
R950193	0 61	9999												
R950194	2.04	9999												
R950195	0.473	9999												
R950196	2.2	9999												
R950197	0.531	9999												
R950198	0.406	>10												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950199	0.408	9999												
R950200	0.245	9999												
R950201	0.261	9999												
R950202	3.218	9999												
R950203	9.035	9999												
R950204	6.285	9999												
R950205	8.997	9999												
R950206	3.66	>10												
R950207	0.164	9999							<0.22		<0.22	0.288	<0 22	<0 22
R950208	0.267	9999												
R950209	0.748	9999												
R950210	10	9999												
R950211	10	9999												
R950212	0.253	9999												
R950213	9999	9999												
R950214	10	9999												
R950215	0.409	9999												
R950216	0.327	9999												
R950217	0.34	9999												
R950218	0.292	9999												
R950219	0.439	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950220	0.489	9999												
R950221	0 636	9999												
R950222	0.865	9999												
R950223	0.763	9999												
R950224	0.687	9999												
R950225	5.283	9999												
R950226	1.374	9999												
R950227	1 029	9999												
R950229	0.98	9999												
R950230	7.91	9999												
R950231	1.968	9999												
R950232	10	9999												
R950233	0.98	9999												
R950234	10	9999												
R950235	4.095	9999												
R950236	0.955	9999												
R950237	9999	9999												
R950238	10	9999												
R950239	2 063	9999												
R950240	1.766	9999												
R950241	3.275	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950251	9999	9999												
R950253	0.697	9999												
R950254	0.496	9999												
R950255	10	9999												
R908698	1.67	9999												
R908699	0.217	9999												
R908700	1.273	9999												
R908701	0.099	7.643												
R908702	0.104	7.395												
R908703	0.63	9999												
R908704	0.511	9999												
R908705	0.801	9999												
R908706	0.445	9999												
R908707	1.834	9999												
R908709	2.414													
R908710	1.838	99												
R908711	1.761													
R908712	0.075	99												
R908734	1 379													
R909255	0.244	9999												
R909259	0.43	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R909260	1.041	9999												
R909261	0.93	9999												
R909263	0.289	9999												
R909264														
R909265	99													
R909266	99													
R909267	0.589	9999												
R909268	0.071	9999												
R909290	0.226													
R909292	1.172													
R909308	0.671	9999												
R909309	0 083	9999												
R920394														
R920395	0.092	9999												
R920396														
R920397														
R920398														
R920399														
R920404														
R920405														
R920406														

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R920407														
R920408														
R920410	0.125	9999												
R920411	0.564	9999												
R925745	1 766	9999												
R926238	9999													
R926752	0 338	9999												
R926753	0 108	9999												
R926754	0.388	9999												
R926755	1.693	9999												
R926756	1.365	9999												
R926757	0 158	9999												
R926759	0.688	9999												
R926760	2.893	9999												
R926761	0.245	9999												
R926762	0.386	9999												
R926763	0.195	9999												
R926794	1.382	9999												
R926826	0.613	9999												
R926827	1.098	9999												
R926828	0.306	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926829	0 688	9999												
R926830	0 569	10												
R926831	0.133	10												
R926832	0.365	9999												
R926833	1.129	9999												
R926834	0.145	9999												
R926835	0.296	9999												
R926836	10	9999												
R926837	2.994	9999												
R926838	0.583	9999												
R926839	0.161	9999												
R926840	1.1	9999												
R926841	0.551	9999												
R926842	7.733	9999												
R926843	7.371	9999												
R926844	1.1	9999												
R926845	2.558	7.812												
R926846	0.86	6.264												
R926847	1.479	6.264												
R926848	0 254	10												
R926851	0.446													

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926855	9999	9999												
R926856	0.734	9999												
R926857	1.209	9999												
R926859														
R926860	1.949	99												
R926862	0.774	9999												
R926863														
R926866														
R926870	3.294													
R926871	2.146													
R926874	0 638	9999												
R926879	0.397	9999												
R926880														
R926881														
R926883														
R926885														
R926886														
R926887	1.747													
R926890	0 361	9999												
R926891	0.152	9999												
R926892	0.685	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926893	10	9999												
R926894	9999	9999												
R926895	0.339	9999												
R926896	1.622	9999												
R926897	1.727	9999												
R926898	1.1	9999												
R926899	1.1	9999												
R926900	9999	9999												
R926902	1.37	4.586												
R926903	0.243	9999												
R926904	0.538													
R926905	99													
R926906	0 794													
R926907	0.764													
R926908	0.585													
R926909	0.379													
R926913	0.548	9999												
R926914	1.86	9999												
R926915	1.713	9999												
R926916	1.958	9999												
R926917	1.169	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926918	2 521	9999												
R926919	1.413	9999												
R926922	0 305	9999												
R926923	0.346	9999												
R926925	0.307	99												
R926926	0.401	9999												
R926927	0.348	9999												
R926928	0 575	9999												
R926929	1 916	9999												
R926930	99	9999												
R926931														
R926932	0.31	9999												
R926933														
R926934														
R926935	4.44													
R926936														
R926937														
R926938														
R926939	3 615													
R926940	7.754													
R926941	4 195													

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926942	4.81													
R926943														
R926944	0.225	99												
R926945	0.457	9999												
R926946														
R926947	0.354	9999												
R926948	0.246	9999												
R926949	0.089	9999												
R926950	99	9999												
R926951	0.183	9999												
R926953	0.049	9999												
R926954	0.284	9999												
R926955	0.36	9999												
R926956	0 211	9999												
R927016	1.408													
R927017	2.449													
R927018	1.446													
R927019	1.179													
R927020	1 316	9999												
R927023	0.918	9999												
R935221	9999	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935222	0 52	9999												
R935223	0.469	9999												
R935224	4.578	9999												
R935225	6.495	9999												
R935237	0.24	9999												
R935238	1.854	9999												
R935239	0.609	9999												
R935240	0.606	9999												
R935242	2.855	9999												
R935248	1.1	9999												
R935249	1.1	9999												
R935250	1.1	9999												
R935251														
R935252														
R935253														
R935255	0.374	9999												
R935256	0.324	9999												
R935258	1.191	9999												
R935259	1.777	9999												
R935261	0.391	9999												
R935262	0.516	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935263	0.106	10												
R935264	0.135	9999												
R935266	2 97													
R935267	2.463													
R935268	1.059													
R935269	1.715													
R935271														
R935276	2.33													
R935277	22.883	8.9												
R935278	4.753	9999												
R935279	0.889	9999												
R935280	99													
R935281	1.399	9999												
R935286	1.158	9999												
R935287	0.403	9999												
R935288	1.58	9999												
R935289	1 688	9999												
R935290	0.34	9999												
R935291	1.364	9999												
R935292	0.483	9999												
R935293	0.141	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935294	0.388	9999												
R935295	1 943	9999												
R935296	99	9999												
R935297	7.328	9999												
R935298	0.252	99												
R935299	0.21	9999												
R935300	0.243	9999												
R935301	4.05	99												
R935302	0.189	9999												
R935303	0.244	99												
R935304	0.188	9999												
R935305	0.495	9999												
R935306	0.345	99												
R935307	0.139	99												
R935308	0.275	9999												
R935309														
R935310														
R935320	2.769													
R935321	2.986													
R935322	3.416													
R935323	9999													

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935324	9999													
R935336	0.341	9999												
R935337	9999													
R935338	0.411	9999												
R935339	9999													
R935340	3.606													
R935351	9999	9999												
R935352														
R935353	9999	9999												
R935354	99	9999												
R935355	9999	9999												
R935356	99													
R935357	99	9999												
R935358	9999	9999												
R935359	1.027	9999												
R935360	0.903	9999												
R935361	1.438	9999												
R935362	0.409	9999												
R935363	0.405	9999												
R935364	0.563	9999												
R935365	0.373	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935366	0.216	9999												
R935367	0.053	9999												
R940079	9999													
R940110	9999	9999												
R940299	2.497	9999												
R940300	10	9999												
R940301	1.975	9999												
R940304	9999	9999												
R940306	1.1	9999												
R940307	0.291	9999												
R940308	0.612	4.168												
R940309	1.132	9999												
R940311	1.95													
R940312	2.557													
R940314	4.197													
R940316	1.858													
R940317	0.913	9999												
R940318	3.792													
R940319	9999													
R940321	9999													
R940323	0.048	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R940337	1.098													
R940338	0.073	9999												
R921303	0.033	99												
R940345	1.712													
R940346	0.142	99												
R940347	0.063	99												
R940348	2 189													
R940349	0.044	7.4												
R940350	0.092	4												
R940351	0.12	2.7												
R940352	0.101	9999												
R940353	0.091	9999												
R940354	0.115	99												
R945236	0.562	9999												
R945237	0.461	9999												
R945242	0.247	9999												
R945263	1.642													
R921304	0.085	9999												
R945299														
R950244	9999													
R950245	9999													

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950246	9999													
R950247	9999													
R950261	0.611	9999												
R950262	0.285	9999												
R950263	0.284	3.299												
R950264	0.198	9999												
R950265	0.312	9999												
R950266	0.645	9999												
R950267	0.18	9999												
R950290	9999	9999												
R950291	9999	9999												
R950293	3.689	8.155												
R950294	2.005	8.005												
R950295	2 041	8.795												
R950296	0.495	9999												
R950344	99													
R950345	1.962	99												
R950346	0.345	9999												
R950347	0.548													
R950348	0.066													
R950349	0.078	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950356														
R950368	0.038	9999												
R950371														
R950372	1.348	9999												
R950373														
R950374	0.599	9999												
R950376	2.539													
R950377	99													
R950378														
R950379	0.545	9999												
R950380	3	9999												
R950381	0.11	99												
R950382														
R950383	0.114	9999												
R950385														
R950386	0.973													
R950388	2.518													
R950389	0.612	9999												
R950391	999	9999												
R950392	0.956	9999												
R950393	0.404	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R945028														
R935241														
R940298														
R940302														
R940303														
R940305														
R935260	9999													
R909258														
R940313	9999													
R940315	9999													
R935275	9999													
R940320	9999													
R940322	9999	9999												
R926910	9999	9999												
R926911	9999	9999												
R926912	9999	9999												
R926853	9999	9999												
R926852	9999	9999												
R926854	9999	9999												
R926920	9999	9999												
R926921	99	9999												

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926924	99	9999												
R926858														
R926861	9999	9999												
R945298	9999	9999												
R940328	9999													
R926869														
R926873	9999													
R926875	9999													
R926876	9999													
R926877	9999													
R940336	9999													
R926878	9999													
R926882	9999													
R926884	9999													
R926889	9999													
R920400	9999													
R920401	9999													
R920402	9999													
R920403	9999													
R940342	99													
R920409	9999													

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R940344	9999													
R926888	9999													
R926758														
R927024	0.326	99												
R927025	0.326													
R927026	9999	9999												
R927027	9999	9999												
R927028	0.208	9999												
R927029														
R927030	0.26	9999												
R927031	0.215	99												
R927032	0.899													
R927035	0.583	9999												
R927036														
R927037	0.233	9999												
R927038	1.05	9999												
R927039	1.23	9999												
R927040	1.05	9999												
R927041	0.788	9999												
R927042														
R935270														

TABLE 1

Test Compound	Low Density								High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4	CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935368	0.082	9999												
R935369	0.255	9999												
R935370														
R935371	0.794	9999												
R935372	0.06	9999												
R935373	0 274	9999												
R935374	0.356	9999												
R935375	10	9999												
R935376														
R935377														
R935378	0.566	9999												
R935379														
R935380	1.61	99												

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R908580					
R908586		9999			
R908587		9999			
R908591	0.075				
R908592	0.05				
R908946	0.51	9999			
R908947	0.496	9999			
R908950	0.074	47.5			
R908951	0.085	5.48			
R908952	0.08	6.07			
R908953	0.084				
R908954	0.084	9999			
R908955	0.293				
R908956	0.34				
R909310	0.207	9999			
R909312	1.759	9999			
R909313	0.663	9999			
R909314	0.293	9999			
R909316	0.2	9999			
R909317	0.028̂7	9999	0.002	0.007	0.006
R909318	1.02	9999			
R909319	0.225	9999			
R909320	0.29	9999			
R909321	0.163	30			
R909322	0.225	9999	0.24	0.14	0.1
R909323	9999	9999			
R926957	1.519	9999			
R926958	0.353	9999			
R926959	0.3	9999			
R926960	0.399	9999			
R926961	1.2	9999			

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926962	0.205	9999			
R926963	0.155	9999			
R926964	0.368	9999			
R926965	9999	9999	9999		
R926966	0.539	9999			
R926967	0.259	9999			
R926968	0.249				
R926969	0.359	9999			
R926970	0.06	9999			
R926971	0.034	9999			
R926972	5.29	9999			
R926973	0.284				
R926974	0.293				
R926975	0.421	30.2			
R926976	0.305	8.3	0.59	0.11	0.25
R926977	0.0359	9999			
R926978	0.995	18			
R926979	0.109	23.5			
R926980	0.68	5.49			
R926981	0.137	9999			
R926982	0.12	9999			
R926983	0.195	9999			
R926984	0.167	9999			
R926985	0.14	4.13			
R926986	0.345				
R926987	10				
R926989	0.199				
R926990	11.3				
R926991	0.436				
R926992	8888				
R926993	0.689				
R926994	0.061				

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926995	9.565	9999			
R927004	0.413				
R927005	1.158				
R927006	2.142				
R927007	5.739				
R927008	1.123				
R927009	4.933				
R927010	5.006				
R927011	0.464				
R927012	3.658				
R927013	5.171				
R927014	0.655				
R927015	9999	9999			
R927043	0.45	9999			
R927044		9999	4.28		
R927045	0.535	9999			
R927046		9999	2.4		
R927047	0.168	9999			
R927048	0.05	9999			
R927049	0.11	9999			
R927050	0.073	3.29	0.103	0.019	0.011
R927051	0.024	12.6			
R927052	0.678				
R927053	0.671				
R927054	9999				
R927055	9999				
R927056	0.144	1.58			
R927057	0.37				
R927058	12.2				
R927059	0.291				
R927060	0.222	5.17			
R927061	0.126	4.72			

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R927062	15.4	9999			
R927063	0.849	9999			
R927064	0.212	7.24	0.005	1.92	0.819
R927065	0.235	9999			
R927066	0.283	15.3			
R927067	0.625	22.5			
R927068	0.89				
R927069	0.076	13	1.35	0.93	1.09
R927070	0.054	5.24			
R927071	0.067				
R927072	0.064				
R927073	0.0668				
R927074	0.072	1.38			
R927075	0.057	15.2			
R927076	0.071				
R927077	0.284	8.8			
R927078	0.245				
R927079	0.599				
R927080	0.204				
R927081	2.27	9999			
R927082	0.256	9999			
R927083	0.316	19			
R927084	0.466	9999			
R927085	7.43	9999			
R927086	0.286	9999			
R927087	0.436	9999			
R927088	0.117	9999			
R927089	0.144	9999			
R927090	0.102	9999			
R927091	0.27	9999			
R927092	0.377	9999			
R927093	0.303	9999			

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R927094	9999	9999			
R927096	0.402	9999			
R927097	0.163	0.847			
R927098	1.53	9999			
R927099	9999	9999			
R927100	6.199	9999			
R927117	0.614	9999			
R927118	0.065	3.49			
R927119	1.162				
R927120	1.018				
R927121	0.389				
R927122	0.328				
R927123	0.087				
R927124	0.415				
R927125	0.255				
R927126	5.167				
R927127	9999				
R927128	1.893				
R927129	1.219				
R927130	1.586				
R927131	1.473				
R927132	2.756				
R927133	0.536				
R927134	1.286				
R927135	0.568				
R927136	0.945				
R927137	9999.000				
R927138	0.463				
R927139	9999.000				
R927140	4.823				
R927141	9999				
R927142	5.000				

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R927143	3.998				
R927144	2.273				
R927145	5.022				
R927146	1.309				
R927147	5.088				
R927148	0.097				
R927149	0.355				
R927150	0.708				
R927151	0.408				
R927152	4.864				
R927153	9999.000				
R927154	4.978				
R927155	8888.000				
R927156	2.779				
R927157	0.072				
R927158	2.284				
R927159	4.830				
R927160	8888.000				
R927162	5.646				
R927163	1.827				
R931930	0.361				
R931931	1.817				
R931932	0.511				
R931933	0.580				
R931934	9999.000				
R931935	4.706				
R931936	0.957				
R931936		9999			
R931937	9999.000				
R931938	0.542				
R931939	0.415				
R931940	1.069				

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R931941	0.494				
R931942	5.665				
R931943	9999.000				
R931944	0.285				
R931945	9999.000				
R931946	5.594	9999			
R931947	2.700	9999			
R931948	0.197				
R931949	0.033				
R931950	1.243				
R931951	0.017				
R931952	0.166				
R935381		9999	7.74		
R935382		9999	0.2		
R935383	0.146	9999			
R935384		9999	9999		
R935385		9999	0.217		
R935386	0.291				
R935389	0.877				
R935390	0.544				
R935391	0.212	9999	0.25	0.19	0.55
R935392	0.204	9999			
R935393	8888	9999	2.44	1.47	0.52
R935394	9999				
R935395	0.276				
R935396	2.58				
R935398	8888				
R935399	0.909				
R935400	0.502				
R935401	0.51				
R935402	0.216				
R935403	0.821				

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935404	0.581				
R935405	0.389				
R935406	1.17				
R935407	0.393				
R935408	0.137	9.94			
R935409	1.17				
R935410	0.417				
R935411	9999				
R935413	0.085	9999			
R935412	0.696				
R935414	0.204				
R935415	0.237				
R935416	0.166				
R935417	0.417				
R935418	0.228	9999			
R935419	0.23				
R935420	0.561				
R935421	2.89				
R935422	0.326				
R935423	0.167				
R935424	0.628				
R935425	8888				
R935426	9999				
R935427	8888				
R935428	1.272				
R935429	0.036	9999			
R935430	0.028	9.3			
R935431	0.124				
R935432	0.036	8.5			
R935433	0.106	16.2			
R935434	0.308				
R935435	0.337				

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935436	0.058				
R935437	0.082				
R935438	0.414	23			
R935439					
R935440	0.176	88			
R935441	0.586				
R935442	0.701				
R935443	8888				
R935444	0.429	9999			
R935445	0.184	11			
R935446	0.395	9999			
R935447	0.511	4.7			
R935448	0.111	4.3			
R935449	0.372	7.8			
R935450	0.494	9999			
R935451	9999	9999			
R935452	0.213	9999			
R935453	0.15	9999			
R935458	8888	9999			
R935459	0.343	4.7			
R935460	0.748	15.6			
R935461	0.134	5.03			
R935462	0.364	9999			
R935463	0.176	9999			
R935464	22.4	9999			
R935465	0.019	4.22			
R935466	0.284				
R935467	0.352				
R935468	0.705	5.37			
R935469	0.039	3.79			
R935469	0.056				
R935470	0.804	4.90			

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935471	0.481				
R935472	1.056				
R935473	0.057				
R935474	0.474				
R935475	0.516				
R935476	0.639				
R935477	0.097				
R935478	1.700				
R935479	1.355				
R935480	4.576				
R935481	0.114				
R935482	0.743				
R935483	0.601				
R935484	1.252				
R935485	0.231				
R935486	1.845				
R935487	3.224				
R935488	4.443				
R935489	0.185				
R935490	1.474				
R935491	6.873				
R935492	26.130				
R935493	0.385				
R935494	3.063				
R935495	1.112				
R935496	1.952				
R935497	0.097				
R935498	1.016				
R935499	1.207				
R935500	1.588				
R935501	0.305				
R935502	1.466				

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935503	0.400				
R935504	2.777				
R935505	0.038				
R935506	0.375				
R935507	0.473				
R935508	0.967				
R935509	0.086				
R935510	0.897				
R935511	1.165				
R935512	2.098				
R935513	0.106				
R935514	1.662				
R935515	2.661				
R935516	2.800				
R935517	0.548				
R935518	2.963				
R935519	0.074				
R935520	0.001				
R935521	0.186				
R935522	1.236				
R935523	0.001				
R935524	0.249				
R935525	1.564				
R935526	9.126				
R935527	0.557				
R935528	3.332				
R935529	0.245				
R935529		9999			
R935531		9999			
R935531	0.871				
R935532		9999			
R935532	0.110				

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935533		9999			
R935533	0.219				
R935534	0.398	5.218			
R940355	99	9999			
R940356	7.21	9999			
R940358	0.03	4.3			
R940361	0.047	2.2	0.06	0.07	0.1
R940363	0.048	9999			
R940364	0.046	9999			
R940365	8888	9999			
R940366	0.037	40	0.03	0.005	0.01
R940367	0.117	14.1			
R940368	0.025	1.58			
R940369	0.023	9999			
R940370 S	0.059	-			
R940371	0.316				
R940372	0.094				
R940373	8888				
R940380	0.042				
R940381	8888				
R940382	0.104				
R940383	0.064				
R940384	1.32				
R940385	0.033				
R940386	3.42				
R940387	1.19				
R940388	0.049				
R940389	0.06				
R940390	9999	9999			
R940391	0.261				
R940392	0.145				
R940393	5.26				

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R940394	16.5353				
R940395	9999				
R940396	22.7164				
R940397	3.7				
R940399	0.051				
R940400	0.103				
R940401	0.125				
R940402	8888				
R945356	1.17	9999			
R945357	9999	9999			
R945358	9999	9999			
R945360	1.37	9999			
R945361	2.36	9999			
R945362	1.57	9999			
R945363	0.687	9999			
R945364	1.002	9999			
R945365	0.257	9999			
R945366	0.112	9999			
R945367		9999	1.29		
R945368		9999	1.71		
R945369		9999	1.27		
R945370	0.522	9999			
R945371	0.713	9999			
R945372		9999	0.923		
R945373	9999				
R945374	9999				
R945375	9999				
R945376	9999				
R945377	1.12				
R945378	0.754				
R945379	9999				
R945380	9999				

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R945381	9999				
R945382	9999				
R945383	0.985				
R945384	0.913				
R945385	1.1				
R945386	1.39				
R945387	1.12				
R945389	0.0748	9999			
R945390	0.118	9999			
R945391	0.094	9999			
R945392	0.085	9999			
R945393	1.34	21.7			
R945394	1.24	5.61			
R945395	1.14	9999			
R945396	2.24				
R945397	0.928				
R945398	7				
R945399	0.163	9999			
R945400	9999				
R945401	8888	9999			
R945402	0.112				
R945403	1.7				
R945404	0.103				
R945405	0.131				
R945406	8888				
R945407	8888				
R945408	9999				
R945409	9999				
R945410	9999				
R945411	2.86				
R945412	0.095				
R945413	1.698				

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R945414	0.038				
R945415	0.046				
R945416	0.053				
R945417	2.52082	9999			
R945418	8888	9999			
R945419	0.125				
R945420	0.436				
R945421	0.371				
R945422	0.092				
R945423	0.145				
R945424	0.188				
R945426	0.256				
R945427	0.279				
R945432	0.049				
R945433	0.276				
R945434	8888				
R945439	8888				
R945440	8888				
R945443	0.081	9999			
R945444	0.043	9999			
R945454	20.6	9999			
R945455	8888	9999			
R945456	8888				
R945457	0.188				
R945458	8888				
R945459	0.038				
R945460	1.184				
R945461	0.803				
R945462	1.722				
R945463	0.722				
R945464	0.943				
R945465	1.960				

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R945466	1.885				
R945467	1.169				
R945470	0.862				
R945471	0.035				
R945472	0.094				
R945473	0.104				
R945474	0.104				
R945475	0.046				
R945476	0.293				
R945477	0.363				
R945478	0.153				
R945479	0.272				
R945480	0.199				
R945485	0.850				
R945486	0.588				
R945491	0.465				
R945492	0.079				
R945493	0.069				
R945498	0.001	9999			
R950405	1.36	9999			
R950406		9999	9999		
R950407		9999	9999		
R950408		9999	4.82		
R950409		9999	3.24		
R950410		9999	9999		
R950411		9999	4		
R950412	0.301				
R950413	9999	9999			
R950414	9999	9999			
R950415	5.19	16.3			
R950416	2.27				
R950417	2.16	9999			

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950418	1.67	9.09			
R950419	3.26	9999			
R950420	0.114	9999			
R950421	0.157	9999			
R950422	0.475	6.53			
R950423	0.05	9999			
R950424	0.236	4.28			
R950425	1.15				
R950426	0.142	30			
R950427	1.9				
R950428	0.123	21			
R950429	3.969				
R950430	0.239				
R950432	2.42				
R950433	9999				
R950434	1.16				
R950436	5.53				
R950437	0.811				
R950438	0.888				
R950439	9999				
R950440	10.47				
R950441	9999				
R950442	9999	9999			
R950443	9999	9999			
R950444	1.73				
R950445	0.379				
R950446	0.148				
R950447	1.41999	9999			
R950448	1.08228	36			
R950449	0.668				
R950450	1.09				
R950451	0.07				

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950452	0.101				
R950453	8888	9999			
R950454	8.6351	9999			
R950455	0.217				
R950456	3.78374	4.4			
R950457	3.08825	9999			
R950458	1.32355	12			
R950459	0.632				
R950460	0.177				
R950461	0.142				
R950462	9999				
R950463	2.46				
R950464	0.244				
R950465	0.351				
R950469	9999	9999			
R950470	16.1729	9999			
R950471	50.5397	9999			
R950472	6.95156	9999			
R950493	1.89				
R950494	9999				
R950495	2.2				
R950496	12.4				
R950497	8888				
R950498	9999				
R950499	0.199				
R950500	1.694				
R950501	0.430				
R950502	2.496				
R950503	2.085				
R950504	1.275				
R950505	9999.000				
R950506	9999.000				

TABLE 1B

Compound	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	BMMC anti-IgE Hexos.	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950507	0.106				
R950508	44.555	9999			
R950509	0.112				
R950510	0.093				
R950511	9999.000				
R950512	6.611				
R950513	7.049				
R950514	0.244				
R950515	0.031				
R950516	0.025				
R950518	1.405				
R950519	6.488				
R950520	0.397	4.513			
R950521	0.145	5.814			
R950522	0.123	9999			
R950523	0.084	7.728			
R950524	0.224	5.963			
R950525	0.292	14.819			

TABLE 2

	High Density									
	CHMC high density hexos	CHMC high density tryptase	CHMC high density histamine	CHMC high density LTC4	CHMC high density TNF-alpha	CHMC high density IL-13	Toxicity Jurkat Light Scat.	Toxicity Jurkat Cell Titer Glo	Toxicity BJAB Light Scat.	Toxicity BJAB Cell Titer Glo
R008951										
R008952										
R008953										
R008955										
R008956										
R008958										
R067934										
R067963										
R070153										
R070791										
R081166										
R088814										
R088815										
R091880										
R092788							9999		9999	
R909241								3.736		
R921219	0.124	0.121	0 162	0.034	0.190	0.175		>10		>10
R925775							9999		9999	
R925778							9999		9999	
R925779							>10		9999	
R925797							>10		9999	

TABLE 2

	High Density									
	CHMC high density hexos	CHMC high density tryptase	CHMC high density histamine	CHMC high density LTC4	CHMC high density TNF-alpha	CHMC high density IL-13	Toxicity Jurkat Light Scat.	Toxicity Jurkat Cell Titer Glo	Toxicity BJAB Light Scat.	Toxicity BJAB Cell Titer Glo
R926108							>10		>10	
R926109	0.783	0.906	1 827	0.808	1.504	1.664	>10		9999	
R926110							>10		>10	
R921218	0.464	0.647	0.463	0.695	1.752	2 0776	>10		>10	
R926113	1.448	1.649	1.848	0.468	5.678	3.569	>10		>10	
R926146							9999		9999	
R926210							>10		9999	
R926240							10		9999	
R926248							>10		9999	
R926249							>10		9999	
R926253							9999		9999	
R926256							>10		9999	
R926258							9999		9999	
R926387							>10		9999	
R926395							>10		9999	
R926396							>10		9999	
R926411							8.5		>10	
R926486	1.088	1.313	1.928	0.834	0.455					
R926488	0.521	0.623	0.792	0.201	2.443	1.012				
R926493	0.889	1.093	1.324	0.474	>2			>4.33		
R926494	0.640	>2	9999	0.326	9999					

TABLE 2

	High Density						Toxicity Jurkat Light Scat.	Toxicity Jurkat Cell Titer Glo	Toxicity BJAB Light Scat.	Toxicity BJAB Cell Titer Glo
	CHMC high density hexos	CHMC high density tryptase	CHMC high density histamine	CHMC high density LTC4	CHMC high density TNF-alpha	CHMC high density IL-13				
R926495	0.100	0.235	0.066	0.241	0.362	0.449		>10		>10
R926496	0.429	0.533	0.809	0.414	0.622					
R926497	1 106	1.234	1.333		1.876	9999				
R926501	>2	>2	9999		9999	9999		>4 33		>4 33
R926502	>2	>2	>2		1.807	>2		1 513		
R926505								4.199		
R926508	0.170	0.434	0.105		0.505	0 763		>10		>10
R926510	0 921	1 115	1.667		0 417	0.686		2.77		
R926511	1.183	1.474	1.73		1.307	>2		>4.33		>4.33
R926614	>10	>10			>10	6.442				
R926696	<1.1	<1.1	<1.1	<1.1	<1.1	1.773		>5.0		
R926699	<1.1	<1.1	1.44	<1 1	<1.1	1.294				
R926700	<1.1	<1.1	<1.1	<1.1	<1.1	2.053				
R926703	1.512	1.947	>2	0.724	>2					
R926704	>2	9999	9999	9999	9999					
R926705	1.007	1.256	0.641	0.494	9999					
R926706	>2	9999	9999	1.491	9999					
R926742	0.104	0.217	0.080		0.385	0.667		9		>10
R926745								>10		>10
R926780								>5.0		
R926782								>4.33		>4 33

TABLE 2

	High Density									
	CHMC high density hexos	CHMC high density tryptase	CHMC high density histamine	CHMC high density LTC4	CHMC high density TNF-alpha	CHMC high density IL-13	Toxicity Jurkat Light Scat.	Toxicity Jurkat Cell Titer Glo	Toxicity BJAB Light Scat.	Toxicity BJAB Cell Titer Glo
R935075	0.647	1.212	0 443	<0.22	>2			>4.33		>4.33
R935154								>4.33		
R935156								4.054		
R940216	<1.1	<1.1	1.176	<1.1	3.188	3 006				
R940233	0 577	0.642	0.586	0.118	2.247	1 781		>4.33		>4.33
R945032	0.357	0.458	0.439	0.0929	1.082	0.291				
R945033	8 151	8 868			>10	5.983				
R945071	<1 1	<1.1	<1.1	<1.1	<1.1	<1.1				
R945128	1.279	1.749	0.547	0.729	>2	ND				
R945140	0.994	1.112	1.551		1.714	9999				
R945142	>2	>2	9999		>2	9999				
R945150								>4.33		>4.33
R921302	0.682	0.795	1.588	0.514	1.173	1.672				
R950141	0.567	0.618	0.627	0.201	1.059	0.798				
R950207								>4.33		

7.7 The 2,4-Pyrimidinediamine Compounds of the Invention Selectively Inhibit the Upstream IgE Receptor Cascade

To confirm that many of the 2,4-pyrimidinediamine compounds of the invention exert their inhibitory activity by blocking or inhibiting the early IgE receptor signal transduction cascade, several of the compounds were tested in cellular assays for ionomycin-induced degranulation, as described below.

7.7.1 CHMC Low Cell Density Ionomycin Activation: Tryptase Assay

Assays for ionomycin-induced mast cell degranulation were carried out as described for the CHMC Low Density IgE Activation assays (Section 7.5.2, *supra*), with the exception that during the 1 hour incubation, 6X ionomycin solution [5mM ionomycin (Signma I-0634) in MeOH (stock) diluted 1:416.7 in MT buffer (2 μM final)] was prepared and cells were stimulated by adding 25 μl of the 6X ionomycin solution to the appropriate plates.

7.7.2 Basophil Ionomycin Activation: Histamine Release Assay

Assays for ionomycin-induced basophil cell degranulation were carried out as described for the Basophil IgE or Dustmite Activation Assay (Section 7.5.5, *supra*), with the exception that following incubation with compound, cells were stimulated with 20 μl of 2 μM ionomycin.

7.7.3 Results

The results of the ionomycin-induced degranulation assays, reported as IC_{50} values (in μM) are provided in TABLE 1, *supra*. Of the active compounds tested (*i.e.*, those that inhibit IgE-induced degranulation), the vast majority do not inhibit ionomycin-induced degranulation, confirming that these active compounds selectively inhibit the early (or upstream) IgE receptor signal transduction cascade.

These results were confirmed for certain compounds by measuring anti-IgE-induced and ionomycin-induced calcium ion flux in CHMC cells. In these Ca^{2+} flux tests, 10 μM R921218 and 10 μM R902420 inhibited anti-IgE-induced Ca^{2+} flux, but had no effect on ionomycin-induced Ca^{2+} flux (See FIG. 4).

7.8 The Inhibitory Effect of the 2,4-Pyrimidinediamine Compounds of the Invention is Immediate

To test the immediacy of their inhibitory effect, certain 2,4-pyrimidinediamines of the invention were added simultaneously with anti-IgE antibody activator in the cellular assays described above. All compounds tested blocked IgE-induced degranulation of CHMC cells to the same extent as observed when the compounds were pre-incubated with CHMC cells for 10 or 30 min. prior to receptor cross-linking.

7.9 Kinetics of Pharmacological Activity *In vitro*

Compounds R921218, R921302, R921219, R926240, R940277, R926742, R926495, R909243 and R926782 were tested in washout experiments. In the experiments, CHMC cells were either activated immediately with anti-IgE antibody in the presence of 1.25 μM compound (time zero), or the compound was washed out followed by activation with anti-IgE antibody at 30, 60 or 120 min. The inhibitory activity of these compounds was greatly diminished 30 min. after compound removal, indicating that constant exposure of mast cells to these compounds is required for maximal inhibition of degranulation The other compounds tested yielded similar results.

7.10 Toxicity: T- and B-Cells

The ability of the compounds of the invention to exert their inhibitory activity without being toxic to cells of the immune system was demonstrated in cellular assays with B- and T-cells. The protocols for the assays are provided below.

7.10.1 Jurkat (T-Cell) Toxicity

Dilute Jurkat cells to $2x10^5$ cells/ml in complete RPMI (10% heat-inactivated fetal bovine serum) media and incubate at 37°C, 5% CO_2 for 18 hours. Add 65 ul cells at 7.7 x 10^5 cells/ml to a 96-well V-bottom plate (TC-treated, Costar) containing 65 ul 2X compound (final vehicle concentration is 0.5% DMSO, 1.5% MeOH). Mix, incubate plates for 18-24 hr at 37°C, 5% CO_2. Toxicity was assessed by flow cytometric analysis of cellular light scatter

7.10.2 BJAB (B-Cell) Toxicity

The B-cell line BJAB was cultured in log phase in RPMI1640 + 10% heat-inactivated fetal bovine serum, 1x L-glutamine, 1x penicillin, 1x streptavidin and 1x beta-mercaptoethanol at 37°C, 5% CO2. First, BJABs were harvested, spun and resuspended in culture medium to a concentration of $7.7x10^5$ cells/mL. 65uL cells were mixed with 65 uL compound, in duplicate and in the presence of 0.1% DMSO in a V-bottomed 96-well tissue culture plate. Cells were incubated with compound at various dilutions at 37°C, 5% CO_2. Toxicity was assessed by flow cytometric analysis of cellular light scatter.

7.10.3 Toxicity: Cell Titer Glo Assay

Seed 50 µl cells ($1x10^6$/ml) into each well containing 50 µl compound. The final vehicle concentration is 0.5% DMSO, 1.5% MeOH. Shake plates for 1 minute to mix cells and compound. Incubate plates at 37°C (5% CO_2) for 18 hours. Next day, harvest 50 µl cells from each well, add to 50 µl Cell Titer Glo reagent (Invitrogen). Shake plates for 1 minute. Read on luminometer.

7.10.4 Results

The results of the T- and B-cell toxicity assays, reported as IC_{50} values (in µM), are presented in TABLE 2, *supra*. With a few exceptions (see TABLE 1), all

compounds tested were non-toxic to both B- and T-cells at effective inhibitory concentrations. Assays performed with primary B-cells yielded similar results.

7.11 The 2,4-Pyrimidine Compounds Are Tolerated In Animals

The ability of the compounds of the invention to exert their inhibitory activity at doeses below those exhibiting toxicity in animals was demonstrated with compounds R921218, R921219 and R921302.

7.11.1 R921218

R921218 was studied in an extensive program of non-clinical safety studies that concluded this agent to be well tolerated in both rodents and non-rodents. To summarize the outcome of toxicology/non-clinical safety testing with R921218; this agent produced no dose limiting toxicity by the intranasal route of administration in non-rodents (rabbits and primates) or by the oral route of administration in rodents (mice and rats) during 14-day repeat-dose toxicity studies at doses many fold above the anticipated dose expected to produce efficacy in man. There were no adverse findings in a core safety pharmacology battery of cardiovascular, respiratory and/or central nervous system function. There was no evidence for mutagenic or clastogenic potential in genetic toxicology testing nor were there untoward effects after exposure to skin and eyes. A short discussion of key toxicology studies is provided.

A 14-day repeat-dose intranasal toxicity study in Cynomolgus monkeys was performed at doses of 2.1, 4.5 or 6.3 mg/kg/day. In life parameters included: clinical observations, body weights, food consumption, ophthalmology, blood pressure, electrocardiography, hematology, clinical chemistry, urinalysis, immunotoxicological assessment, gross necropsy, organ weights, toxicokinetic assessments and histopathology (including the nasal cavity). There were no adverse findings attributed to R921218 in any study parameter and the NOAEL (no observed adverse effect level) was considered 6.3 mg/kg/day.

A 14-day repeat-dose intranasal toxicity study in New Zealand White rabbits was performed at doses of 1.7, 3.4 or 5.0 mg/kg/day. In life parameters included: clinical observations, body weights, food consumption, ophthalmology, hematology, clinical chemistry, gross necropsy, organ weights, toxicokinetic assessments and histopathology (including the nasal cavity). There were no adverse findings attributed to R921218 in any

study parameter and the NOAEL (no observed adverse effect level) was considered 5.0 mg/kg/day.

7.11.2 R921219

In pilot dose finding studies a single dose oral dose of 600 mg/kg was considered a NOEL (no observed effect level) while multiple (7-day) doses of 200 mg/kg/day and above were not tolerated.

In the *in vitro Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay (Ames test), R921219 was found to test positive in tester strain TA1537, with and without metabolic activation, confirming the results of an earlier study. R921219 was not found to adversely affect any of the other 4 tester strains. R921219 was not found to possess clastogenic potential when studied in an *in vitro* chromosomal aberration assay.

7.11.3 R921302

Several non-GLP pilot toxicity studies have been conducted in rodents. In the mouse an oral dose of 1000 mg/kg was tolerated for up to 7-days. In a 14-day oral toxicity study in the mouse was conducted with doses of 100, 300 and 1000 mg/kg. A dose of 1000 mg/kg was not tolerated, while a dose of 300 mg/kg promoted evidence for histopathological changes in the vulva. A dose of 100 mg/kg was considered the NOAEL (no observed adverse effect level) in the study. A 28-day oral toxicity study in the mouse was conducted at doses of 100 mg/kg q.d., 100 mg/kg b.i.d., 300 mg/kg q.d. and 300 mg/kg b.i.d. R921302 was not tolerated at 300 mg/kg q.d. or b.i.d. The lower doses (100 mg/kg q.d. or b.i.d.) appeared to be well tolerated (results of clinical and histopathology are not yet known). In the rat oral doses of 50, 150 and 300 mg/kg given for 32 days appeared to be well tolerated (results of clinical and histopathology are not yet known).

In the *in vitro Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay (Ames test), R921302 was found to test positive in tester strain TA98 with S9 and TA1537, with and without metabolic activation. R921302 was not found to adversely affect any of the other 3 tester strains. R921302 was not clastogenic when assessed in an *in vitro* chromosomal aberration assay.

7.12 The 2,4-Pyrimidinediamine Compounds Are Orally Bioavailable

Over 50 2,4-pyrimidinediamine compounds of the invention were tested for oral bioavailability. For the study, compounds were dissolved in various vehicles (e.g. PEG 400 solution and CMC suspension) for intravenous and oral dosing in the rats. Following administration of the drug, plasma samples were obtained and extracted. The plasma concentrations of the compounds were determined by high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) methods. Pharmacokinetic analyses were performed based on the plasma concentration data. The pharmacokinetic parameters of interest include Clearance (CL), Volume of distribution at steady-state (Vss), terminal half-life ($t_{1/2}$), and oral bioavailability (%F).

These pharmacokinetic studies indicate that many of the 2,4-pyrimidinediamine compounds are orally available, with %F up to approximately 50% (in the range of 0-50%). The half-lives ranged from 0.5 to 3 hr. In particular, Compounds R940350, R935372, R935193, R927050 and R935391 exhibited good oral bioavailabilities and half-lives in rats. Thus, these studies confirm that these 2,4-pyrimidinediamine compounds are suitable for oral administration.

7.13 The Compounds Are Effective for the Treatment of Allergies

The *in vivo* efficacy of compounds R926109, R921218, R921219, R921302, R926495, R926508, R926742, R926745 and R945150 towards allergies was evaluated in the mouse model of passive cutaneous anaphylaxis (PCA). This model provides a direct measure of IgE-induced degranulation of tissue mast cells. In this model, IgE primed animals are exposed to an allergen challenge, and the change in permeability of dermal vasculature that results from histamine release from mast cells is measured by change in the amount of dye leakage into surrounding tissue. Inhibition of mediator release by compounds that modulate mast cell degranulation is easily measured by extracting the dye from the tissue.

7.13.1 Study Protocol and Results

In the PCA assay mice are passively sensitized by intradermal injection with anti-dinitrophenol (DNP) IgE antibodies (Day –1). At predetermined times animals are treated with the test agent (Day 0). The modulatory effect of the agent on cutaneous mast cell degranulation is measured following intravenous injection of DNP conjugated to human

serum albumin (HSA-DNP), together with Evans blue dye. The resulting cross-linking of the IgE receptor and subsequent mast cell degranulation-induced increase in vascular permeability is determined by measuring the amount of dye extravasation into the tissue. Dye is extracted from the tissue by formamide, and the absorbance of this extract is read at 620 nm. The inhibitory effect of drug treatment is reported as the percent inhibition compared to vehicle treatment, that is, the percent reduction in A_{620}.

Two compounds have been tested as positive controls: the histamine antagonist diphenhydramine and the serotonin antagonist cyproheptadine. Both mediators (histamine and serotonin) are released upon IgE-mediated degranulation from the mouse mast cell. Both reference compounds inhibit the PCA response; cyproheptadine was used routinely in subsequent experiements. Cyproheptadine reproducibly inhibited the PCA response by 61% +/- 4% (8 mg/kg, i.p., 30 minutes pretreatment time, n=23 experiments).

7.13.1.1 Results

A dose-dependent inhibition of the FcεR--mediated vascular leakage was observed with increasing doses of R921218, R926109, R921219 and RR921302. These compounds were administered either in a solution formulation (67%PEG/33% citrate buffer) or an aqueous suspension (1.5% Avicel). These results demonstrate the strong correlation between compound plasma levels, in vivo efficacy, and *in vitro* potency. The most potent compound, R921219, was active with circulating exposure levels of approximately 10 μg/ml (68% inhibition at a dose level of 100 mg/kg) compared with R921302, a relatively less potent molecule, which reduced plasma extravasation by 42% at a dose level of 100 mg/kg. Further, the length of exposure to circulating compound was reflected in the duration of inhibitory activity. R921302, determined to be the most metabolically stable compound in pharmacokinetics studie, inhibited the vascular permeability for 1-2 hours prior to antigen-induced receptor signaling, where after the efficacy began to decrease. These data are summarized in TABLE 3 and TABLE 4.

TABLE 3

Efficacy of R921218, R926109, R921219 and R921302 in the PCA Assay

Compound	Route	Vehicle	Pretreatment time (min)	Dose (mg/kg)	% Inhibition	Plasma level (μg/ml)
R921218	PO	67%PEG/33% citrate buffer	10	50	7	3
				100	11	4
				200	50	18
R926109	PO	67%PEG/33% citrate buffer	15	50	22	N.D.
				100	32	
				200	48	
R921219	PO	1.5% Avicel/water	15	30	25	0.4
				100	68	4
				300	92	11
R921302	PO	1.5% Avicel/water	60	50	35	25
				100	42	38
				150	56	64
				200	93	105

TABLE 4

Duration of action of R921219 and R921302 in the PCA Assay

Compound	Route	Vehicle	Dose (mg/kg)	Pretreatment time (min)	% Inhibition	Plasma level (μg/ml)
RR921302	PO	1.5% Avicel/water	200	30	89	88
				60	83	53
				120	82	61
				240	37	8

Similar in vivo activity was observed with compounds R926495, R926508, R926742, R926745 and R926150, which were able to inhibit the PCA response after administration by the oral route in a PEG-based formulation (data not shown).

7.14 The Compounds Are Effective in the Treatment of Asthma

The efficacy of compounds R921218, R921302, R926495, R926508, R926742 and R921219 in the treatment of asthma was demonstrated in the sheep model of allergic asthma. Sheep develop bronchoconstriction within minutes of exposure to inhaled antigen (Ascaris suum), with maximal airflow obstruction during the early allergic response (EAR). Release of preformed mast cell mediators is likely responsible for this early phase of airflow obstruction. In addition to the EAR, the sheep model allows us to evaluate the effect of our compounds on the late asthmatic reaction (LAR) and non-specific airway hyperresponsiveness (AHR), which occur as a result of topical or local administration of allergen to the airway. In the sheep, AHR develops a few hours following antigen challenge, and can persist for up to 2 weeks. The results described below demonstrate the potential of the tested compounds to inhibit a cascade of events that may be a result of release of cytokines from the mast cell.

7.14.1 Study Protocol

In the sheep model of allergic asthma, sheep are administered aerosols of test article *via* an endotracheal tube, followed by an aerosol challenge with antigen extracted from the roundworm, Ascaris suum, to which the sheep are naturally allergic. Allergen challenge leads to direct bronchoconstriction (both EAR and LAR) and a persistent non-specific AHR. These three characteristics are similar to those seen in human allergic asthmatics. The activity of the test agent is determined by changes in the lung resistance (R_L), which is calculated from measurements of transpulmonary pressure, flow, and respiratory volume. The historical control data obtained from the same sheep following saline treatment compared with an allergen challenge show that a sharp increase of R_L occurs during the EAR and persists for approximately 2-3 hours following allergen challenge. The LAR is a less pronounced increase in R_L, which starts approximately 5-6 hours following allergen challenge and is resolved by 8 hours post-challenge. Twenty-four hours after the challenge, a dose response to carbachol is measured to determine the AHR, which is expressed as the dose of carbachol required to increase R_L by 400% over baseline. (This measurement is referred to as the provocative concentration of carbachol that elicits a 400% increase in RL over baseline (PC_{400}). The data are compared to historical control data for the same individual when administered a saline control aerosol and challenged with Ascaris suum.

7.14.2 Result

All the compounds tested showed inhibitory effects in the LAR and the AHR, and several of these agents inhibited the EAR as well. The optimal response for each compound in a series of studies to evaluate activity at several pretreatment times and using several different solution and suspension formulations are shown in TABLE 5. The efficacy of R921218 on the EAR appeared to be dependent on the formulation, with the greatest effect seen at 30 mg/sheep administered as a solution aerosol in 10% ethanol. R926495, R926742, R926508 and R921219, administered in four different sheep at 45 mg/sheep in an aqueous suspension 60 minutes prior to allergen challenge, demonstrate that the LAR and AHR is blocked. In addition to these late parameters, the EAR was greatly reduced by treatment with R921219, R926508 or R926495. The efficacy of RR921302 was investigated using a 45%PEG400/55% citrate buffer vehicle. Under these conditions, R921302, administered at 30 mg/sheep 60 minutes prior to challenge, blocked the LAR and AHR, and EAR was unaffected.

These data clearly demonstrate that these compounds are able to block the asthmatic responses in allergic sheep. All compounds inhibited the AHR and LAR significantly when compared to the historical control. The EAR was significantly inhibited by R921219, R926508 and R926495 (54%, 21% and 33% respectively). In contrast, R921218, R921302 and R926742 failed to inhibit the EAR when administered in an aqueous suspension.

TABLE 5

Efficacy Of Exemplary Compounds In A Sheep Model Of Allergic Asthma

Compound	Dose (mg/sheep)	Pretreatment time (min)	Vehicle	EAR (% inhibition)	LAR (% inhibition)	AHR (% inhibition)
R921218	30	15	10% ethanol	66	78	101
R926742	45	60	Aqueous suspension	-19	87	94
R926495	45	60		33	85	41
R926508	45	60		21	90	88
R921219	45	60		56	75	90
RR921302	30	60	45%PEG400/55% citrate buffer	-28	86	82

7.15 The Compounds Are Effective In The Treatment of Asthma

The efficacy of compounds R921304 and R921219 in the treatment of asthma was also demonstrated in a mouse model of allergic asthma.

7.15.1 Study protocol

Mice are sensitized to ovalbumin (chicken protein) in the presence of an adjuvant (Alum) by the intraperitoneal route on day 0 and day 7. One week later, mice are challenged intranasally with ovalbumin on Days 14, 15 and 16 (more stringent model) or on Day 14 (less stringent model). This sensitization and challenge regimen leads to airway hyperresponsiveness and inflammation in the lungs, which are two dominant characteristics of human allergic asthma. In the mouse model, the in vivo airway responses are measured using a whole body plethysmograph which determines the PENH (enhanced Pause, Buxco Electronics). The PENH is a dimensionless value comprised of the peak inspiratory flow (PIF), peak expiratory flow (PEF), time of inspiration, time of expiration and relaxation time, and is considered a validated parameter of airway responsiveness. Responses to allergen challenge (OVA) are compared with animals challenged with saline only. Twenty-four hours after challenge, mice are exposed to increasing doses of methacholine (muscarinic receptor agonist) which results in smooth muscle contraction. The ovalbumin-challenged mice demonstrate a significant airway hyperresponsiveness to methacholine when compared to the saline challenged mice. In addition, a cellular infiltrate in the airway is observed in ovalbumin challenged mice when compared with the saline challenged mice. This cellular infiltrate is mainly characterized by eosinophils, but a smaller influx of neutrophils and mononuclear cells is also present.

The use of this model for the evaluation of small molecule inhibitors of mast cell degranulation has been validated is several ways. First, using mast cell deficient mice (W/W^v) it has been shown that the ovalbumin-induced responses are dependent upon the presence of mast cells. In the mast cell deficient mice, ovalbumin sensitization and challenge did not result in airway hyperresponsiveness and eosinophil influx. Second, the mast cell stabilizer, Cromolyn, was able to block the ovalbumin-induced airway hyperresponsiveness and inflammation (data not shown). The use of this model to evaluate compounds for the treatment of asthmatic responses that may be mediated by mechanisms other than mast cell stablization, is further supported by the inhibitory effect of the steroids, dexamethasone and budesonide, on methacoline-induced bronchocontriction.

7.15.2 Results

The efficacy of R921304 was evaluated by intranasal administration on 10 consecutive days, from Day 7 through Day 16, at a dose level of 20 mg/kg, with the last 3 doses administered 30 minutes prior to either saline or ovalbumin challenge. R921304 was able to inhibit the ovalbumin-induced airway hyperresponsiveness to methacholine when compared to the vehicle treated mice.

In a less stringent protocol, in which the mice were challenged with ovalbumin only once on Day 14, R921219 administered subcutaneously at 70 mg/kg in 67%PEG400/33% citrate buffer 30 minutes prior to saline or ovalbumin challenge, demonstrates that R921219 completely blocked the ovalbumin-induced airway hyperresponsiveness and cellular influx.

These results clearly demonstrate that R921219 and R921304 are efficacious in inhibiting the airway responses in a mouse model of allergic asthma.

7.16 2,4-Pyrimidinediamine Compounds Inhibit Phosphorylation of Proteins Downstream of Syk kinase in Activated Mast Cells

The inhibitory effect of the 2,4-pyrimidinediamine compounds on the phosphorylation of proteins downstream of Syk kinase was tested with compounds R921218, R218219 and R921304 in IgE receptor-activiated BMMC cells.

For the assay, BMMC cells were incubated in the presence of varying concentrations of test compound (0.08 μM, 0.4 μM, 2 μM and 10 μM) for 1 hr at 37°C. The cells were then stimulated with anti-IgE antibody as previously described. After 10 min, the cells were lysed and the cellular proteins separated by electrophoresis (SDS PAGE).

Following electrophoresis, the phosphorylation of the proteins indicated in FIGS. 7, 10 and 11A-D were assessed by immunoblot. Antibodies were purchased from Cell Signaling Technology, Beverley, MA.

Referring to FIGS. 7, 10 and 11A-D, the indicated compounds tested inhibited phosphorylation of proteins downstream of Syk, but not upstream of Syk, in the IgE receptor signaling cascade, confirming both that the compounds inhibit upstream IgE induced degranulation, and that the compounds exhert their inhibitory activity by inhibiting Syk kinase.

7.17 2,4-Pyrimidinediamine Compounds Inhibit Syk Kinase in Biochemical Assays

Several 2,4-pyrimidinediamine compounds were tested for the ability to inhibit Syk kinase catalyzed phosphorylation of a peptide substrate in a biochemical fluorescenced polarization assay with isolated Syk kinase. In this experiment, Compounds were diluted to 1% DMSO in kinase buffer (20 mM HEPES, pH 7.4, 5 mM $MgCl_2$, 2 mM $MnCl_2$, 1 mM DTT, 0.1 mg/mL acetylated Bovine Gamma Globulin). Compound in 1% DMSO (0.2% DMSO final) was mixed with ATP/substrate solution at room temperature. Syk kinase (Upstate, Lake Placid NY) was added to a final reaction volume of 20 uL, and the reaction was incubated for 30 minutes at room temperature. Final enzyme reaction conditions were 20 mM HEPES, pH 7.4, 5 mM $MgCl_2$, 2 mM $MnCl_2$, 1 mM DTT, 0.1 mg/mL acetylated Bovine Gamma Globulin, 0.125 ng Syk, 4 uM ATP, 2.5 uM peptide substrate (biotin-EQEDEPEGDYEEVLE-CONH2, SynPep Corporation). EDTA (10 mM final)/anti-phosphotyrosine antibody (1X final)/fluorescent phosphopeptide tracer (0.5X final) was added in FP Dilution Buffer to stop the reaction for a total volume of 40 uL according to manufacturer's instructions (PanVera Corporation) The plate was incubated for 30 minutes in the dark at room temperature. Plates were read on a Polarion fluorescence polarization plate reader (Tecan). Data were converted to amount of phosphopeptide present using a calibration curve generated by competition with the phosphopeptide competitor provided in the Tyrosine Kinase Assay Kit, Green (PanVera Corporation).

The results of the assay are shown in TABLE 6, below:

Table 6

Compound	SYK Kinase IC50 (in μM)	Compound	SYK Kinase IC50 (in μM)	Compound	SYK Kinase IC50 (in μM)
R908701	0.022	R927060	0.62	R940376	0.067
R908702	0.038	R927061	0.158	R940380	0.029
R908712	0.024	R927064	0.466	R940381	4999.846
R908952	0.041	R927069	0.111	R940382	0.144
R908953	0.017	R927077	0.602	R940384	9999
R908956	1.178	R927078	0.222	R940386	19.49
R909236	2.071	R927080	0.254	R940387	9999
R921219	0.041	R927082	0.312	R940388	0.268
R909268	0.125	R927083	0.449	R940389	0.053
R909309	0.09	R935138	0.229	R940390	9999
R909317	0.008	R935189	0.354	R945071	0.43

Table 6					
Compound	SYK Kinase IC50 (in μM)	Compound	SYK Kinase IC50 (in μM)	Compound	SYK Kinase IC50 (in μM)
R909321	0.104	R935190	0.047	R945140	0.611
R909322	0.141	R935191	0.045	R945142	2.007
R920410	0.187	R935193	0.11	R945144	0.612
R921218	0.254	R935194	0.169	R945157	1.762
R926242	1.81	R935196	0.266	R921304	0.017
R926252	9999	R935198	0.2	R945299	0.022
R926321	5049	R935202	0.035	R945365	0.465
R926500	0.929	R935237	0.046	R945366	0.059
R926501	0.193	R935293	0.047	R945369	1.85
R926502	0.217	R935302	0.027	R945370	1.05
R926505	0.07	R935304	0.042	R945371	1.3
R926508	0.097	R935307	0.057	R945385	2.12
R926562	9999	R935309	0.098	R945389	0.035
R926594	0.771	R935310	0.206	R945390	0.009
R926715	0.534	R935366	0.38	R945391	0.01
R926742	0.076	R935372	0.205	R945392	0.014
R926745	0.093	R935375	2.8	R945398	0.182
R926753	0.108	R935391	0.223	R945399	0.166
R926757	0.51	R935393	0.45	R945400	17.925
R926763	0.024	R935413	0.195	R945401	0.007
R926780	0.107	R935414	0.152	R945402	0.418
R926782	0.117	R935416	0.196	R945402	0.418
R926791	0.207	R935418	0.558	R945404	9999
R926797	9999	R935431	0.132	R945405	0.168
R926798	9999	R935432	0.05	R945407	9999
R926813	0.405	R935433	0.07	R945412	0.308
R926816	0.062	R935436	0.064	R945413	9999
R926834	0.292	R935437	0.127	R945416	0.515
R926839	0.055	R940233	0.151	R945417	9999
R926891	0.116	R940255	0.771	R945418	9999
R926931	0.255	R940256	3.211	R945419	0.127
R926946	10.218	R940269	0.685	R945422	0.087
R926949	0.076	R940275	0.734	R945423	0.273
R926953	3.05	R940276	0.127	R945424	0.665

Table 6					
Compound	SYK Kinase IC50 (in μM)	Compound	SYK Kinase IC50 (in μM)	Compound	SYK Kinase IC50 (in μM)
R926956	0.38	R940277	0.214	R945426	0.301
R926968	0.235	R940290	0.187	R945427	0.479
R926970	0.057	R940323	0.05	R945432	4444.247
R926971	0.008	R940338	0.028	R945433	0.431
R926975	0.767	R921303	0.003	R945434	9999
R926976	0.421	R940346	0.11	R921302	0.268
R926977	0.007	R940347	0.038	R950349	0.033
R926979	0.013	R940350	0.121	R950367	0.341
R926981	0.01	R940351	0.25	R950368	0.011
R926982	0.028	R940352	0.13	R950373	0.067
R926983	0.012	R940353	0.325	R950428	0.127
R926984	0.459	R940358	0.023	R950430	0.15
R926985	0.203	R940361	0.069	R950431	9999
R926989	0.228	R940363	0.006	R950440	9999
R927016	0.954	R940364	0.001	R950466	1.81
R927017	2.351	R940366	0.003	R950467	9999
R927020	9999	R940367	0.013	R950468	9999
R927042	0.051	R940368	0.001	R950473	19.49
R927048	0.002	R940369	0.043	R950474	9999
R927049	0.004	R940370	0.069	R950475	9999
R927050	0.114	R940371	3.643	R950476	9999
R927051	0.01	R940372	0.253	R940376	0.067
R927056	0.473	R940373	9999	R940380	0.029

These data demonstrate that all of the compounds tested, except for R945142 and R909236 inhibit Syk kinase phosphorylation with IC_{50}s in the submicromolar range. All compounds tested inhibit Syk kinase phosphorylation with IC_{50}s in the micromolar range.

7.18 The Compounds Are Effective for the Treatment of Autoimmunity

The *in vivo* efficacy of certain 2,4-pyrimidinediamine compounds towards autoimmune diseases was evaluated in the reverse passive Arthus reaction, an acute model of antigen-antibody mediated tissue injury, and in several disease models of autoimmunity and inflammation. These models are similar in that antibody to a specific antigen mediates

immune complex-triggered (IC-triggered) inflammatory disease and subsequent tissue destruction. IC deposition at specific anatomic sites (central nervous system (CNS) for experimental autoimmune encephalomyelitis (EAE) and synovium for collagen-induced arthritis (CIA)) leads to activation of cells expressing surface FcγR and FcεR, notably mast cells, macrophages, and neutrophils, which results in cytokine release, and neutrophil chemotaxis. Activation of the inflammatory response is responsible for downstream effector responses, including edema, hemorrhage, neutrophil infiltration, and release of pro-inflammatory mediators. The consequences of these IC-triggered events are difficult to identify in autoimmune disorders; nonetheless, many investigators have demonstrated that inhibition of the FcγR signaling pathway in these animal models has resulted in a significant reduction in disease onset and severity.

7.18.1 The Compounds Are Effective In Mouse Arthus Reaction

The in vivo efficacy of compounds R921302, R926891, R940323, R940347, and R921303 to inhibit the IC-triggered inflammatory cascade was demonstrated in a mouse model of Reverse Passive Arthus Reaction (RPA reaction).

7.18.1.1 Model

Immune complex (IC)-mediated acute inflammatory tissue injury is implicated in a variety of human autoimmune diseases, including vasculitis syndrome, sick serum syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, Goodpasture's syndrome, and glomerulonephritis. The classical experimental model for IC-mediated tissue injury is the reverse passive Arthus reaction. The RPA reaction model is a convenient *in vivo* method to study localized inflammation, induced by ICs, without systemic effects. Intradermal injection of antibodies (Abs) specific to chicken egg albumin (rabbit anti-OVA IgG), followed by intravenous (IV) injection of antigens (Ags), specifically chicken egg albumin (ovalbumin, OVA), causes perivascular deposition of ICs and a rapid inflammatory response characterized by edema, neutrophil infiltration and hemorrhage at the injection sites. Aspects of the mouse RPA reaction model resemble the inflammatory response of patients with rheumatoid arthritis, SLE and glomerulonephritis.

7.18.1.2 Study Protocol

In this model system, test compounds are administered at several timepoints prior to administration of Abs and Ags. A solution of rabbit anti-OVA IgG (50μg in 25μl/mouse) is

injected intradermally, and immediately following is an intravenous injection of chicken egg albumin (20 mg/kg of body weight) in a solution containing 1% Evans blue dye. The degree of edema and hemorrhage is measured in the dorsal skin of C57BL/6 mice using the Evan's Blue dye as an indicator of local tissue damage. Purified polyclonal rabbit IgG is used as a control.

Pretreatment time, in which the test compounds are administered prior to Ab/Ag challenge, depends on the pharmacokinetic (PK) properties of each individual compound. Four hours after induction of Arthus reaction, mice are euthanized, and tissues are harvested for assessment of edema. This model system allows us to rapidly screen the in vivo activity of many inhibitors.

7.18.1.3 Results

All compounds tested were administered by the oral route.

R921302, when administered at a dose level of 50 mg/kg, 100 mg/kg, and 200 mg/kg 60 minutes prior to Ab/Ag challenge in C57Bl6 mice, showed dose-dependent inhibition of edema formation (49.9 %, 93.2 %, and 99.1 %, respectively). Furthermore, R921302 showed not only a prophylactic inhibition of edema, but also therapeutic efficacy in which the edema was inhibited by 77.5% when the compound was administered 30 minutes post-challenge at a dose level of 100 mg/kg.

R940323 and R926891 showed the efficacy of edema inhibition by 32.4% and 54.9%, respectively, when administered at 200 mg/kg, 60 minutes prior to challenge. These compounds are much less bioavailable when administered orally, and systemic exposure levels were approximately 50-fold less that that seen with R921302 (data not shown). R940347 inhibited edema by 89% when administered at a dose level of 100 mg/kg, 2 hours prior to challenge.

Compound R921303 showed 100%, 100%, and 93.6%, inhibition of edema formation when administered at a dose level of 200 mg/kg and a pretreatment time of 30, 60, and 120 minutes, respectively). The compound also demonstrated a dose-dependent inhibition of 65.4%, 81.2% and 100%, at doses of 50 mg/kg, 100 mg/kg and 200 mg/kg, respectively. Results for the compounds tested are summarized in Table 7.

Table 7				
			% inhibition to vehicle control	Plasma Concentration ± SEM (ng/ml)
Compound Name	Dosage (mg/kg)	Pretreatment Time (hrs)	Edema Size ± SEM	Exposure = Pretreatment Time + 4 hours
R921302	100	0.5	89.44 ± 4.8	25200 ± 3910
	100	1	82.1 ± 10.9	N/A
	50	1	50.0 ± 6.4	1149 ± 172
	100	1	92.3 ± 4.2	2072 ± 447
	200	1	99.1 ± 0.9	4789 ± 1182
R940323	200	0.5	5.5 ± 9.3	2333 ± 618
		1	32.4 ± 13.0	878 ± 235
		2	26.9 ± 11.2	892 ± 434
R926891	200	0.5	44.8 ± 3.0	163 ± 70
		1	46.2 ± 4.1	37.2 ± 8
		1.5	28.1 ± 10.6	58.6 ± 19
R921303	200	0.5	100 ± 0	3703 ± 785
		1	100 ± 0	2653 ± 833
		2	93.3 ± 4.4	2678 ± 496
	50	1	64.1 ± 13.3	430 ± 115
	100	1	80.5 ± 9.8	983 ± 180
	200	1	100 ± 0	2361 ± 1224
R935372	100	0.5	-0.6 ± 6.2	0.6 ± 1
		1	23.5 ± 7.4	4.2 ± 4
		2	-4.4 ± 17.7	52.65 ± 39
R920410	100	1	42.6 ± 15.1	1216 ± 239
R927050	100	0.5	-0.3 ± 6.6	619 ± 130
		1	14.9 ± 20.5	837 ± 104
		2	64.0 ± 8.9	557 ± 78
R940350	100	0.5	-15.6 ± 27.2	176 ± 58
		1	53.2 ± 15.1	129 ± 55
		2	38.9 ± 24.3	96 ± 28
R940347	100	0.5	36.7 ± 22.4	1596 ± 485
		1	48.2 ± 5.7	3014 ± 590

Table 7				
			% inhibition to vehicle control	Plasma Concentration ± SEM (ng/ml)
Compound Name	Dosage (mg/kg)	Pretreatment Time (hrs)	Edema Size ± SEM	Exposure = Pretreatment Time + 4 hours
		2	88.9 ± 9.1	1992 ± 247
R940363	100	0.5	-16.4 ± 10.9	32 ± 10
		1	67.6 ± 12.1	42 ± 5
		2	52.3 ± 22.7	37 ± 18
R927050	100	1	7 ± 19	1018 ± 189
R927070	50	1	56 ± 15	1755 ± 310
	100	1	61 ± 14	2851 ± 712
R940363	100	1	61 ± 8	625 ±60
R935429	100	1	85 ± 5	401 ± 96
R927070	50	1.5	31.1 ±17.29	1077 ± 296
	100	1.5	55.5 ± 7.7	4095 ± 1187
R935429	50	1.5	-5.1 ± 14.9	164 ± 89
	100	1.5	67.1 ± 13.8	206 ± 115
R935429	100	0	-2.8 ± 14.8	NA
	100	1	34.08 ± 7.9	NA
	100	2	55.5 ± 7.9	NA
	100	4	35.0 ± 11.4	NA
R927087	50	1.5	-10.4 ± 14.4	26.9 ± 8.0
	100	1.5	28.7 ± 16.6	28.7 ± 10.8
R935451	50	1.5	74.9 ± 7.5	385.0 ± 149.4
	100	1.5	77.1 ± 8.0	1459.0 ± 444.4
R935451	10	1.5	-14.4 ± 13.3	14.4 ± 1.8
	30	1.5	-30.6 ± 15.4	78.0 ± 32.0
R940388	100	1.5	75.0 ± 6.2	44.2 ± 8.9
R921302	50	1	49.9	1.1
	100	1	93.2	2.1
	200	1	99.1	4.8
R940323	200	1	32.4	0.9
R926891	200	1	54.9	0.04
R940347	100	1	48	nd*

Table 7				
			% inhibition to vehicle control	Plasma Concentration ± SEM (ng/ml)
Compound Name	Dosage (mg/kg)	Pretreatment Time (hrs)	Edema Size ± SEM	Exposure = Pretreatment Time + 4 hours
	100	2	89	nd
R921303	50	1	65.4	0.4
	100	1	81.2	0.98
	200	1	100	2.4

*nd=not determined

7.18.2 The Compounds are effective in Mouse Collagen Antibody Induced Arthritis Model

The in vivo efficacy of compound R921302 towards autoimmune diseases was demonstrated a mouse model of collagen antibody-induced arthritis (CAIA).

7.18.2.1 Model

Collagen-induced arthritis (CIA) in rodents is frequently used as one of the experimental models for IC-mediated tissue injury. Administration of type II collagen into mice or rats results in an immune reaction that characteristically involves inflammatory destruction of cartilage and bone of the distal joints with concomitant swelling of surrounding tissues. CIA is commonly used to evaluate compounds that might be of potential use as drugs for treatment of rheumatoid arthritis and other chronic inflammatory conditions.

In recent years, a new technique emerged in CIA modeling, in which the anti-type II collagen antibodies are applied to induce an antibody-mediated CIA. The advantages of the method are: Short time for induction of disease (developing within 24-48 hrs after an intravenous (IV) injection of antibodies); arthritis is inducible in both CIA-susceptible and CIA-resistant mouse strains; and the procedure is ideal for rapid screening of anti-inflammatory therapeutic agents.

Arthrogen-CIA® Arthritis-inducing Monoclonal Antibody Cocktail (Chemicon International Inc.) is administered intravenously to Balb/c mice (2mg/mouse) on Day 0.

Forty-eight hours later, 100 μl of LPS (25μg) is injected intraperitoneally. On Day 4, toes may appear swollen. By Day 5, one or two paws (particular the hind legs) begin to appear red and swollen. On Day 6, and thereafter, red and swollen paws will remain for at least 1-2 weeks. During the study, the clinical signs of inflammation are scored to evaluate the intensity of edema in the paws. The severity of arthritis is recorded as the sum score of both hind paws for each animal (possible maximum score of 8). The degree of inflammation with involved paws is evaluated by measurement of diameter of the paws. Body weight changes are monitored.

Animals are treated at the time of induction of arthritis, beginning on Day 0. Test compounds and control compounds are administered once a day (q.d.) or twice a day (b.i.d.), via per os (PO), depending on previously established PK profiles.

At the end of the study (1-2 weeks after induction of arthritis), mice are euthanized and the paws are transected at the distal tibia using a guillotine and weighed. The mean ± standard error of the mean (SEM) for each group is determined each day from individual animal clinical scores, and hind paw weights for each experimental group are calculated and recorded at study termination. Histopathological evaluation of paws are obtained.

7.18.2.2 Results

Administration of R921302 significantly suppressed the development of arthritis and the severity of the disease ($p<0.005$), as shown by the changes in mean daily arthritis clinical scores (FIG. 12). The mean daily arthritic scores, from day 4 to 14, in treatment group were reduced between 71 to 92 % comparing to that of vehicle control group. The degree of paw inflammation, by measurement of the paw weight, was reduced in animals treated with R921302 compared with the vehicle control group (FIG. 13). At the end of study, the degree of swelling was evaluated by measuring the weight of paws, which is indicated by a 99.9 % reduction in group treated with R921302 compared with mean paw weight of the vehicle control group ($p<0.002$).

Histopathological evaluation of the resected paws revealed a marked synovitis consistent with CIA. Marked lesions were noted in animals treated with saline or vehicle; while lesions of lesser severity were found in R921302 treatment group. The joints were thickened with marked proliferation of the synovium. There is an increase in fibroblasts with a dense infiltration of neutrophils, lymphocytes, monocytes, macrophages and plasma cells. There is vascular proliferation with congestion, hemorrhage and edema. Pannus

formation was present in the joint space and there was cartilage destruction. In drug treated group, the joints were close to normal or showed limited inflammation but without cartilage involvement.

Table 8. Group Average Histopathological Score (0-15)

Treatment	Average total score ± SD
Saline control	9.8 ± 2.1
Vehicle control	9.3 ± 4.5
R921302 (100 mg/kg), twice daily	5.1 ± 1.9
Naive	0.0 ± 0.0

Arthritic clinical scores and paw edema were reduced by an average of 20% in animals treated with R050 twice daily at a dose level of 100 mg/kg compared with untreated control (vehicle, $p = 0.1$). Paw edema was inhibited by approximately 26% compared with untreated control (vehicle), by measurement of hind paw thickness ($p = 0.1$). R050 did not exhibit arthritis at a dose level of 30 mg/kg.

R070, a salt form of R050, administered at dose levels of 50 or 100 mg/kg twice daily inhibited clinical disease by an average of 39.75 % ($p < 0.0002$) or 35.28% ($p < 0.0004$) inhibition, respectively, compared with untreated control (vehicle). Paw thickness was reduced by approximately 50%.

R429, salt of R363, administered twice daily at 50 or 100 mg/kg showed an average of 23.81 % ($p < 0.05$) or 20.82 % ($p = 0.05$) inhibition of arthritic clinical scores, respectively, compared with untreated control (vehicle). Likewise, paw thickness was reduced.

R347 did not affect arthritic scores at the dose levels tested (30 and100 mg/kg twice daily).

7.18.3 The Compounds Are Effective In Rat Collagen-Induced Arthritis

The in vivo efficacy of compound R921302 towards autoimmune diseases was demonstrated in a rat model of collagen-induced arthritis (CIA).

7.18.3.1 Model Description

Rheumatoid arthritis (RA) is characterized by chronic joint inflammation eventually leading to irreversible cartilage destruction. IgG-containing IC are abundant in the synovial tissue of patients with RA. While it is still debated what role these complexes play in the etiology and pathology of the disease, IC communicate with the hematopoetic cells via the FcγR.

CIA is a widely accepted animal model of RA that results in chronic inflammatory synovitis characterized by pannus formation and joint degradation. In this model, intradermal immunization with native type II collagen, emulsified with incomplete Freund's adjuvant, results in an inflammatory polyarthritis within 10 or 11 days and subsequent joint destruction in 3 to 4 weeks.

7.18.3.2 Study Protocol

Syngeneic LOU rats were immunized with native type II collagen on Day 0, and efficacy of R921302 was evaluated in a prevention regimen and a treatment regimen. In the prevention protocol, either vehicle or various doses of R921302 were administered via oral gavage starting on day of immunization (Day 0). In the treatment protocol, after clinical signs of arthritis developed on Day 10, treatment with R921302 was initiated (300 mg/kg by oral gavage, qd) and continued until sacrifice on Day 28. In both protocols, clinical scores were obtained daily, and body weights are measured twice weekly. At Day 28, radiographic scores were obtained, and serum levels of collagen II antibody were measured by ELISA.

7.18.3.3 Results

By 10 days after immunization, rats developed clinical CIA, as evidenced by an increase in their arthritis scores (FIG. 14). The mean arthritic score gradually increased in the rats treated with vehicle alone after Day 10, and by Day 28 the mean clinical score reached 6.75 ± 0.57. Mean clinical scores in animals treated from the day of immunization (Day 0) with the high dose of R921302 (300 mg/kg/day) were significantly reduced ($p<0.01$) on Days 10-28 compared with vehicle controls. In the rats treated with 300 mg/kg R921302 at disease onset, there was a significantly lower arthritis score beginning on Day 16, and this difference was observed until the end of the study on Day 28. Blinded radiographic scores (scale 0-6) obtained on Day 28 of CIA were 4.8 ± 0.056 in the vehicle

group compared with 2.5 ± 0.0.16, 2.4 ± 0.006, and 0.13 ± 0.000001 in animals treated once daily with 75, 150, and 300 mg/kg/day, respectively, in a prevention regimen, and 0.45 ± .031 in animals treated once daily with 300 mg/kg/day at onset of disease. R921302 treatment at 300 mg/kg/day, either prophylactically (at immunization) or after disease onset precluded the development of erosions and reduced soft tissue swelling. Similarly, R921302 treatment resulted in marked reduction of serum anti-collagen II antibody (data not shown).

7.18.4 The Compounds Are Effective In Mouse Experimental Autoimmune Encephalomyelitis

The in vivo efficacy of compound R921302 towards autoimmune diseases was demonstrated in a mouse model of experimental autoimmune encephalomyelitis (EAE)

7.18.4.1 Model Description

EAE is a useful model for multiple sclerosis (MS), an autoimmune disease of the CNS that is caused by immune-cell infiltration of the CNS white matter. Inflammation and subsequent destruction of myelin cause progressive paralysis. Like the human disease, EAE is associated with peripheral activation of T cells autoreactive with myelin proteins, such as myelin basic protein (MBP), proteolipid protein (PLP), or myelin oligodendrocyte protein (MOG). Activated neuroantigen-specific T cells pass the blood-brain barrier, leading to focal mononuclear cell infiltration and demyelination. EAE can be induced in susceptible mouse strains by immunization with myelin-specific proteins in combination with adjuvant. In the SJL mouse model used in these studies, hind limb and tail paralysis is apparent by Day 10 after immunization, the peak of disease severity is observed between Days 10 and 14, and a cycle of partial spontaneous remission followed by relapse can be observed up to Day 35. The results described below demonstrate the potential of the test agent (R921302) to suppress disease severity and prevent relapse of disease symptoms that may be the result of FcγR-mediated cytokine release from immune cells.

7.18.4.2 Study Protocol

In the SJL murine model of EAE, each mouse is sensitized with PLP/CFA. (150 μg PLP139-151 with 200 μg CFA in 0.05 ml of homogenate on four sites of hind flank for a total of 0.2 ml emulsion is used to induce EAE). In a suppression protocol, either vehicle or various doses of R921302 are administered via oral gavage starting on the day of

immunization (Day 0). In a treatment protocol, at onset of disease, animals are separated to achieve groups with a similar mean clinical score at onset and administered vehicle or various dose frequencies of test articles via oral gavage. In both protocols, clinical scores are monitored daily, and body weights are measured twice weekly.

7.18.4.3 Results

By 10 days after PLP immunization, SJL mice developed clinical EAE, as evidenced by an increase in their mean clinical scores (FIG. 15). The paralytic score gradually increased in the animals treated with vehicle only from the day of immunization (Day 0), and by Day 14 the mean score reached a peak of 5.1 + 0.3. At disease peak (Day 14), the mean clinical score in animals treated with either 100 mg/kg daily or 100 mg/kg twice daily was significantly reduced ($p < 0.05$, 4.3 + 1.3 and 4.3 + 1.4, respectively). By Day 16, all animals exhibited a partial remission of mean clinical severity, which is a characteristic of the SJL model. The markedly lower clinical scores in animals treated twice daily with 100 mg/kg R921302 remained significant ($p < 0.05$) throughout the experiment until the animals were sacrificed on Day 30. These lower scores throughout the treatment period are reflected in the significantly lower cumulative disease index (CDI) and increase in cumulative weight index (CWI) as seen in Table 9. In the group treated with vehicle only, 2/5 of the mice relapsed. In the 100 mg/kg/day group, 3/8 of the mice relapsed. None of the mice in the 100 mg/kg twice daily group relapsed.

TABLE 9

SJL female mice treated with Rigel compound R921302 starting on day of immunization with 150 μg PLP 139-151/200 μg MTB (CFA)

	Incidence	Onset	Peak	Mortality	CDI	CWI
Placebo Control	10/10	11.8 ± 0.5	5.1 ± 0.3	1/10[a]	53.2 ± 7.1	118.1 ± 6.4
100 mg/kg 1x/day	10/10	12.3 ± 0.7	4.3 ± 1.3	0/10	44.1 ± 14.5	124.4± 6.0
100 mg/kg 2x/day	10/10	13.0 ± 1.2[b]	4.3 ± 1.4	3/10[a]	33.7 ± 11.4[b]	133.5 ± 6.8[b]

CDI = Cumulative Disease Index to day +26
CWI= Cumulative Weight Index to day +23
a= Mortality due to non-EAE, feeding related injuries or sacrificed hydrocephalic animals.
b= Significant difference between Control vs. Experimental groups ($p < 0.05$) determined via Students two-tailed t test.

SJL mice treated with R921302 at disease onset (Day 11) at a dose level of 200 mg/kg twice daily showed a significant decrease ($p = 0.003$) in CDI (53.5 ± 16.9 in animals treated with R921302 compared with 72.9 ± 8.9 in the animals treated with vehicle alone). Further, there was a dramatic decrease in the number of relapses in animals treated with R921302 (2/12) compared with the number of relapses in animals treated with vehicle (7/11). Results are summarized in Table 10 and FIG. 16.

TABLE 10

SJL female mice treated with Rigel compound R921302 starting on day of onset

	Incidence	Mean score at treatment	Peak	Mortality	Relapses	CDI
Control	11/11	3.9 ± 1.6	5.0 ± 0.4	0/11	7/11	72.9 ± 8.9
200 mg/kg 2x/day	12/12	3.4 ± 1.6	4.3 ± 0.7	1/12	2/12	53.5 ± 16.9
P value	1.00	0.48	0.02	0.97	0.055	0.003

CDI = Cumulative Disease Index to day +27

7.18.5 The 2,4-Pyrimidinediamine Compounds of the Invention Inhibit T-Cell Activation

7.18.5.1 Description

The ability of the 2,4-pyrimidinediamine compounds of the invention to inhibit activation of T-Cells was shown using a variety of assays utilizing a Jurkat T-cell cell line and Primary T-cell cultures. Inhibition of activation of Jurkat T-cells in response to T-cell receptor (TCR) stimulation was measured by quantifying the upregulation of the cell surface marker CD69. Inhibition of primary T-cell activation was measured by quantifying the release of cytokines, including tumor necrosis factor alpha (TNF), interleukin 2 (IL-2), interleukin 4 (IL-4) interferon gamma (IFNg) and granulocyte macrophage colony stimulating factor (GMSCF), in response to TCR/CD28 co-stimulation.

7.18.5.2 Screening for Inhibition of Jurkat T-Cell Activation

Human Jurkat T-cells (clone N) were routinely cultured in RPMI 1640 medium (Mediatech) supplemented with 10% fetal calf serum (FBS) (Hyclone), penicillin and streptamycin. The screening process took place over three days.

On the first day of the screen, cultured cells were spun down on a centrifuge (1000 rpm, 5 minutes) and resuspended at 3.0 X 10^5 cells/ml in RPMI + 5% FBS. On the second day of the screen, cells were spun down at 1000 rpm for 5 minutes and resuspended in RPMI + 5% FBS at 1.3 X 10^5 cells/ml. 85 µl of this cell suspension were added to the wells of U-bottom 96 well plates (Corning). 85µl of compound or diluted RPMI + 5% FBS (as a control) only was added to each well and incubated at 37° C for 1 hour. The cells were then stimulated with anti-TCR (C305) at: 500 ng/ml by adding a 8X solution in 25 µl to the plated cells. The cells were then incubated at 37°C for 20 hrs.

On the third day of the screen, the plates were spun at 2500 RPM for 1 minute on a Beckman GS-6R centrifuge, and the medium was then removed. 50 µl staining solution (1:100 dilution of anti-CD69-APC antibody (Becton Dickenson) in PBS + 2% FBS) was then added to each well, followed by incubation of the plates 4 degrees for 20 minutes in the dark. 150 µl of wash buffer (PBS + 2% FBS) was then added to each well, and the plates

were spun at 3000 RPM for 1 minute. The supernatant wase again removed, and the pellet was resuspended by vortexing gently. 75 µl of PBS + 2% FBS + Cytofix (1:4 dilution) was then added, the plates gently vortexed and wrap in aluminum foil. Cells from the plates were read using a flow cytometer coupled to an automated liquid handling system.

Varied concentrations of compound were compared to solvent only to determine the inhibition of T-cell activation IC_{50} of each compound. Representative IC_{50}s for 2,4-pyrimidinediamine compounds of the invention are shown in Table 11.

7.18.5.3 Isolation of Primary T-Cells

2E8-4E8 PBMC or proliferating T cells grown in rIL-2 from healthy human donors were suspended in PBS were spun down (1500 rpm, 8-10 minutes) and resuspended in 100 ml RPMI Complete media (1% Pen-Strep, 1% L-Glutamine, 10 mM HEPES). The cells were plated in T175 flasks (37°C, 5% CO_2) and monocytes were allowed to adhere for 2-3 hours. After monocyte attachment, non-adherent cells were harvested, counted by hemocytometer, washed several times with PBS then resuspended in Yssels Complete Media (Modified IMDM Media with 1% Human AB Serum, 1% Pen-Strep, 1% L-Glutamine, 10 mM HEPES) at 1.5 4E6 cells/mL. 90 uL of the cell dilution were then added to compounds diluted to 2X in Yssel's media and incubated for 30 minutes at 37°C (5% CO_2). After this preincubation step the compound/cell mixture was transferred to stimulation plates, as described below.

7.18.5.4 Screening for Inhibition of Cytokine Production in Stimulated Primary T-Cell

Stimulation plates were prepared by coating 96 well plates with 5 µg/ml αCD3 (BD PharMingen, Catalog# 555336) + 10 µg/ml αCD28 (Beckman Coulter, Catalog# IM1376) in PBS (no Ca^{2+}/Mg^{2+}) at 37°C (5% CO_2) for at 3-5 hours. After incubation with the stimulation antibodies, the cocktail was removed and the plates washed 3 times with PBS prior to addition of the primary T cell/compound mixture.

The compound/cell mixture was transferred to the stimulation plates and incubated for 18 hr at 37°C (5% CO_2). After the cell stimulation, ~150 µl supernatant were transferred from each well into 96-well filter plates (Corning PVDF Filter Plates) spun

down (2000 rpm, 2-3 minutes) and either used immediately for ELISA or LUMINEX measurements or frozen down at -80°C for future use.

IL-2 ELISAs were performed using the Quantikine Human IL-2 ELISA kit (R&D Systems, Catalog# D2050) as described by the manufacturer and absorption was measured on a spectrophotometer at 450 nm wavelength. Blank values were substracted and absorbances were converted to pg/mL based on the standard curve.

Luminex immunoassay multiplexing for TNF, IL-2, GMSCF, IL-4 and IFNg was performed essentially as described by the manufacturer (Upstate Biotechnology). Essentially 50 uL of sample was diluted into 50 uL assay diluent and 50 uL incubation buffer, then incubated with 100uL of the diluted detection antibody for 1 hr at RT in the dark. The filter plate was washed 2x in Wash Buffer, then incubated with 100 uL of the diluted secondary reagent (SAV-RPE) for 30 min at RT in the dark. Finally the plates were washed 3 times and bead identification and RPE fluorescent measured by the Luminex instrument.

Varied concentrations of compound were compared to solvent only to determine the inhibition of T-cell activation IC_{50} of each compound. Representative IC_{50}s for 2,4-pyrimidinediamine compounds of the invention are shown in Table 11.

7.18.6 The 2,4-Pyrimidinediamine Compounds of the Invention Inhibit B-Cell Activation

7.18.6.1 Description

The ability of the 2,4-pyrimidinediamine compounds of the invention to inhibit activation of B-cells was shown using primary B-cells in a cell surface marker assay using a fluorescence activated cell sorter (FACS). Inhibition of activation of primary B-cells in response to B-cell receptor (BCR) stimulation was measured by quantifying the upregulation of the cell surface marker CD69.

7.18.6.2 Isolation of Primary B-Cells

Primary human B-cells were isolated from buffy coat, the white cell layer that forms between the red cells and the platelets when anti-coagulated blood is centrifuged, or from fresh blood

using CD19-Dynal® beads and a FACS. Buffy coat was obtained from the Stanford Medical School Blood Centre, prepared on the same day by the blood bank, stored and transported cold (with ice). The buffy coat (approx 35 mL) was placed in a 500 mL conical sterile centrifuge pot and cooled on ice, then diluted with cold PBS containing 0.2% BSA (Sigma: A7638) and sodium citrate (0.1%, Sigma: S-5570) (P-B-C) to a total volume of 200mL and mixed gently. Fresh blood was collected from donors in 10 mL vacutainers containing heparin (1 vacutainer collects approximately 8.5mL blood). The blood was cooled on ice, transferred into 50mL falcon tubes (20 mL/tube) or a 500 mL conical sterile centrifuge pot, and diluted with an equal volume P-B-C.

25mL diluted blood or buffy coat was layered onto 15 mL cold ficoll and placed back on ice. The ficoll layered blood was centrifuged (Beckman GS-6R) for 45 minutes at 2000 rpm, 4°C to separate the Peripheral Blood Mononuclear Cells (PBMC) from the Red Blood Cells (RBC) and granulocytes. The top aqueous layer was then aspirated until 1 inch above the PBMC layer. The PBMCs were transferred from every 2 ficoll tubes into one clean 50 mL falcon tube (=approx 10mL/tube). The transferred PBMCs were diluted 5x with icecold PBS with 0.2% BSA (P-B) and centrifuged for 20 min at 1400 rpm and 4°C. The supernatant (this may be cloudy) was then aspirated and the PBMCs resuspended into 25 mL P-B and the cells counted (using a 1:5 dilution) and kept on ice.

The cells were then positively selected using anti-CD19 antibody coupled to magnetic beads (Dynal®) as per manufacturer's instructions. The approximate required amount of CD19-Dynal® beads (CD19-coated dyna beads M-450 (pabB), Dynal®) was calculated by estimating the number of B-cells as 5% of PBMCs counted and adding approximately10 beads per cell from the bead stock ($4x10^8$ beads/mL). The CD19-Dynal® beads were washed 2x in P-B in a 5 mL tube using the Dynal® magnet, then added into the suspended PBMCs. This mixture was then passed through the Dynal® magnet and washed several times to separate the bead-bound cells.

7.18.6.3 Screening Compounds for Inhibition of B-cell Activation

After separation, the beads and antibody were removed using Dynal® CD19-DETACHaBEAD® for 45 min at 30°C. Yield is typically $2X10^7$ B-cells per buffy coat. B-

cells were washed and resuspended as 1E6 cells/mL in RPMI1640+10%FBS+ Penicillin/Streptavidin+ 1 ng/mL IFNα8. Cells were rested overnight at 37°C and 5% CO_2.

The following day, cells were washed and resuspended in RPMI+2.5% FBS to $1X10^6$ cells/mL. Cells were then aliquoted into a V-bottom 96-well plate (Corning) at 65 uL cells per well. By robot, 65uL of a 2x compound was added to the cells with final concentration of DMSO at 0.2%, and incubated for 1 hr at 37°C. Cells were then stimulated with 20 uL 7.5x α-IgM from Jackson laboratories (final 5 ug/mL) for 24 hrs. At day 3, the cells were spun down and stained for CD69 and analyzed by FACS gated on the live cells (by light scatter).

Varied concentrations of compound were compared to solvent only to determine the inhibition of B-cell activation IC_{50} of each compound. Representative IC_{50}s for 2,4-pyrimidinediamine compounds of the invention are shown in Table 11.

7.18.7 The 2,4-Pyrimidinediamine Compounds of the Invention Inhibit Macrophage Activation

7.18.7.1 Description

The ability of the 2,4-pyrimidinediamine compounds of the invention to inhibit activation of differentiated macrophages was shown by measuring the release of cytokines from stimulated macrophages. Release of tumor necrosis factor alpha (TNF) and interleukin 6 (IL-6) was quantified in response to IgG or LPS stimulation.

7.18.7.2 Purification and Culture of Human Macrophages

CD14+ monocytes were purified from from PBMC (Allcells # PB002) using the Monocyte Isolation kit (Miltenyi biotec #130-045-501) as per the manufacturer's instructions. Purity was assessed by measuring the percentage of CD14+ cells by flow cytometry. Typically > 90% purity is achieved. The purified CD14+ cells are then plated out ($6x10^6$.cells/150 cm TC dish in 15mls media) in Macrophage-SFM (Gibco #12065-074) with 100ng/ml of M-CSF (Pepro Tech #300-25) and allowed to differentiate for five days. At the end of that period, cell morphology and cell surface markers (CD14, HLA-DR, B7.1, B7.2, CD64, CD32, and CD16) reflected the presence of mature differentiated macrophage.

7.18.7.3 Stimulation with IgG

Immulon 4HBX 96 well plates (VWR #62402-959) were coated with pooled human IgG (Jackson Immunoresearch lab#009-000-003) at 10ug/well overnight at 4°C or 1hr at 37°C. A negative control consisting of the F(ab')2 fragment was also coated to assess background stimulation. Unbound antibody was washed away 2X with 200ul PBS. 20ul of 5X compound was added to each well, followed by the addition 15k cells of differentiated macrophage in 80uL that had been scraped off of the plates. The cells were incubated for 16 hr in a 37°C incubator, and supernatants were collected for Luminex analysis for IL-6 and TNFα, essentially as described for the primary T-cells, above.

7.18.7.4 Stimulation with LPS

For stimulation with LPS, 10 uL of a 10X stock solution was added to the preincubated cell-compound mixture to a final concentration of 10 ng/mL. The cells were then incubated for 16hr at 37°C and supernatants were analyzed as described above.

Varied concentrations of compound were compared to solvent only to determine the IC_{50} of each compound for each cytokine. Representative IC_{50}s for 2,4-pyrimidinediamine compounds of the invention are shown in Table 11.

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R070790	9999								
R908696	9999								
R908697	9999								
R908698	3.748								
R908699	1.033								
R908700	13.724								
R908701	0.302								
R908702	0.37								
R908703	1.399								
R908704	3.037								
R908705	5.876								
R908706	0.405								
R908707	9.372								
R908709	3.394								
R908710	4.277								
R908711	4.564								
R908712	0.348								
R908734	3.555								
R908953							1.982		

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R909236	9999								
R909237	9999								
R909238	5.021								
R909239	3.063								
R909240	2.845								
R909241	3.52								
R909242	3.8								
R909243	2.245								
R921219	0.441		0.546				0.131		
R909245	0.78								
R909246	2.166								
R909247	3								
R909248	33.258								
R909249	9999								
R909250	9999								
R909251	0.664								
R909252	0.655								
R909253	3.082								
R909255	1.973								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R909259	9999								
R909260	3.329								
R909261	2.935								
R909263	6.195								
R909264	3.241								
R909265	11.988								
R909266	12.983								
R909267	9999								
R909268	0.997								
R909290	1.562								
R909292	3.315								
R909317	0.224	0.595	1.324	1.743	0.876	1.573			
R909322	3.028							1.259	0.839
R920395	0.726								
R920410	1.981	2.989	3.36	3.2	0.546	4.307	0.706		
R920664	9999								
R920665	10.883								
R920666	9999								
R920668	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R920669	19.813								
R920670	14.322								
R920671	9999								
R920672	9999								
R920818	9999								
R920819	9999								
R920820	9999								
R920846	10.404								
R920860	9999								
R920861	3.28								
R920893	1.4								
R920894	2.024								
R920910	2.38								
R920917	2.649								
R925734	9999								
R925745	9999								
R925746	9999								
R925747	9999								
R925755	1.906								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R925757	9999								
R925758	18.209								
R925760	20.246								
R925765	9999								
R925766	9999								
R925767	9999								
R925768	9999								
R925769	9999								
R925770	9999								
R925771	7.187								
R925772	9999								
R925773	14.414								
R925774	7.498								
R925775	9999								
R925776	17.059								
R925778	3.398								
R925779	9999								
R925783	9999								
R925784	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R925785	3.117								
R925786	9999								
R925787	9999								
R925788	16.898								
R925790	16.992								
R925791	9999								
R925792	8.65								
R925794	9999								
R925795	9999								
R925796	1.827								
R925797	1.511								
R925798	9999								
R925799	9999								
R925800	9999								
R925801	9999								
R925802	9999								
R925803	9999								
R925804	9999								
R925805	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R925806	9999								
R925807	9999								
R925808	9999								
R925810	21.332								
R925811	9999								
R925812	9999								
R925814	14.163								
R925815	9999								
R925816	4.664								
R925819	9999								
R925820	9999								
R925821	9999								
R925822	9999								
R925823	9.326								
R925838	9999								
R925842	9999								
R925845	6.968								
R925846	9999								
R925849	8.022								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R925852	9999								
R925853	9999								
R925855	9999								
R925856	9999								
R925857	9999								
R925858	9999								
R925860	41.865								
R925861	20.195								
R925862	9999								
R925863	2.962								
R925864	19.127								
R925865	9999								
R926016	9999								
R926017	20.775								
R926018	9999								
R926037	9999								
R926038	9999								
R926039	9999								
R926058	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926064	9999								
R926065	6.731								
R926068	11.416								
R926069	4.307								
R926072	9999								
R926086	6.635								
R926108	10.373								
R926109	16.117								
R926110	3.474								
R921218	3.935		3.24				1.081		
R926113	4.379								
R926114	9.913								
R926145	17.689								
R926146	9999								
R926147	9999								
R926206	9999								
R926209	9999								
R926210	4.379								
R926211	14.957								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926212	0.56								
R926213	8.864						44		
R926218	9999								
R926220	9999								
R926221	9999								
R926222	9999								
R926223	9999								
R926224	9999								
R926225	9999								
R926228	9999								
R926229	9999								
R926230	9999								
R926234	9999								
R926237	9999								
R926238	9999								
R926240	9999								
R926241	13.768								
R926242	3.824								
R926243	2.986								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926245	11.086								
R926248	1.537								
R926249	0.954								
R926252	9999								
R926253	9999								
R926254	9999								
R926255	9999								
R926256	9999								
R926257	9999								
R926258	9999								
R926259	12.96								
R926319	15.584								
R926320	9999								
R926321	1.293								
R926325	9999								
R926331	9999								
R926339	2.149								
R926340	9999								
R926341	3.676								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926376	9999								
R926386	9999								
R926387	3.852								
R926394	9999								
R926395	17.741								
R926396	6.594								
R926397	12.469								
R926398	9999								
R926399	9999								
R926400	9999								
R926401	9999								
R926402	9999								
R926403	9999								
R926404	9999								
R926405	7.617								
R926408	9999								
R926409	3.539								
R926411	16.926								
R926412	2.383								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926461	3.388								
R926467	9999								
R926469	9999								
R926474	10.775								
R926475	9999								
R926476	3.904								
R926477	9999								
R926479	9999								
R926480	9999								
R926481	9999								
R926482	8.261								
R926483	9999								
R926484	9999								
R926485	9999								
R926486	1.745								
R926487	48.937								
R926488	2.429								
R926489	9999								
R926491	2.727								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926492	3.335								
R926493	3.524								
R926494	12.507								
R926495	11.904		0.643						
R926496	4.387								
R926497	3.267								
R926498	5.732								
R926499	0.56								
R926500	2.367								
R926501	1.681								
R926502	1.626								
R926503	2.599								
R926504	1.784								
R926505	1.145								
R926506	2.676								
R926508	1.006		0.917				0.948		
R926509	1.078								
R926510	0.122								
R926511	1.729								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926514	15.6								
R926516	17.782								
R926526	9999								
R926527	21.197								
R926528	9999								
R926535	9999								
R926536	9999								
R926555	9999								
R926559	11.248								
R926560	9999								
R926561	9999								
R926562	1.246								
R926563	9999								
R926564	9999								
R926565	9999								
R926566	9999								
R926567	9999								
R926569	9999								
R926571	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926572	9999								
R926574	9999								
R926576	9999								
R926585	9999								
R926586	9999								
R926587	9999								
R926588	9999								
R926589	9999								
R926591	9999								
R926593	1.282								
R926594	1.252								
R926595	9999								
R926604	9999								
R926605	9999								
R926614	6.537								
R926615	1.871								
R926616	1.912								
R926617	9999								
R926620	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg, IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926623	10.015								
R926662	9999								
R926675	2.369								
R926676	9999								
R926680	5.703								
R926681	2.002								
R926682	5.946								
R926683	7.635								
R926688	3.779								
R926690	13.398								
R926696	7.645								
R926698	9999								
R926699	1.861								
R926700	0.51								
R926701	9999								
R926702	18.583								
R926703	7.873								
R926704	9.271								
R926705	2.651								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926706	9999								
R926707	2.683								
R926708	3.299								
R926709	2.47								
R926710	4.273								
R926711	3.788								
R926712	6.351								
R926713	8.219								
R926714	5.632								
R926715	2.357								
R926716	3.618								
R926717	3.75								
R926718	12.441								
R926719	9999								
R926720	9999								
R926721	3.461								
R926722	9999								
R926723	9999								
R926724	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926725	3.368								
R926726	9999								
R926727	9999								
R926728	9999								
R926730	1.84								
R926731	9999								
R926732	5.256								
R926733	3.594								
R926734	11.276								
R926735	5.982								
R926736	14.12								
R926737	2.384								
R926738	2.216								
R926739	2.093								
R926740	9999								
R926741	4.593								
R926742			0.717						
R926743	9999								
R926744	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926745	1.484		1.498						
R926746	3.696								
R926747	3.278								
R926748	2.769								
R926749	4.684								
R926750	0.535								
R926751	5.592								
R926752	1.734								
R926753	0.393								
R926754	13.245								
R926755	7.364								
R926756	3.774								
R926757	2.737								
R926759	1.71								
R926760	10.25								
R926761	0.694								
R926762	0.703								
R926763	3.717								
R926764	2.165								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926765	8.003								
R926766	4.24								
R926767	2.667								
R926768	0.973								
R926769	2.79								
R926770	0.891								
R926771	3.473								
R926772	2.043								
R926773	1.844								
R926774	12.741								
R926775	9999								
R926776	12.475								
R926777	9999								
R926778	9999								
R926779	9999								
R926780	2.158								
R926781	9.811								
R926782	1.221								
R926783	2.95								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926784	2.379								
R926785	2.583								
R926786	7.361								
R926787	9999								
R926788	9999								
R926789	9999								
R926790	9999								
R926791	1.751								
R926792	9.975								
R926795	9999								
R926796	4.205								
R926797	9999								
R926798	9999								
R926799	9999								
R926800	9999								
R926801	9999								
R926802	5.909								
R926803	9999								
R926804	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926805	9999								
R926806	6.076								
R926807	10.136								
R926808	1.76								
R926809	9999								
R926810	5.069								
R926811	1.284								
R926812	6.76								
R926813	5.101								
R926814	9999								
R926815	9999								
R926816	0.739								
R926826	3.732								
R926827	2.135								
R926828	1.006								
R926829	3.095								
R926830	4.161								
R926831	1.271								
R926832	2.988								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926833	11.797								
R926834	2.568								
R926835	3.585								
R926836	14.528								
R926837	9999								
R926838	10.684								
R926839	2.485								
R926840	12.234								
R926841	3.279								
R926842	9999								
R926843	9999								
R926844	9999								
R926845	9999								
R926846	9999								
R926847	11.782								
R926848	1.72								
R926851	3.089								
R926852	9999								
R926853	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926854	48.759								
R926855	9999								
R926856	9999								
R926857	9999								
R926858	9999								
R926859	9999								
R926860	9999								
R926861	9999								
R926862	7.746								
R926863	9999								
R926866	9999								
R926869	9999								
R926873	9999								
R926875	9999								
R926876	9999								
R926877	9999								
R926878	9999								
R926879	2.554								
R926880	6.239								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926881	11.025								
R926882	9.049								
R926883	9999								
R926884	9999								
R926885	9999								
R926886	1.136								
R926887	5.92								
R926888	5.582								
R926889	9999								
R926890	11.291								
R926891	1.548						0.803	1.135	0.942
R926892	1.635								
R926893	9999								
R926894	9999								
R926895	9999								
R926896	9999								
R926897	9999								
R926898	9999								
R926899	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926900	9999								
R926902	9999								
R926903	9999								
R926904	1.363								
R926905	6.488								
R926906	9999								
R926907	17.14								
R926908	30.57								
R926909	4.65								
R926910	9999								
R926911	9999								
R926912	9999								
R926913	5.652								
R926914	9999								
R926915	9999								
R926917	4.741								
R926918	4.689								
R926919	9999								
R926920	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926921	9999								
R926922	6.123								
R926923	7.203								
R926924	3.228								
R926925	5.868								
R926926	13.105								
R926927	5.527								
R926928	9999								
R926929	3.998								
R926930	10.481								
R926931	2.933								
R926932	2.907								
R926933	2.79								
R926934	6.011								
R926935	11.794								
R926936	7.883								
R926937	9999								
R926938	9999								
R926939	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R926940	9999								
R926941	9999								
R926942	9999								
R926943	18.527								
R926944	3.43								
R926945	4.243								
R926946	9.4								
R926947	13.298								
R926956	0.749								
R926968	2.024								
R926976	1.16							4.369	7.618
R926982							0.394		
R927016	7.156								
R927017	8.157								
R927018	17.68								
R927019	9999								
R927050	0.112	0.6	0.928	1.118	0.275	0.916	0.438	0.108	0.066
R927064	2.735		9999	9999		9999	1.754		
R927069	0.93							8.505	5.65

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R935000	9999								
R935001	9999								
R935002	9999								
R935003	9999								
R935004	9999								
R935005	9999								
R935006	9999								
R935016	5.363								
R935019	9999								
R935020	9999								
R935021	9999								
R935023	9999								
R935025	7.949								
R935075	5.366								
R935076	9999								
R935077	9999								
R935114	9999								
R935117	9999								
R935134	9999		36.11						

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R935135	9999								
R935136	9999								
R935137	24.124								
R935138	0.46								
R935139	10.963								
R935140	2.158								
R935141	9999								
R935142	9.665								
R935143	3.843								
R935144	9999		13.31						
R935145	5.339								
R935146	9999								
R935147	1.981								
R935148	9999								
R935149	9999								
R935150	20.372								
R935151	1.961								
R935152	19.866								
R935153	7.071								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R935154	1.646								
R935155	9999								
R935156	1.845								
R935157	9999								
R935158	2.47								
R935159	9999								
R935160	2.37								
R935161	3.134								
R935162	3.377								
R935163	9999								
R935164	3.319								
R935165	9999								
R935166	9999								
R935167	9999								
R935168	3.71								
R935169	7.539								
R935170	6.027								
R935171	3.927								
R935172	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R935173	3.908								
R935174	3.99								
R935175	1.743								
R935176	1.981								
R935177	4.154								
R935178	3.04								
R935179	2.999								
R935180	3.571								
R935181	8.983								
R935182	23.856								
R935183	2.271								
R935184	4.082								
R935185	4.107								
R935186	1.095								
R935187	9999								
R935188	1.803								
R935189	0.736								
R935190	3.472								
R935191	2.938								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R935192	5.39								
R935193	1.596								
R935194	0.732								
R935196	1.103								
R935197	2.428								
R935198	1.453								
R935199	2.509								
R935202	1.941								
R935203	9999								
R935204	3.869								
R935205	10.715								
R935206	9999								
R935207	9999								
R935208	2.877								
R935209	9999								
R935211	7.06								
R935212	4.682								
R935213	3.089								
R935214	1.378								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R935215	7.955								
R935216	3.475								
R935217	9999								
R935218	22.692								
R935219	5.567								
R935220	8.067								
R935221	9999								
R935222	3.535								
R935223	4.574								
R935224	9999								
R935225	7.422								
R935237	9999								
R935238	6.727								
R935239	1.726								
R935240	2.709								
R935242	9999								
R935248	1.898								
R935249	4.833								
R935250	6.236								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R935255	0.668								
R935256	0.92								
R935258	6.26								
R935259	3.458								
R935261	2.181								
R935262	3.113								
R935263	2.017								
R935264	1.408								
R935266	9999								
R935267	3.93								
R935268	2.906								
R935269	7.578								
R935271	0.858								
R935279	1.984								
R935286	2.497								
R935287	1.697								
R935288	9999								
R935289	5.338								
R935290	3.43								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R935291	3.139								
R935292	3.61								
R935293	1.337								
R935294	8.16								
R935295	14.241								
R935296	9999								
R935297	5.701								
R935298	2.317								
R935299	0.824								
R935300	3.384								
R935301	2.317								
R935302	0.8								
R935303	0.653								
R935304	0.497								
R935305	1.834								
R935306	4.726								
R935307	1.407								
R935308	1.265								
R935309	0.779								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R935310	0.88								
R935320	9999								
R935321	9999								
R935322	9999								
R935323	9999								
R935324	9999								
R935336	2.878								
R935337	2.537								
R935338	5.891								
R935339	9999								
R935340	9999								
R935366	4.182								
R935368	9999								
R935372	30.713								
R935391	6.041						0.669	1.157	0.959
R935393	9999								
R940079	9999								
R940089	9999								
R940090	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R940095	9999								
R940100	9999								
R940110	9999								
R940215	9999								
R940216	1.283								
R940217	9999								
R940222	9.471								
R940233	2.171								
R940253	17.367								
R940254	3.763								
R940255	1.509								
R940256	4.745								
R940257	9999								
R940258	9999								
R940260	9999								
R940261	10.948								
R940262	6.448								
R940263	10.05								
R940264	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R940265	5.563								
R940266	9999								
R940267	9999								
R940269	1.895								
R940270	9999								
R940271	9999								
R940275	16.37								
R940276	2.532								
R940277	1.223								
R940280	9999								
R940281	9999								
R940282	6.709								
R940283	9999								
R940284	78.15								
R940285	9999								
R940286	4.4								
R940287	6.197								
R940288	3.485								
R940289	3.646								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R940290	1.16								
R940291	9.446								
R940292	2.781								
R940293	9999								
R940294	9999								
R940296	1.23								
R940297	9999								
R940299	24.942								
R940300	9.284								
R940301	1.314								
R940304	9999								
R940306	11.036								
R940307	2.063								
R940309	9999								
R940311	4.123								
R940312	16.178								
R940314	7.032								
R940316	4.278								
R940317	3.282								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R940318	1.387								
R940320	7.818								
R940321	3.68								
R940322	4.57								
R940323	0.557						0.11		
R940336	9999								
R940337	1.821								
R940338	0.708								
R940342	5.124								
R921303	0.423	0.796	1.02	1.178	0.366	1.28	0.217		
R940344	7.735								
R940345	5.395								
R940346	2.086								
R940347	0.581	0.0992	1.894	1.613	0.212	1.673	0.47	0.038	0.019
R940350	0.308	1.513	2.993	2.45	0.501	2.471	0.297		
R940352	3.53						0.876		
R940353	20.699								
R940358	0.159								
R940361	0.39								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R940363	0.141						0.242	0.133	0.095
R940366	0.086							0.086	0.097
R945025	7.033								
R945032	15.179								
R945033	9999								
R945034	9999								
R945035	9999								
R945036	9999								
R945037	9999								
R945038	9999								
R945040	9999								
R945041	9999								
R945042	9999								
R945043	9999								
R945045	7.602								
R945046	4.078								
R945047	3.206								
R945048	2.231								
R945051	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R945052	9999								
R945053	2.674								
R945056	9999								
R945057	9999								
R945060	6.076								
R945061	9999								
R945062	9999								
R945063	6.038								
R945064	4.684								
R945065	14.427								
R945066	43.243								
R945067	9999								
R945068	9999								
R945070	9999								
R945071	0.631								
R945096	2.802								
R945097	9999								
R945109	9.637								
R945110	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R945117	9999								
R945118	9.492								
R945124	6.161								
R945125	9999								
R945126	9999								
R945127	11.084								
R945128	4.311								
R945129	6.08								
R945130	9999								
R945131	19.162								
R945132	20.194								
R945133	9.14								
R945135	4.367								
R945137	5.429								
R945138	9999								
R945139	13.869								
R945140	2.094								
R945142	1.88								
R945144	1.656								

Table 11									
	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
Compound	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R945145	9999								
R945146	9999								
R945147	9999								
R945148	16.217								
R945149	1.226								
R945150	1.112								
R945151	9999								
R945152	9999								
R945153	9.738								
R945155	7.067								
R945156	2.29								
R945157	1.477								
R945162	9999								
R945163	9999								
R945164	9999								
R945165	9999								
R945166	9999								
R945167	5.072								
R945168	9999								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R945169	2.38								
R945170	4.123								
R945171	3.194								
R945172	3.132								
R945173	2.884								
R945175	3.787								
R945236	2.921								
R945237	0.838								
R945242	1.707								
R945263	4.467								
R921304	0.141	1.497	2.772	1.567	0.366	2.894	0.167		
R945298	9.467								
R945299	1.063								
R950083	9999								
R950090	9999								
R921302	3.513	1.628	5.185	3.207	0.245	3.896	1.17		
R950092	9999								
R950093	11.28								
R950100	5.67								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R950107	5.424								
R950108	9999								
R950109	12.782								
R950120	12.062								
R950121	6.265								
R950122	13.894								
R950123	9999								
R950125	9999								
R950129	6.88								
R950130	9999								
R950131	9999								
R950132	4.638								
R950133	4.701								
R950134	6.455								
R950135	9999								
R950137	5.904								
R950138	9999								
R950139	5.454								
R950140	22.366								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R950141	2.376								
R950142	29.078								
R950143	4.569								
R950144	9999								
R950145	6.13								
R950146	9999								
R950147	I4.803								
R950148	9999								
R950149	9999								
R950150	9999								
R950151	14.221								
R950152	2.654								
R950153	9999								
R950154	9999								
R950155	9999								
R950156	9999								
R950157	9999								
R950158	21.381								
R950159	8.446								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R950160	9999								
R950162	8.918								
R950163	24.106								
R950164	18.213								
R950165	7.594								
R950166	9999								
R950167	9999								
R950168	10.692								
R950169	9999								
R950170	9999								
R950171	4.358								
R950172	23.117								
R950173	9.184								
R950174	9999								
R950175	9999								
R950176	9999								
R950177	9999								
R950178	22.59								
R950179	29.867								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R950180	2.869								
R950181	2.689								
R950182	9999								
R950183	9999								
R950184	9999								
R950185	9999								
R950186	5.944								
R950187	22.312								
R950188	17.862								
R950189	21.963								
R950190	7.17								
R950191	2.586								
R950192	1.732								
R950193	2.826								
R950194	5.131								
R950195	1.804								
R950196	2.081								
R950197	2.582								
R950198	1.99								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R950199	3.214								
R950200	2.264								
R950201	4.502								
R950202	9999								
R950203	9999								
R950204	9999								
R950205	24.548								
R950206	9999								
R950207	1.085								
R950208	1.766								
R950209	3.796								
R950210	9999								
R950211	9999								
R950212	9.497								
R950213	9999								
R950214	9999								
R950215	5.006								
R950216	3.856								
R950217	2.795								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R950218	3.425								
R950219	2.11								
R950220	2.678								
R950221	20.345								
R950222	2.008								
R950223	2.775								
R950224	2.423								
R950225	2.325								
R950226	2.917								
R950227	7.112								
R950229	3.773								
R950230	8.235								
R950231	8.688								
R950232	9.161								
R950233	5.305								
R950234	9999								
R950235	6.262								
R950236	9.693								
R950237	12.901								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R950238	9999								
R950239	9999								
R950240	8.925								
R950241	5.185								
R950244	9999								
R950245	9999								
R950246	9999								
R950247	9999								
R950251	9999								
R950253	10.547								
R950254	2.35								
R950255	9999								
R950261	17.375								
R950262	3.148								
R950263	1.911								
R950264	1.988								
R950265	0.982								
R950266	3.66								
R950267	1.985								

Table 11

Compound	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R950290	9999								
R950291	9999								
R950292	9999								
R950293	9999								
R950294	9.793								
R950295	4.713								
R950296	1.947								
R950344	9999								
R950345	6.09								
R950346	1.948								
R950347	2.704								
R950348	0.224								
R950349	0.363								
R950356	5.731								
R950368	0.125								
R950371	1.105								
R950372	2.192								
R950373	3.614								
R950374	1.65								

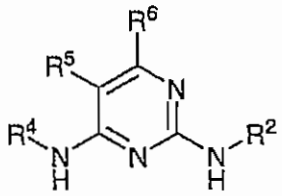
Table 11									
	Jurkat	1° T-Cell					1° B-Cell	Monocytes/Macrophage	
Compound	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL2 IC50 (in μM)	GMSCF IC50 (in μM)	IL4 IC50 (in μM)	IFNg IC50 (in μM)	CD69 IC50 (in μM)	TNF IC50 (in μM)	IL-6 IC50 (in μM)
R950376	18.08								
R950377	5.962								
R950378	9999								
R950379	0.878								
R950380	8.688								
R950381	0.805								
R950382	1.547								
R950383	1.026								
R950385	2.58								
R950386	11.354								

Although the foregoing invention has been described in some detail to facilitate understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims. Accordingly, the described embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims.

All literature and patent references cited throughout the application are incorporated by reference into the application for all purposes.

CLAIMS

1. A compound for formula (1a)



or a salt thereof wherein

R^5 is selected from the group consisting of R^6, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C1-C4) alkanyl optionally substituted with one or more of the same or different R^8 groups, (C2-C4) alkenyl optionally substituted with one or more of the same or different R^8 groups and (C2-C4) alkynyl optionally substituted with one or more of the same or different R^8 groups;

each R^6 is independently selected from the group consisting of hydrogen, halogen, an electronegative group, $-OR^d$, $-SR^d$, (C1-C3) haloalkyloxy, (C1-C3) perhaloalkyloxy, $-NR^cR^c$, (C1-C3) haloalkyl, (C1-C3) perhaloalkyl, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$; $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)NR^cR^c$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-OC(O)R^d$, $-SC(O)R^d$, $-OC(O)OR^d$, $-SC(O)OR^d$, $-OC(O)NR^cR^c$, $-SC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-SC(NH)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$ and $-[NHC(NH)]_nNR^cR^c$, (C5-C10) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups, (C6-C16) arylalkyl optionally substituted with one or more of the same or different R^8 groups, 5-10 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups and 6-16 membered heteroarylalkyl optionally substituted with one or more of the same or different R^8 groups;

R^8 is selected from the group consisting of R^a, R^a substituted with one or more of the same or different R^a or R^b, R^b, $-OR^a$ substituted with one or more of the same or different R^a or R^b, $-B(OR^a)_2$, $-B(NR^cR^c)_2$, $-(CH_2)_m-R^b$, $-(CHR^a)_m-R^b$, $-O-(CH_2)_m-R^b$,

$-S-(CH_2)_m-R^b$, $-O-CHR^aR^b$, $-O-CR^a(R^b)_2$, $-O-(CHR^a)_m-R^b$, $-O-(CH_2)_m-CH[(CH_2)_mR^b]R^b$, $-S-(CHR^a)_m-R^b$, $-C(O)NH-(CH_2)_m-R^b$, $-C(O)NH-(CHR^a)_m-R^b$, $-O-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-S-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-O-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-S-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-NH-(CH_2)_m-R^b$, $-NH-(CHR^a)_m-R^b$, $-NH[(CH_2)_mR^b]$, $-N[(CH_2)_mR^b]_2$, $-NH-C(O)-NH-(CH_2)_m-R^b$, $-NH-C(O)-(CH_2)_m-CHR^bR^b$ and $-NH-(CH_2)_m-C(O)-NH-(CH_2)_m-R^b$;

each R^a is independently selected from the group consisting of (C1-C6) alkyl, morpholinyl, piperazinyl, hydrogen, (C3-C8) cycloalkyl, cyclohexyl, (C4-C11) cycloalkylalkyl, (C5-C10) aryl, phenyl, (C6-C16) arylalkyl, benzyl, 2-6 membered heteroalkyl, 3-8 membered cycloheteroalkyl, homopiperazinyl, piperidinyl, 4-11 membered cycloheteroalkylalkyl, 5-10 membered heteroaryl and 6-16 membered heteroarylalkyl;

each R^b is a suitable group independently selected from the group consisting of $-C(O)R^d$, $-C(O)OR^d$, =O, $-OR^d$, (C1-C3) haloalkyloxy, $-OCF_3$, =S, $-SR^d$, $=NR^d$, $=NOR^d$, $-NR^cR^c$, halogen, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)_2NR^cR^c$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-C(NR^a)NR^cR^c$, $-C(NOH)R^a$, $-C(NOH)NR^cR^c$, $-OC(O)R^d$, $-OC(O)OR^d$, $-OC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-OC(NR^a)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NR^aC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NR^aC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$, $-[NR^aC(O)]_nNR^cR^c$, $-[NHC(NH)]_nNR^cR^c$ and $-[NR^aC(NR^a)]_nNR^cR^c$;

each R^c is independently a protecting group or R^a, or, alternatively, each R^c is taken together with the nitrogen atom to which it is bonded to form a 5 to 8-membered cycloheteroalkyl or heteroaryl which may optionally include one or more of the same or different additional heteroatoms and which may optionally be substituted with one or more of the same or different R^a or suitable R^b groups;

each R^d is independently R^a or a protecting group;

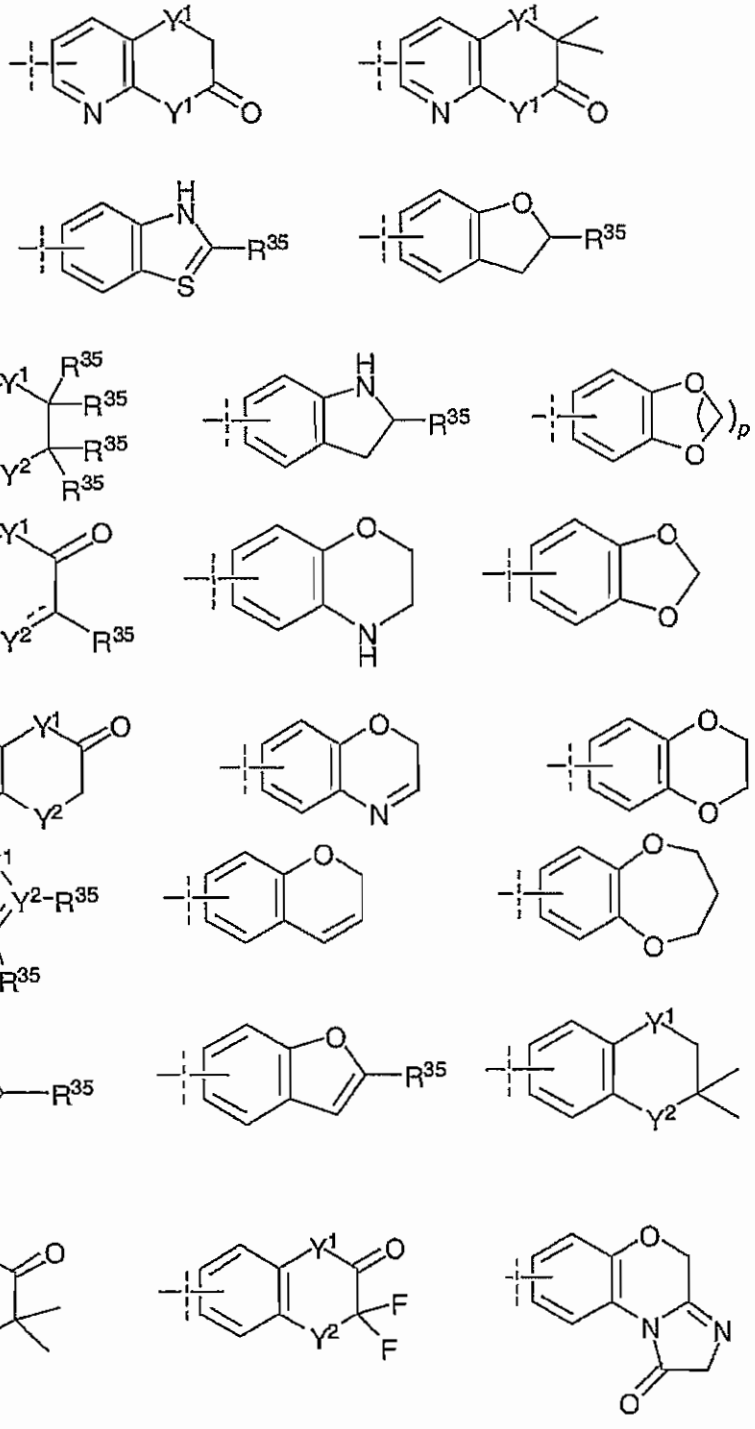
each m is independently an integer from 1 to 3; and

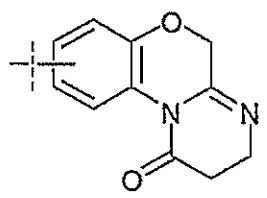
each n is independently an integer from 0 to 3.

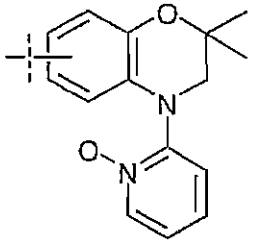
R^2 is selected from the group consisting of phenyl optionally substituted with one or more of the same or different R^8 groups, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally

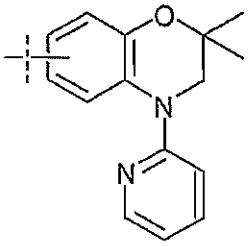
substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

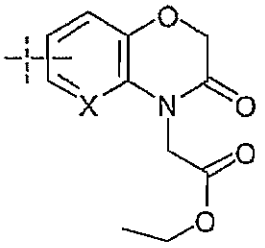
R^4 is

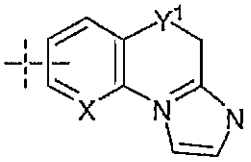


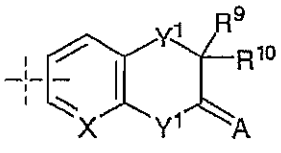


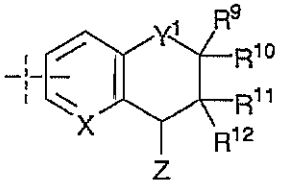


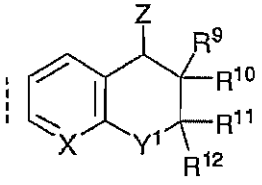


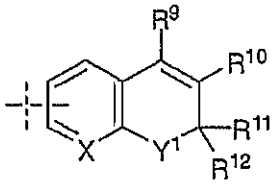


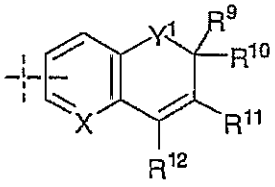


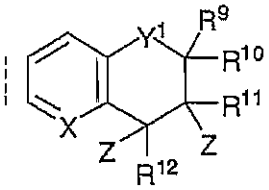


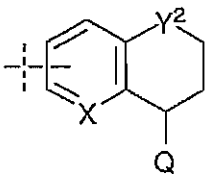


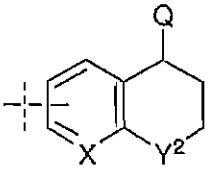


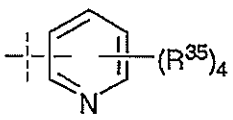


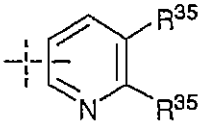


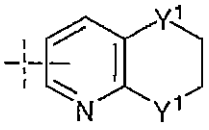


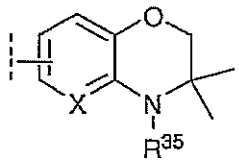


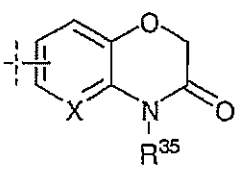


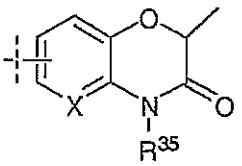


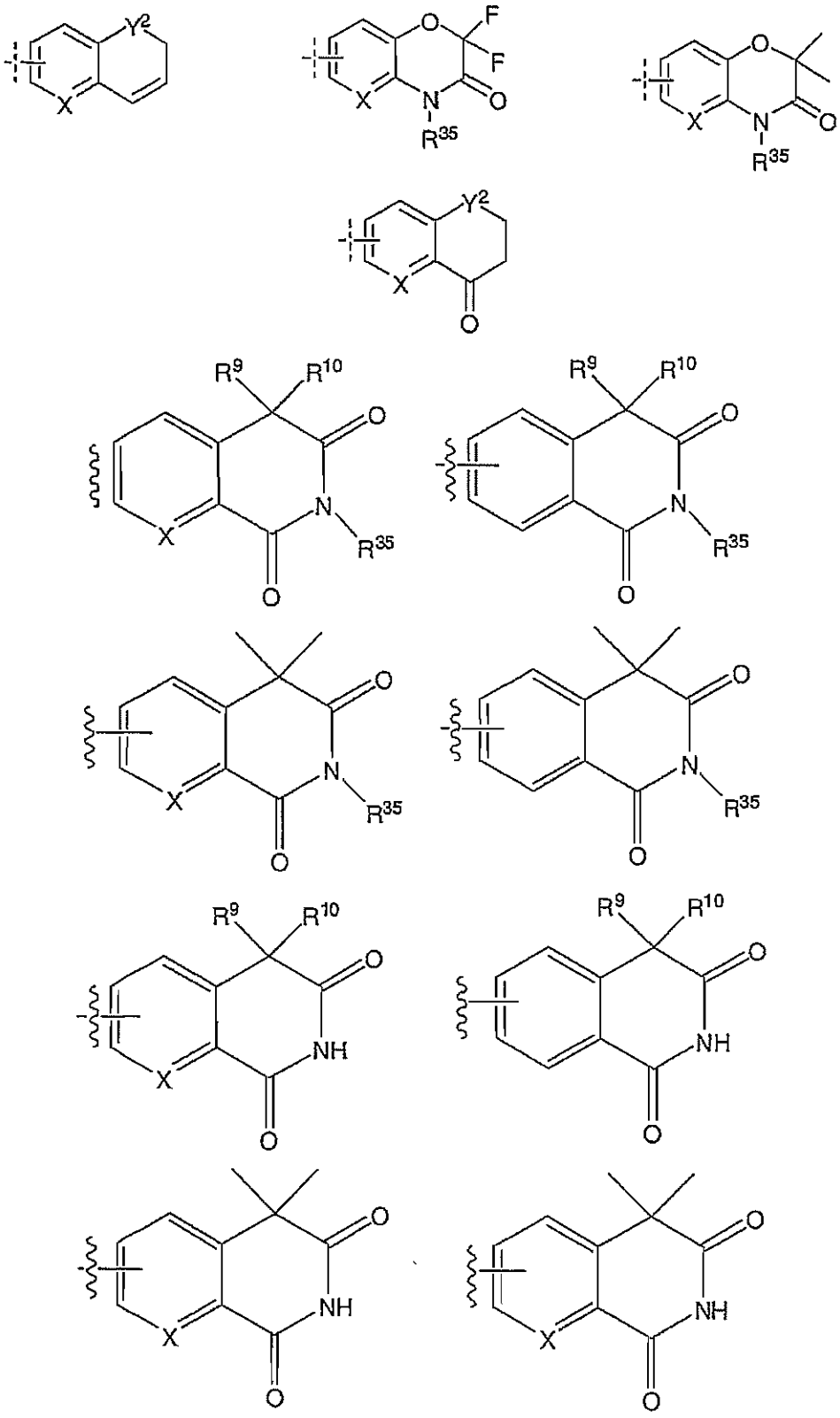












wherein:

p is an integer from one to three;

each - - - independently represents a single bond or a double bond;

R^{35} is hydrogen or R^8, where R^8 is as previously defined for structural formula (I);

X is selected from the group consisting of CH, N and N-O;

each Y is independently selected from the group consisting of O, S and NH;

each Y^1 is independently selected from the group consisting of O, NR^{37}, S, SO, SO_2, $SONR^{36}$ and NH;

each Y^2 is independently selected from the group consisting of CH, CH_2, O, S, N, NH and NR^{37};

R^{36} is hydrogen or alkyl;

R^{37} is selected from the group consisting of hydrogen or a progroup selected from the group consisting of $-CH_2-PO(OR^8)_2$, aryl, arylalkyl, heteroaryl, R^a, R^b–CR^aR^b-O-C(O)R^8, $-CR^aR^b$-O-$PO(OR^8)_2$, $-CH_2$-O-$PO(OR^8)_2$, -C(O)-CR^aR^b-$N(CH_3)_2$, $-CR^aR^b$-O-C(O)-CR^aR^b-$N(CH_3)_2$, -C(O)R^8, $-C(O)CF_3$ and -C(O)-NR^8-C(O)R^8;

A is selected from the group consisting of O, NH and NR^{38};

R^{38} is selected from the group consisting of alkyl and aryl;

R^9, R^{10}, R^{11} and R^{12} are each, independently of one another, selected from the group consisting of alkyl, alkoxy, halogen, haloalkoxy, aminoalkyl and hydroxyalkyl, or, alternatively, $R^9$and R^{10} and/or R^{11} and R^{12} are taken together form a ketal;

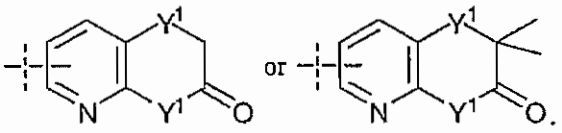
each Z is selected from the group consisting of hydroxyl, alkoxy, aryloxy, ester, carbamate and sulfonyl;

Q is selected from the group consisting of -OH, OR^8, $-NR^cR^c$, $-NHR^{39}$-C(O)R^8, $-NHR^{39}$-C(O)OR^8, $-NR^{39}$-CHR^{40}-R^b, $-NR^{39}$-$(CH_2)_m$-R^b and $-NR^{39}$-C(O)-CHR^{40}-NR^cR^c;

R^{39} and R^{40} are each, independently of one another, selected from the group consisting of hydrogen, alkyl, aryl, alkylaryl; arylalkyl and NHR^8.

2. The compound according to claim 1, wherein R^5 is fluoro and R^6 is H.

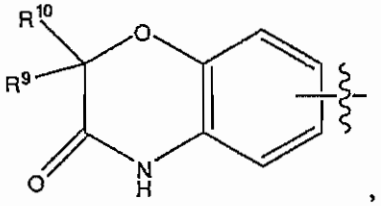
3. The compound according to claim 2, wherein R^4 is



4. The compound according to claim 2, wherein R^8 is independently selected from the group consisting of R^d, $-NR^cR^c$, $-(CH_2)_m-NR^cR^c$, $-C(O)NR^cR^c$, $-(CH_2)_m-C(O)NR^cR^c$, $-C(O)OR^d$, $-(CH_2)_m-C(O)OR^d$ and $-(CH_2)_m-OR^d$.

5. The compound according to claim 2, wherein

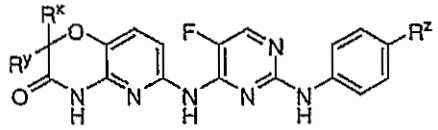
R^4 is



wherein R^9, R^{10} are each, independently of one another, selected from the group consisting of alkyl, alkoxy, halogen, haloalkoxy, aminoalkyl and hydroxyalkyl, or, alternatively, $R^9$and R^{10} are taken together form a ketal, or each independently H;

R^2 is phenyl substituted with one or more R^8.

6. The compound according to claim 1 of formula



wherein:

R^x and R^y independently are H or methyl; and

R^z is (a) piperizin-1-yl substituted on the N at the 4 position with methoxycarbonyl, methylcarbonyl, or methyl, or (b) morpholinyl.

7. A compound that is

5-Fluoro-N2-(4-morpholinophenyl)-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine;

N4-(2,2-Dimethyl-2H-3-oxo-4H-5-pyrido[1,4]oxazin-6-yl]-5-fluoro-N2-

[4-(4-methoxycarbonylpiperazino)phenyl]-2,4-pyrimidinediamine;

N2-[4-(4-Acetylpiperazino)phenyl]-N4-(2,2-dimethyl-2H-3-oxo-4H-5-pyrido[1,4]oxazin-6-yl)-5-fluoro-2,4-pyrimidinediamine;

N4-(2,2-Dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-(4-morpholinophenyl)-2,4-pyrimidinediamine;

5-Fluoro-N2-[4-(4-methylpiperazino)phenyl]-N4-(2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-2,4-pyrimidinediamine;

N4-(2,2-Dimethyl-2H-3-oxo-4H-5-pyrid[1,4]oxazin-6-yl)-5-fluoro-N2-[4-(4-methylpiperazino)phenyl]-2,4-pyrimidinediamine; or

a pharmaceutically acceptable salt of one of the foregoing.

8. A composition comprising a compound according to one of claims 1 to 7 and a pharmaceutically acceptable carrier, excipient or diluent.