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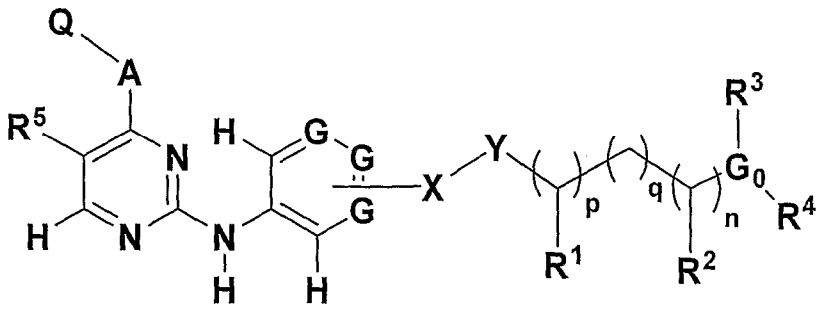
(54) Title: BI-ARYL META-PYRIMIDINE INHIBITORS OF KINASES



(A)

(57) Abstract: The invention provides biaryl meta-pyrimidine compounds having the general structure (A). The pyrimidine compounds of the invention are capable of inhibiting kinases, such as members of the Jak kinase family, and various other specific receptor and non receptor kinases.

WO 2007/053452 A1

BI-ARYL META-PYRIMIDINE INHIBITORS OF KINASES

FIELD OF INVENTION

[0001] The present invention relates to the field of inhibitors of protein tyrosine kinases, their pharmaceutically acceptable compositions comprising the compounds of the invention and the methods of using the compositions in the treatment of various disorders. In particular, the present invention relates to inhibitors of the JAK family of protein tyrosine kinases.

BACKGROUND OF INVENTION

[0002] Protein kinases are families of enzymes that catalyze the phosphorylation of specific residues in proteins, broadly classified into tyrosine and serine/threonine kinases. Inappropriate kinase activity, arising from mutation, over-expression, or inappropriate regulation, dys-regulation or de-regulation, as well as over- or under-production of growth factors or cytokines has been implicated in many diseases, including but not limited too cancer, cardiovascular diseases, allergies, asthma and other respiratory diseases, autoimmune diseases, inflammatory diseases, bone diseases, metabolic disorders, and neurological and neurodegenerative disorders such as Alzheimer's disease. Inappropriate kinase activity triggers a variety of biological cellular responses relating to cell growth, cell differentiation, survival, apoptosis, mitogenesis, cell cycle control, and cell mobility implicated in the aforementioned and related diseases.

[0003] Protein kinases have emerged as an important class of enzymes as targets for therapeutic intervention. In particular, the JAK family of cellular protein tyrosine kinases (Jak1, Jak2, Jak3, and Tyk2) play a central role in cytokine signaling (Kisseleva et al, Gene, 2002, 285, 1; Yamaoka et al. Genome Biology 2004, 5, 253)). Upon binding to their receptors, cytokines activate JAK which then phosphorylate the cytokine receptor, thereby creating docking sites for signaling molecules, notably, members of the signal transducer and activator of transcription (STAT) family that ultimately lead to gene expression. Numerous cytokines are known to activate the JAK family. These cytokines include, the IFN family (IFN-αs/β/ω/Limitin, IFN-γ, IL-10, IL-19, IL-20, IL-22), the gp130 family (IL-6, IL-11,

OSM, LIF, CNTF, NNT-1/BSF-3, G-CSF, CT-1, Leptin, IL-12, IL-23), γC family (IL-2, IL-7, TSLP, IL-9, IL-15, IL-21, IL-4, IL-13), IL-3 family (IL-3, IL-5, GM-CSF), single chain family (EPO, GH, PRL, TPO), receptor tyrosine kinases (EGF, PDGF, CSF-1, HGF), and G-protein coupled receptors (AT1).

[0004] Until recently, the therapeutic potential of JAK inhibitors has focused on diseases affecting various pathologies of the immune system. These include, but are not limited to atopy (allergic asthma, atopic dermatitis, allergic rhinitis), cell mediated hypersensitivity (allergic contact dermatitis, hypersensitivity pneumonitis), rheumatic diseases (systemic lupus erythematosus (SLE), rheumatoid arthritis, juvenile arthritis, Sjogren's Syndrome, scleroderma, polymyositis, ankylosing spondylitis, psoriatic arthritis), transplantation (transplant rejection, graft vs host disease), viral diseases (Epstein Barr Virus, Hepatitis B, Hepatitis C, HIV, HTLV1, Vaicella-Zoster Virus, Human Papilloma Virus), cancer (leukemia, lymphoma), cardiovascular disease (cardiac hypertrophy, atherosclerosis and arteriosclerosis), neurodegenerative diseases (motor neuron disease), food allergy, inflammatory bowel disease, Crohn's disease, cutaneous inflammation, and immune suppression induced by solid tumors. Most efforts to date have targeted JAK3 inhibition for immunosuppression, for example organ transplantation and allograft acceptance (for a review, see Borie et al. Current Opinion in Investigational Drugs, 2003, 4(11), 1297).

[0005] Most recently, two significant findings of the role of the EPO-JAK2 signaling pathway in myeloproliferative disorders and prolfierative diabetic retinopathy were found. First, a gain-of-function, somatic (acquired) mutation of the JAK2 kinase (V617F) was reported to be a causative factor in a number of "typical" myeloproliferative disorders, including polycethemia vera, essential thrombocythemia and melofibrosis with myeloid metaplasia, and the mutation has been found in patients with either "atypical" myeloproliferative disorders and myelodysplastic syndrome (for reviews see Tefferi and Gilliland, Cell Cycle 2005, 4(8), e61; Pesu et. al. Molecular Interventions 2005, 5(4), 211). Additionally it was found that (a) the V617F JAK2 mutation was associated with constitutive phosphorylation of JAK2 and its downstream effectors as well as induction of erythropoietin hypersensitivity in cell based experiments, (b) V617F JAK2-indcued cell proliferation signals were inhibited by small molecule inhibitors of JAK2, and (c) murine bone marrow transduced with a retrovirus containing V617F JAK2 incuded erythrocytosis in the transplanted mice.

[0006] Furthermore, recently it has been found that mutations in EPO-R also keep the JAK pathway constitutively activated leading to myleoproliferative disorders.

[0007] Second, EPO was found to be a potent angiogenic factor in proliferative diabetic retinopathy, a major cause of vision loss affecting diabetic, working-age persons (see for example Aiello, New England Journal of Medicine, 2005, 353 (8), 839; Watanabe et al. New England Journal of Medicine 2005 353 (8), 782).

[0008] Further, findings from the Watanabe research showed (a) intraocular EPO levels and VEGF (another well-known angiogenic factor in proliferative diabetic retinopathy) were significantly higher among those with proliferative diabetic retinopathy than those with quiescent disease or non-diabetic control, (b) EPO and VEGF levels were not closely correlated, (c) EPO levels were more strongly correlated with the presence of proliferative diabetic retinopathy than VEGF, (d) EPO stimulated growth and intracellular signaling in retinal endothelial cells, and (e) inhibitors of either EPO or VEGF reduced hypoxia-induced retinal neovascularization in rodent models.

[0009] Recently it has been shown that mutations in the EPO receptor may also affect the signaling related to the JAK pathway and this may have implications in terms of disease states where JAK signaling is important in the cell cycle.

[0010] There is another feature regarding inhibitors of the JAK pathway. It has been demonstrated that the JAK pathway may be recruited in cell survival and proliferation. For example, in the case of the cells that are Philadelphia chromosome positive that result in chronic myelogenous leukemia (CML), there is evidence that the Jak pathway is recruited in constitutive activation. Accordingly, using a JAK inhibitor may have use in CML in which the Philadephia chromosome has been shown to produce the hybrid Bcr-Abl, thus keeping cells constitutively active.

[0011] More telling is that in cases of resistance mutations that arise on account of specific inhibitors to BCR-ABL, as in the case of the T315I gatekeeper mutation, or any other mutation, it may be possible to use a JAK inhibitor on account of the pathway used by the BCR-ABL mutant (as in the case of BCR-ABL(T315I) mutation) utilizing the Jak pathway. Thus Jak inhibitors may be used in the treatment of patients with resistance to known

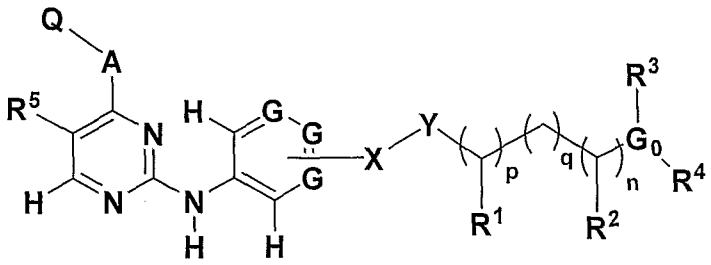
therapies where BCR-ABL is directly targeted and drug resistance has now been shown as the dominant (50-90%) of all resistance in patients where existing therapies fail.

[0012] The use of JAK inhibitors may also find utility in other myeloid disease states, both blood disorders and other disease states with myeloid implications, and other disease states in which the JAK pathway is implicated directly or indirectly.

[0013] Accordingly, there is a need to develop compounds useful as inhibitors of kinases, particularly, JAK kinase, given the inadequate treatments available for the aforementioned diseases where the JAK signaling pathway is dysregulated, or recruited directly or indirectly.

SUMMARY

[0014] According to one embodiment, a compound having the structure (A) is provided:



(A)

[0015] According to another embodiment, a method is provided for treating an angiogenic-associated disorder, the method including administering to a subject in need thereof a therapeutically effective amount of at least one compound having the structure (A), or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, crystal forms, N-oxides, and individual enatiomers and diastereomers thereof, to a subject in need of such treatment.

[0016] According to other embodiments, pharmaceutical compositions and articles of manufacture are provided, including at least one compound having the structure (A), or pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers thereof.

DETAILED DESCRIPTION

A. Terms and Definitions.

[0017] The following terminology and definitions apply as used in the present application, generally in conformity with the terminology recommended by the International Union of Pure and Applied Chemistry (IUPAC):

[0018] The term "heteroatom" refers to any atom other than carbon, for example, N, O, or S.

[0019] The term "aromatic" refers to a cyclically conjugated molecular entity with a stability, due to delocalization, significantly greater than that of a hypothetical localized structure, such as the Kekulé structure.

[0020] The term "heterocyclic," when used to describe an aromatic ring, refers to the aromatic rings containing at least one heteroatom, as defined above.

[0021] The term "heterocyclic," when not used to describe an aromatic ring, refers to cyclic (i.e., ring-containing) groups other than aromatic groups, the cyclic group being formed by between 3 and about 14 carbon atoms and at least one heteroatom described above.

[0022] The term "substituted heterocyclic" refers, for both aromatic and non-aromatic structures, to heterocyclic groups further bearing one or more substituents described below.

[0023] The term "alkyl" refers to a monovalent straight or branched chain hydrocarbon group having from one to about 12 carbon atoms, for example, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl (also known as *n*-amyl), *n*-hexyl, and the like. The term "lower alkyl" refers to alkyl groups having from 1 to about 6 carbon atoms.

[0024] The term "substituted alkyl" refers to alkyl groups further bearing one or more substituents such as hydroxy, alkoxy, mercapto, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, halogen, cyano, nitro, amino, amido, aldehyde, acyl, oxyacyl, carboxyl, sulfonyl, sulfonamide, sulfuryl, and the like.

[0025] The term "alkenyl" refers to straight-chained or branched hydrocarbyl groups having at least one carbon-carbon double bond, and having between about 2 and about 12 carbon atoms, and the term "substituted alkenyl" refers to alkenyl groups further bearing one or more substituents described above.

[0026] The term "alkynyl" refers to straight-chained or branched hydrocarbyl groups having at least one carbon-carbon triple bond, and having between about 2 and about 12 carbon atoms, and the term "substituted alkynyl" refers to alkynyl groups further bearing one or more substituents described above.

[0027] The term "aryl" refers to aromatic groups having between about 5 and about 14 carbon atoms and the term "substituted aryl" refers to aryl groups further bearing one or more substituents described above.

[0028] The term "heteroaryl" refers to aromatic rings, where the ring structure is formed by between 3 and about 14 carbon atoms and by at least one heteroatom described above, and the term "substituted heteroaryl" refers to heteroaryl groups further bearing one or more substituents described above.

[0029] The term "alkoxy" refers to the moiety —O—alkyl, wherein alkyl is as defined above, and the term "substituted alkoxy" refers to alkoxy groups further bearing one or more substituents described above.

[0030] The term "cycloalkyl" refers to alkyl groups having between 3 and about 8 carbon atoms arranged as a ring, and the term "substituted cycloalkyl" refers to cycloalkyl groups further bearing one or more substituents described above.

[0031] The term "alkylaryl" refers to alkyl-substituted aryl groups and the term "substituted alkylaryl" refers to alkylaryl groups further bearing one or more substituents described above.

[0032] The term "arylalkyl" refers to aryl-substituted alkyl groups and the term "substituted arylalkyl" refers to arylalkyl groups further bearing one or more substituents described above.

[0033] The term "arylalkenyl" refers to aryl-substituted alkenyl groups and the term "substituted arylalkenyl" refers to arylalkenyl groups further bearing one or more substituents described above.

[0034] The term "arylalkynyl" refers to aryl-substituted alkynyl groups and the term "substituted arylalkynyl" refers to arylalkynyl groups further bearing one or more substituents described above.

[0035] The term "arylene" refers to divalent aromatic groups having between 5 and about 14 carbon atoms and the term "substituted arylene" refers to arylene groups further bearing one or more substituents described above.

[0036] The term "chemically connected" is defined as forming a chemical entity in which two moieties form a direct chemical bond between them.

[0037] The term "kinase" refers to any enzyme that catalyzes the addition of phosphate groups to a protein residue; for example, serine and threonine kinases catalyze the addition of phosphate groups to serine and threonine residues.

[0038] The term "JAK kinase" refers to an enzyme found in cells in the immune system that participates in the cell signaling process resulting in the development of white blood cells.

[0039] The term "therapeutically effective amount" refers to the amount of the compound or pharmaceutical composition that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician, e.g., restoration or maintenance of vasculostasis or prevention of the compromise or loss or vasculostasis; reduction of tumor burden; reduction of morbidity and/or mortality.

[0040] The term "pharmaceutically acceptable" refers to the fact that the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0041] The terms "administration of a compound" or "administering a compound" refer to the act of providing a compound of the invention or pharmaceutical composition to the subject in need of treatment.

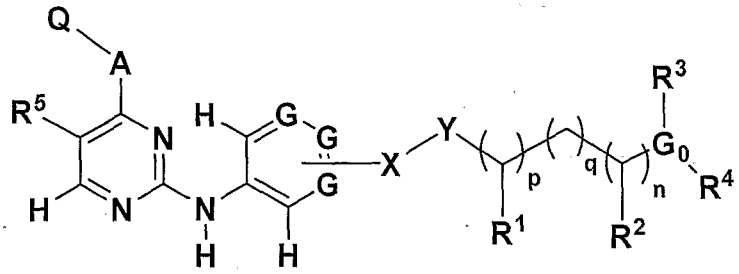
[0042] The term "antibody" refers to intact molecules of polyclonal or monoclonal antibodies, as well as fragments thereof, such as Fab and $F(ab')_2$, Fv and SCA fragments which are capable of binding an epitopic determinant.

[0043] The term "vasculostasis" refers to the maintenance of the homeostatic vascular functioning leading to the normal physiologic functioning.

[0044] The term "vasculostatic agents" refers to agents that seek to address conditions in which vasculostasis is compromised by preventing the loss of or restoring or maintaining vasculostasis.

B. Embodiments of the Invention.

[0045] According to an embodiment of the invention, compounds having the structure (A) are provided for treatment of various diseases, disorders, and pathologies:



(A)

[0046] In the structure (A), X can be any of a bond, O, C=O, SO_2, or CH_2 and Y can be a bond or NR^9; or X and Y taken together can be a bond. Further, in the structure (A) each of R^1 and R^2 can be any of H, C_1-C_6 substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or R^1 and R^2 taken together can be a bond; or R^1 and R^2 taken together can form a moiety such as one of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, or $(CH_2)_r$–O–$(CH_2)_m$, wherein each of p, q, r, n, m is idependently an integer having the value between 0 and 6.

[0047] Further, in the structure (A) R^9 can be one of H, C_1-C_6 alkyl, C_1-C_6 cycloalkyl, C_1-C_6 branched alkyl, C_1-C_6 substituted alkyl, C_1-C_6 aminoalkyl, or C_1-C_6 hydroxyalkyl; G_0 can be one of N, O, H, of CH, with the proviso that if G_0 is N, then each of R^3 and R^4 can be one of H, C_1-C_6 alkyl, C_1-C_6 substituted or unsubstituted hydroxyalkyl or aminoalkyl, C_1-C_6 substituted or unsubstituted branched alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or R^3 and R^4 taken together can form a moiety such as one of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, or $(CH_2)_r$–O–$(CH_2)_m$.

[0048] There are some additional provisos further directed to G_0 in the structure (A). More specifically, if G_0 is N, then R^1 and R^9 taken together can form a moiety such as one of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, or $(CH_2)_r$–O–$(CH_2)_m$; or R^1 and R^4 taken together can form a moiety such as one of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, or $(CH_2)_r$–O–$(CH_2)_m$; or R^9 and R^4 taken together can form a moiety such as one of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, or $(CH_2)_r$–O–$(CH_2)_m$; or R^3 and R^4 taken together can form a moiety such as one of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^6–$(CH_2)_m$, or $(CH_2)_r$–O–$(CH_2)_m$.

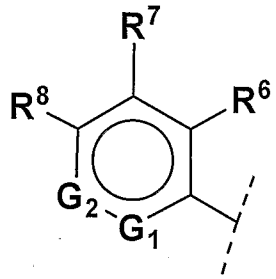
[0049] If in the structure (A) G_0 is O, then R^3 can be one of H, C_1-C_6 alkyl and C_1-C_6 substituted or unsubstituted hydroxyalkyl or aminoalkyl, substituted or unsubstituted branched alkyl, substituted or unsubstituted cycloalkyl, substituted heterocyclic connected through carbon or nitrogen, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl connected through carbon or nitrogen, with no group R^4; R^1 and R^9 taken together can form a moiety such as one of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, or $(CH_2)_r$–O–$(CH_2)_m$; or R^1 and R^3 taken together can form a moiety such as one of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, or $(CH_2)_r$–O–$(CH_2)_m$; or R^9 and R^3 taken together can form a moiety such as one of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, or $(CH_2)_r$–O–$(CH_2)_m$.

[0050] If in the structure (A) G_0 = CH, then each of R^3 and R^4 can be one of H, C_1-C_6 alkyl, C_1-C_6 substituted or unsubstituted hydroxyalkyl or aminoalkyl, C_1-C_6 substituted or unsubstituted branched alkyl, substituted or unsubstituted aryl, C_1-C_6 substituted or unsubstituted heterocycle connected through carbon or nitrogen, or substituted or unsubstituted heteroaryl connected through carbon or nitrogen, or R^3 and R^4 taken together can form a moiety such as one of $(CHR^9)_r$–$(CHR^9)_m$–$(CHR^9)_p$, $(CHR^9)_r$–S–$(CHR^9)_m$, $(CHR^9)_r$–SO–$(CHR^9)_m$, $(CHR^9)_r$–SO_2–$(CHR^9)_m$, $(CHR^9)_r$–NR^9–$(CHR^9)_m$, or $(CHR^9)_r$–O–$(CHR^9)_m$.

[0051] Further, in the structure (A) G can be N or CR^6, and each G is independent of each other G, with the further proviso that not more than two groups G can be N, with the further proviso that for each CR^6, each R^6 is independent of each other group R^6.

[0052] Further, in the structure (A) R^5 is methyl and the moiety Q is as shown below

Q =

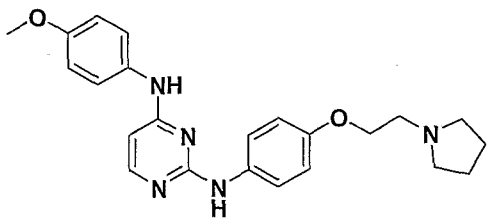


[0053] In the moiety Q, each of R^6, R^7, R^8 can be one of H, C_1-C_6 substituted or unsubstituted alkyl, C_1-C_6 substituted or unsubstituted alkenyl, C_1-C_6 substituted or unsubstituted alkynyl, C_1-C_6 substituted or unsubstituted hydroxyalkyl or aminoalkyl, C_1-C_6 substituted or unsubstituted branched alkyl, C_1-C_6 substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl connected through carbon or a heteroatom, substituted or unsubstituted heteroaryl connected through carbon or a heteroatom, C_1-C_6 alkoxy, a halogen, CF_3, –OCF_3, CHR^3R^4, SR^3, SOR^3, SO_2R^3, $SO_2NR^3R^4$, SO_3R^3, POR^3, PO_2R^3, $PO_2NR^3R^4$, $PO_2CR^3R^4$, PO_3R^3, NR^3R^4, NO_2, CN, OH, $CONR^3R^4$, COR^3, $COOR^3$, N R^3CO R^4, $NR^3CONR^3R^4$, $OCONR^3R^4$, $CSNR^3R^4$, CSR^3, $NR^3CSNR^3R^4$, $SCONR^3R^4$, $SCSNR^3R^4$, or $SCSNR^3R^4$; or any of R^6 and R^7 taken together, or R^7 and R^8 taken together, or R^6 and R^8 taken together can form a moeity independently selected from any of –HN–CH=CH–, –HN–N=CH–, –HN–N=N–, $–O(CH_2)_nO–$, $–S(CH_2)_nS–$, –N=CH–S–, –CH=N–O–, –CH=N–S–, –N=CH–O–, –C=N–O–, –C=N–O–, –CH=CH–CH=CH–, –N=CH–CH=CH–,

–CH=N–CH=CH–, –O–CH=CH, and –S–CH=CH–; or R^3 and R^4 taken together can form a moiety such as one of $(CHR^9)_r$–$(CHR^9)_m$–$(CHR^9)_p$, $(CHR^9)_r$–S–$(CHR^9)_m$, $(CHR^9)_r$–SO–$(CHR^9)_m$, $(CHR^9)_r$–SO_2–$(CHR^9)_m$, $(CHR^9)_r$–NR^9–$(CHR^9)_m$, or $(CHR^9)_r$–O–$(CHR^9)_m$.

[0054] Further, in the structure (A), A can be one of O, NR^3, CR^3R^4, S, SO, and SO_2; and in the moiety Q, G_1 can be any of CH, N, NH, S, and O, and G_2 can be any of CR^7, N, NH, S, and O, with each group R^7 being independent of every other group R^7; and if G_1 or G_2 is NH, S, or O, then Q is a five membered heteroaromatic ring, optionally fused to a six member aromatic or non-aromatic ring; and if G_1 or G_2 is N, then Q is a five or a six membered aromatic ring, optionally fused to a six member aromatic or non-aromatic ring, with the further proviso that X or G_0 includes at least one heteroatom included with X and selected from O, S and N, or G_0 comprises at least four non-hydrogen atoms, inclusive of the heteroatom, and R^3 and R^4, or R^1 and R^9, or R^1 and R^4, or R^9 and R^4 taken together can form an aromatic, heteroaromatic, cyclic or heterocyclic ring system, or if a noncyclic system is present, then more than one heteroatom is present, and if A is NR_3, then any of R_6, R_7 or R_8, or any combination thereof independently includes at least two non-hydrogen substituents, or if A is NR_3, then Q forms a fused ring from R_6 to R_7, or from R_7 to R_8.

[0055] Some exemplary compounds described by structure (A) that can be used include, but are not limited to, the following compounds **I** through **CLXII** shown below:



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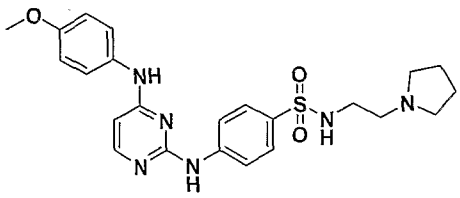

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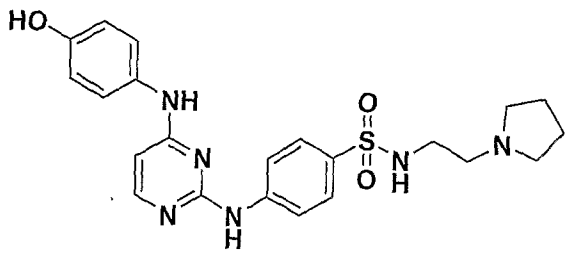

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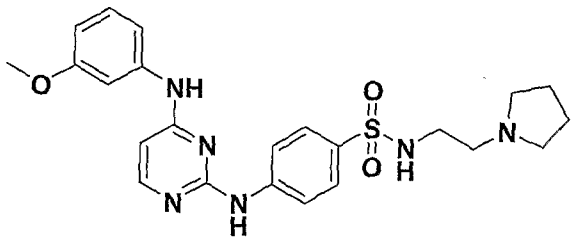

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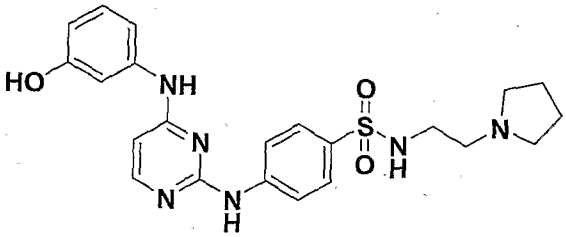

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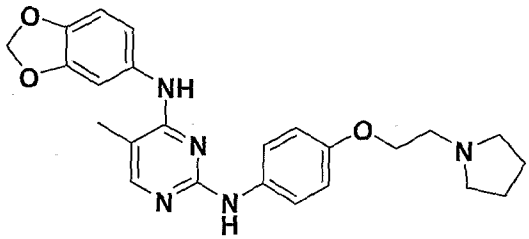

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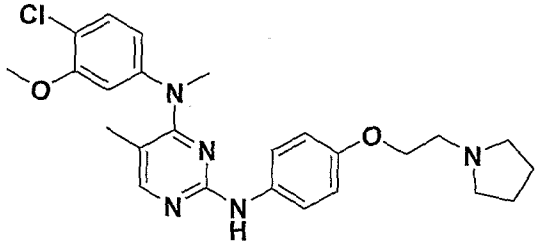

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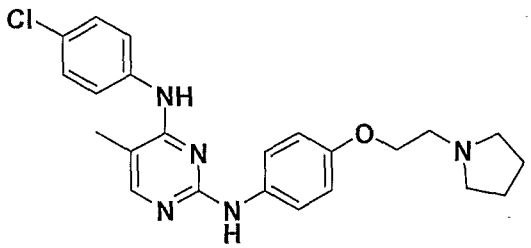

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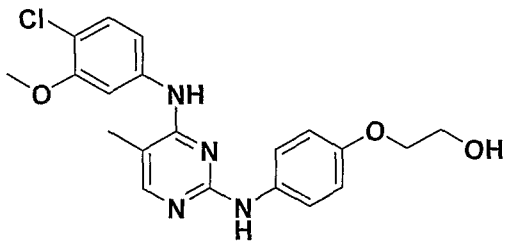

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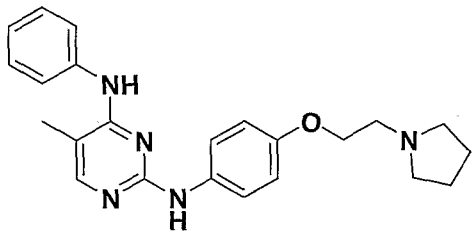

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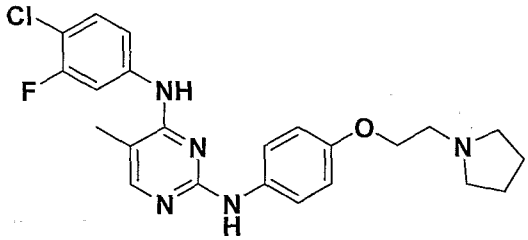

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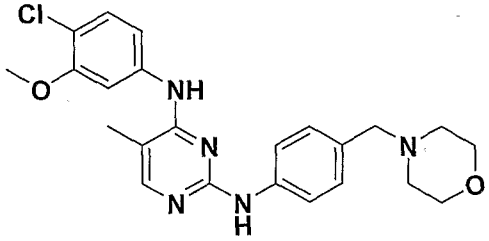

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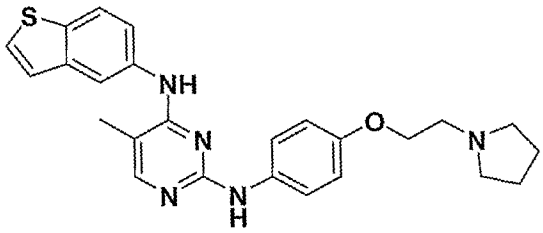

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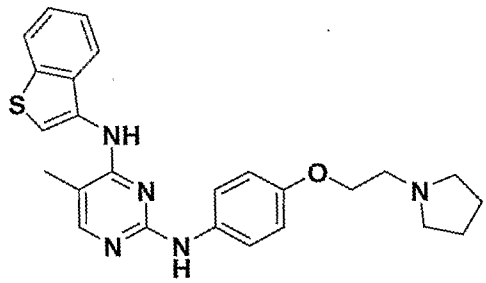

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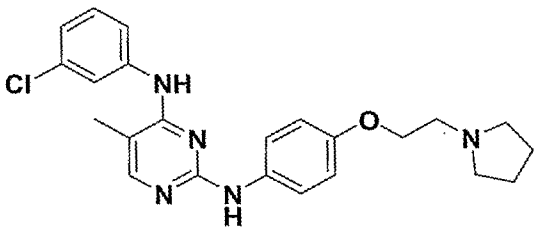

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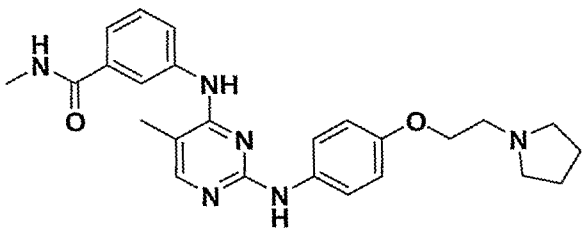

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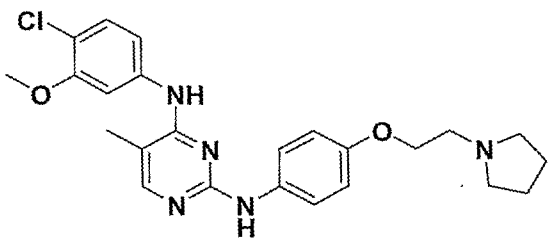

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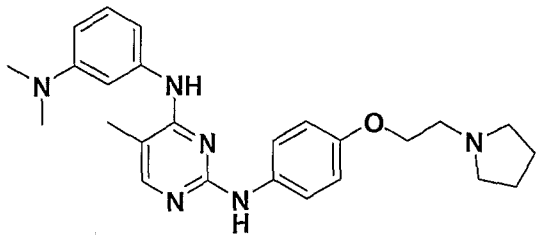

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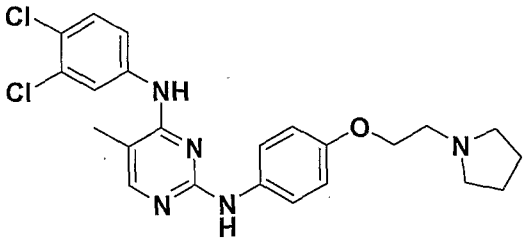

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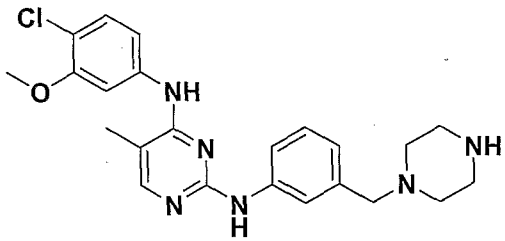

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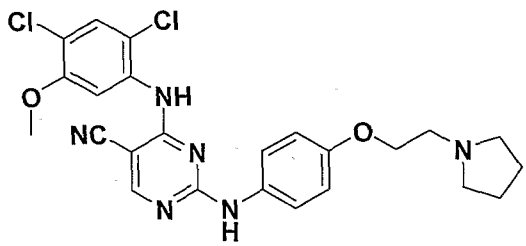

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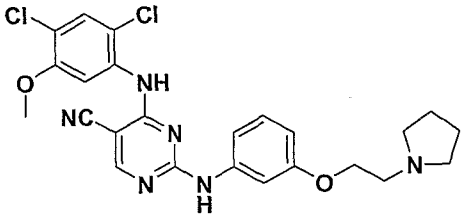

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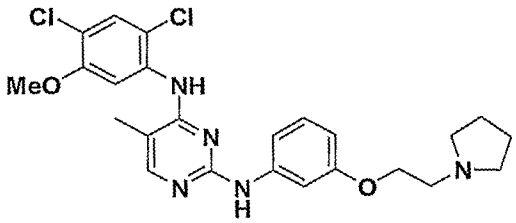

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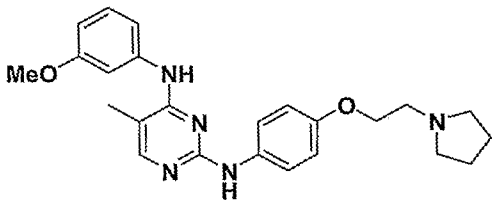

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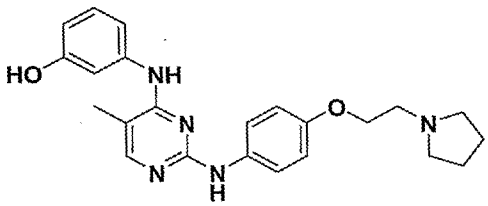

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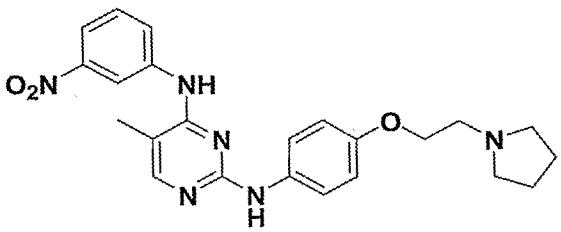

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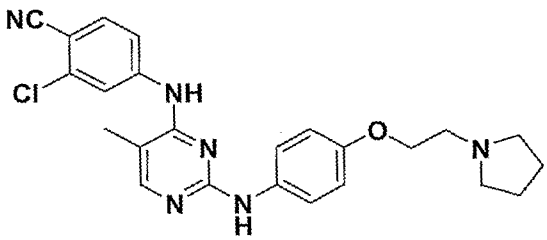

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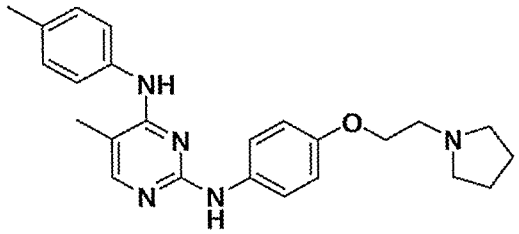

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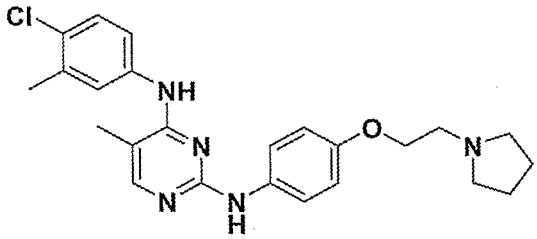

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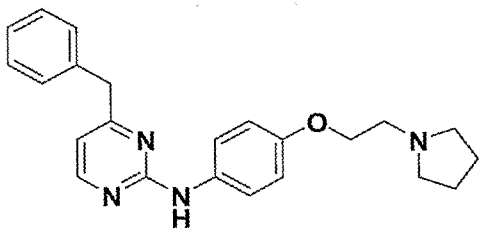

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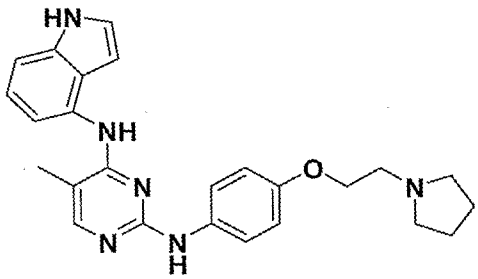

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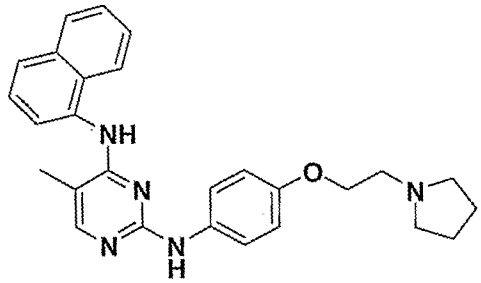

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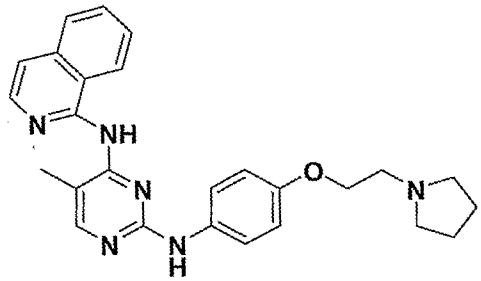

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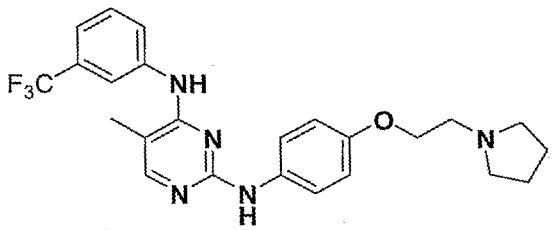

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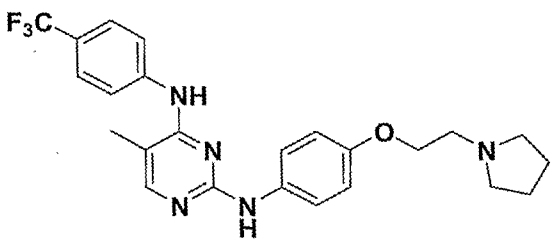

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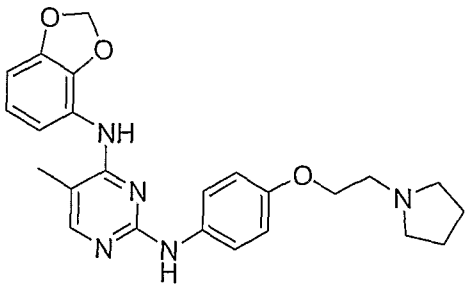

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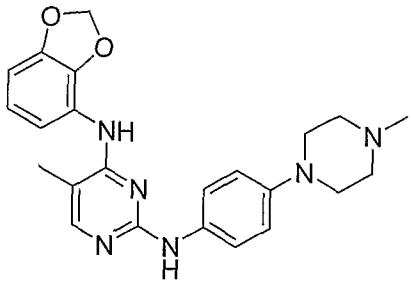

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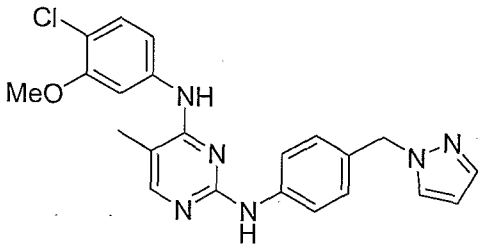

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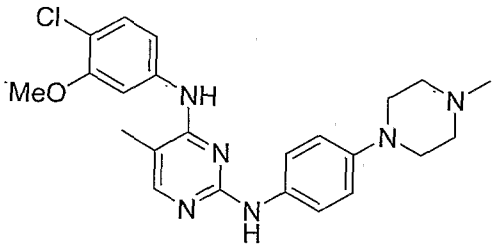

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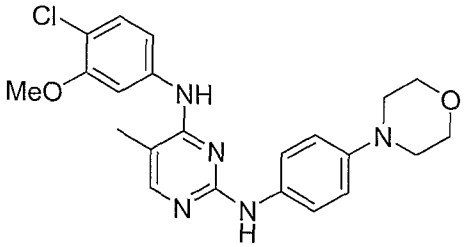

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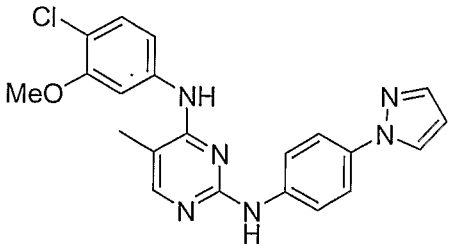

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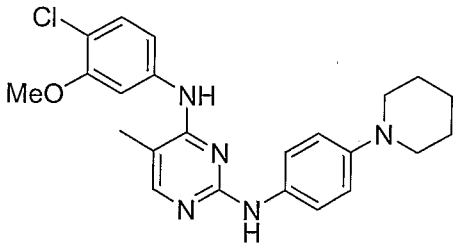

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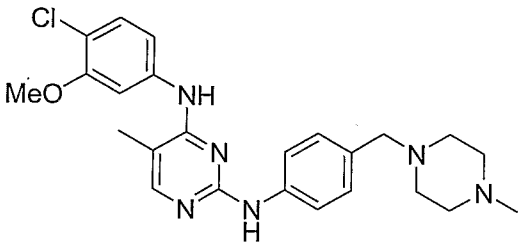

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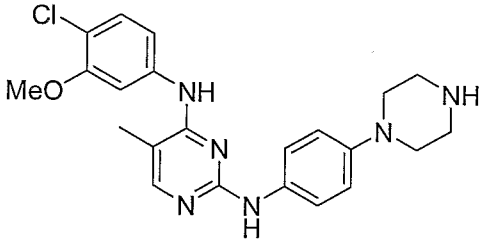

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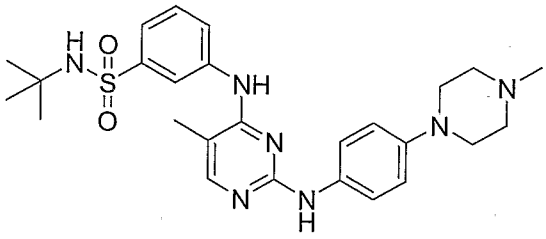

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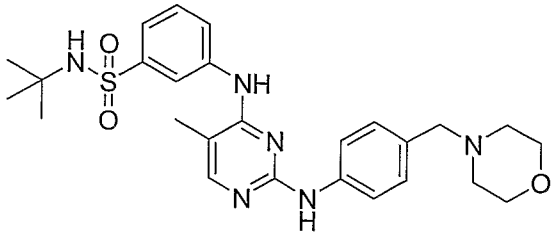

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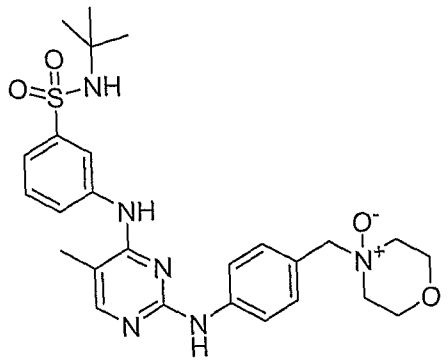

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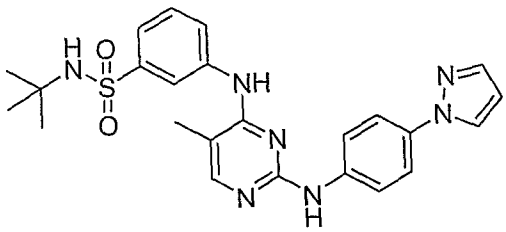

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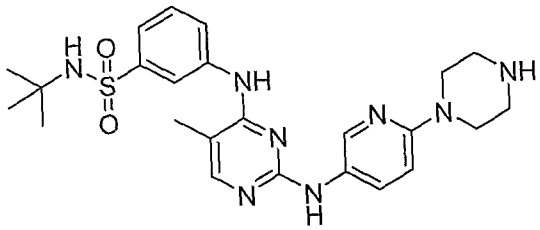

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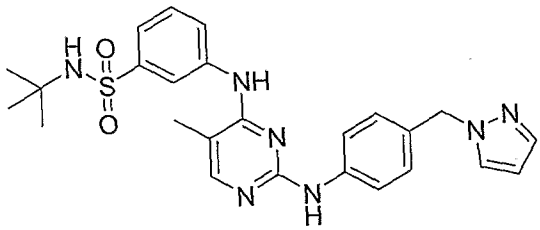

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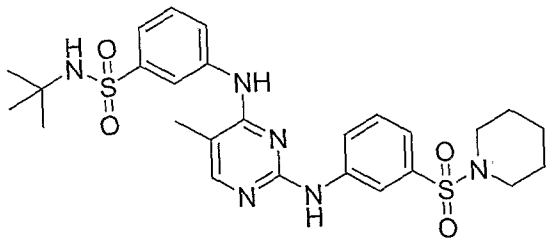

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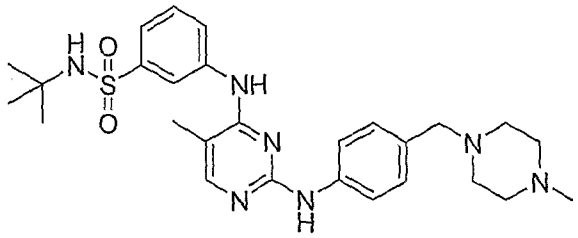

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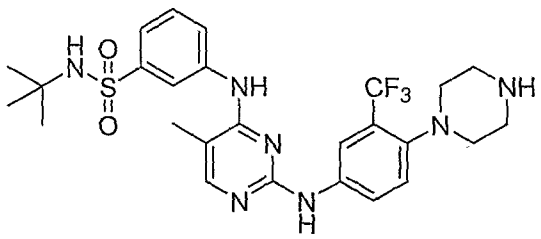

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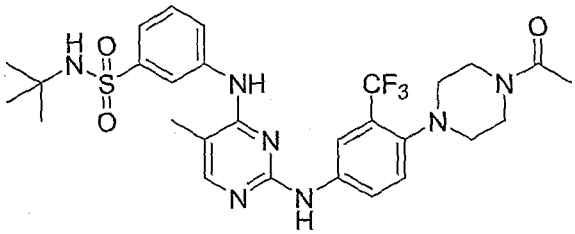

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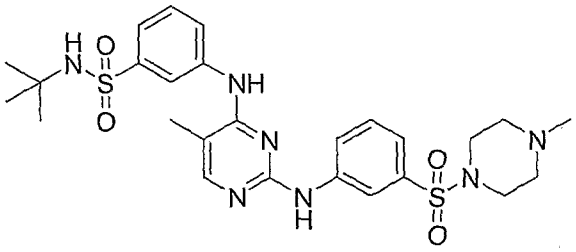

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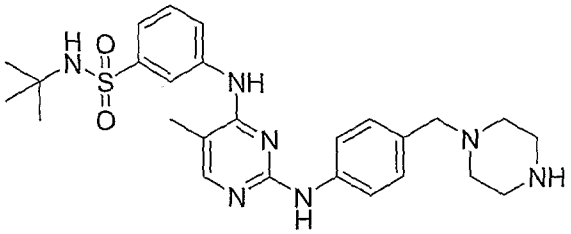

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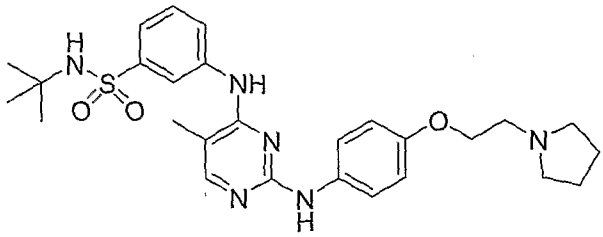

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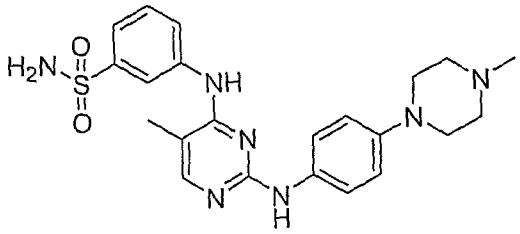

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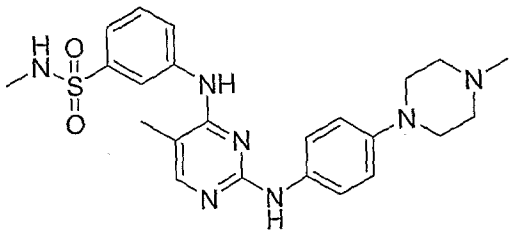

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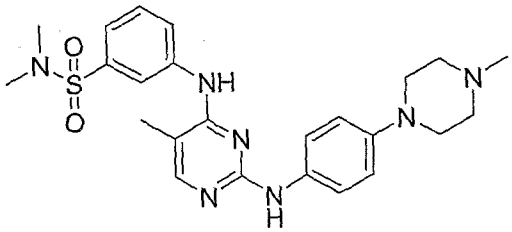

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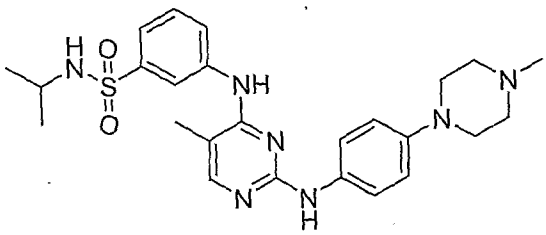

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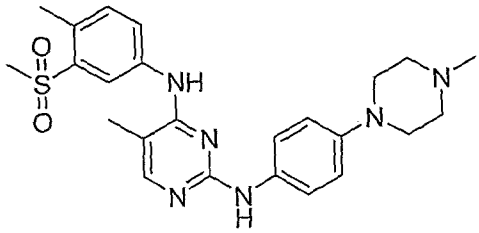

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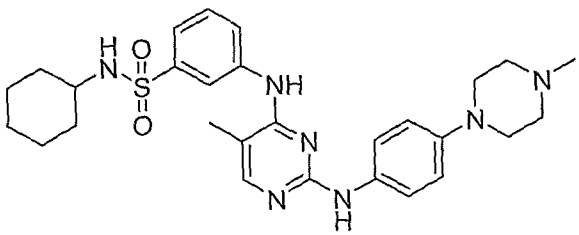

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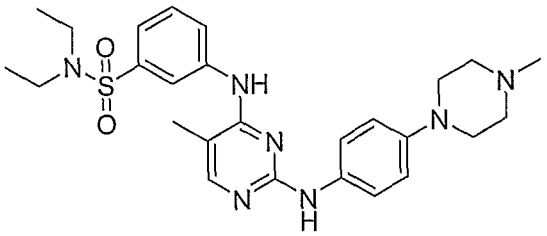

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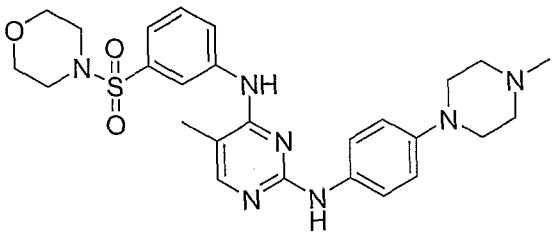

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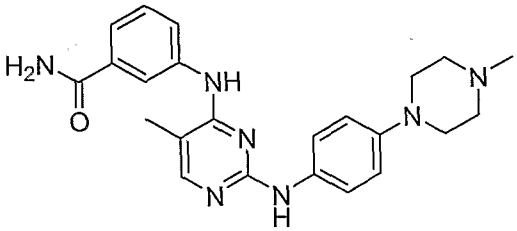

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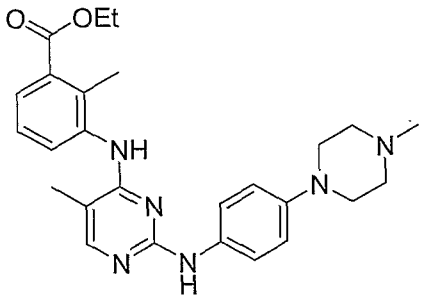

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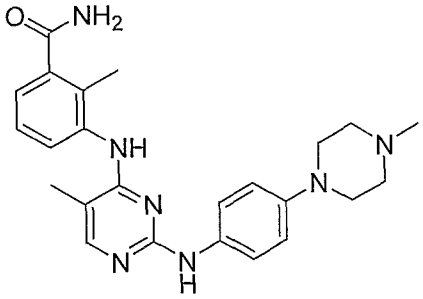

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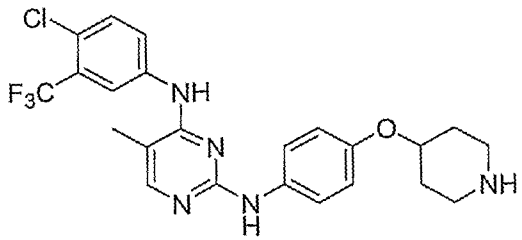

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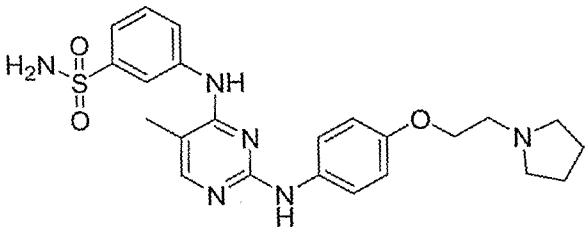

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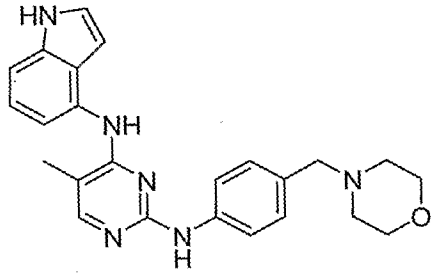

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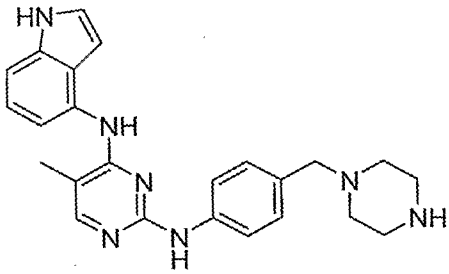

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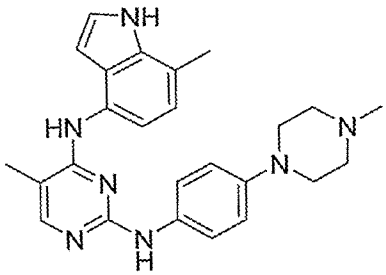

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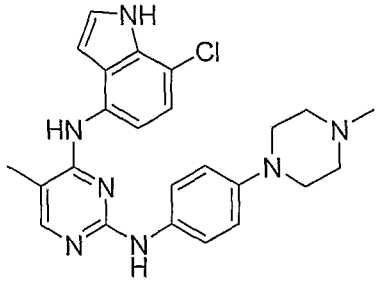

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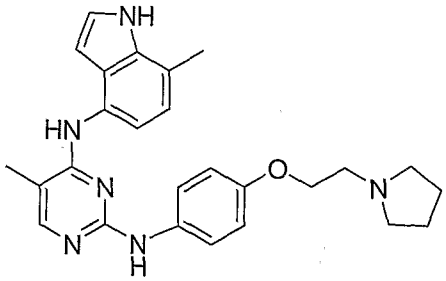

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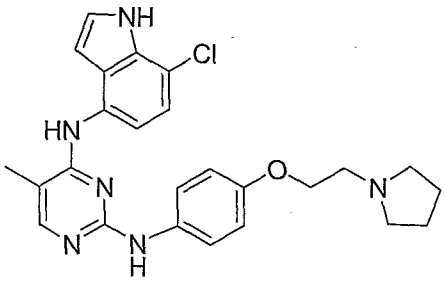

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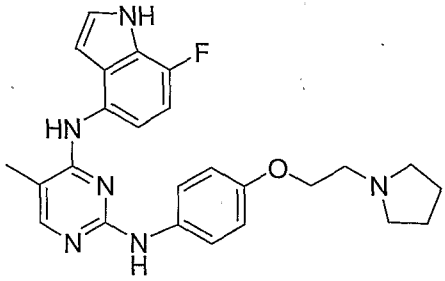

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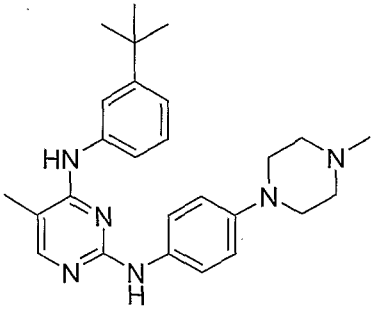

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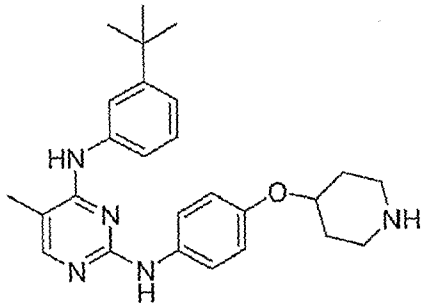

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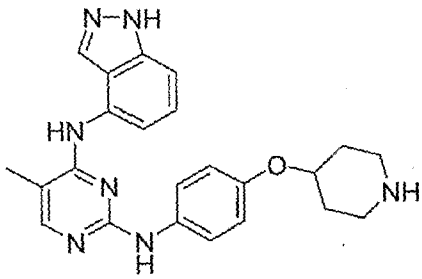

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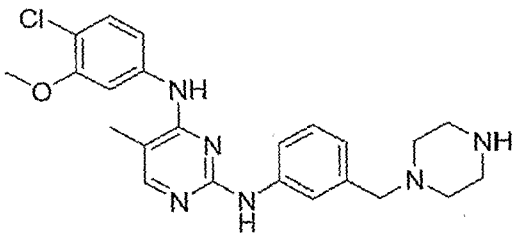

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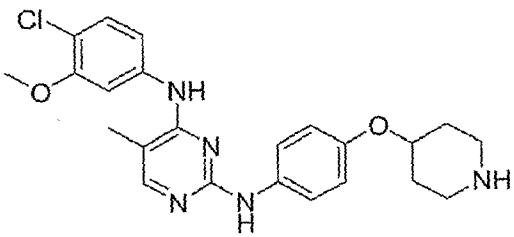

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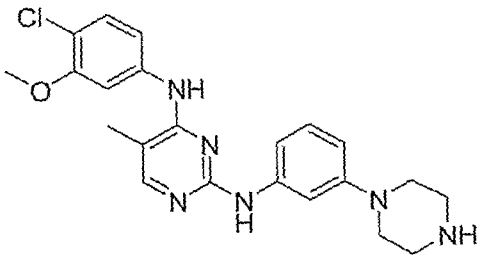

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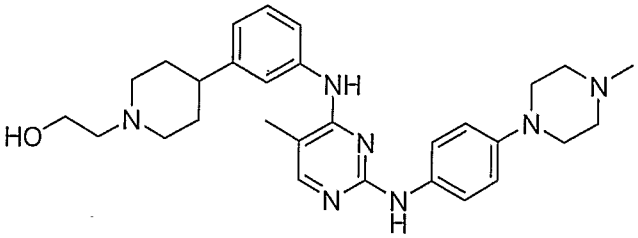

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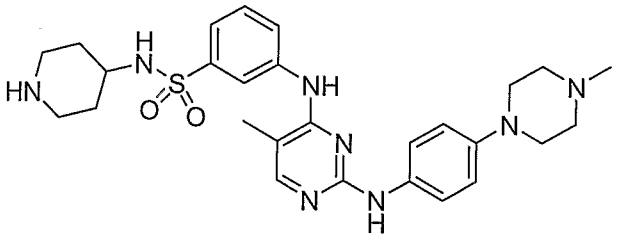

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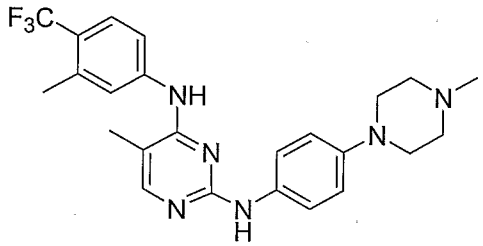

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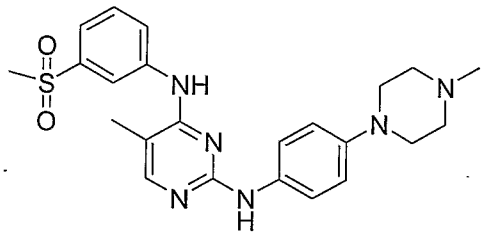

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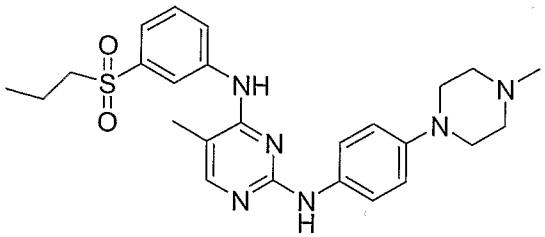

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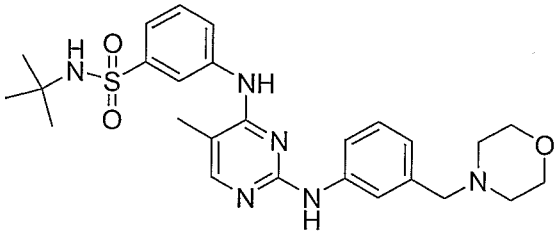

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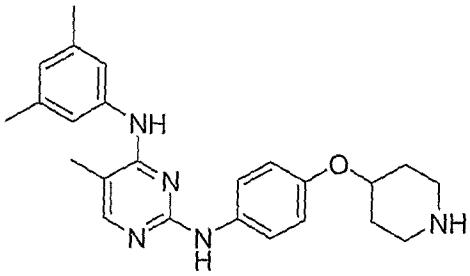

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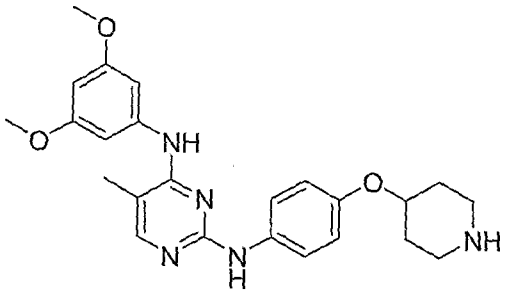

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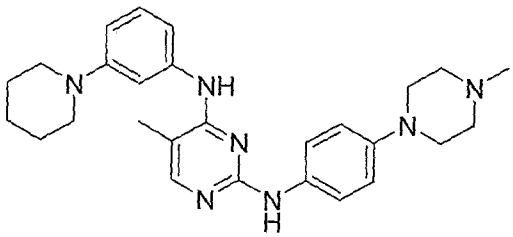

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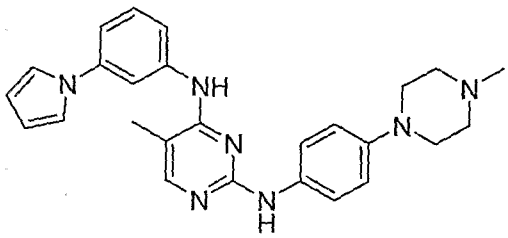

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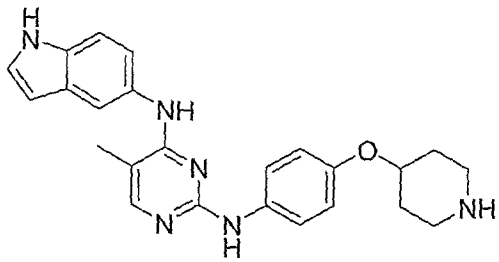

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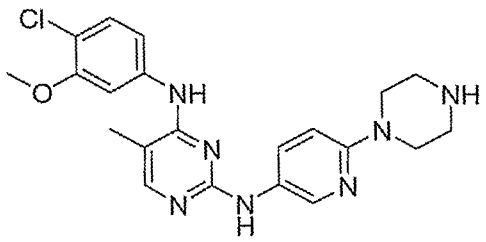

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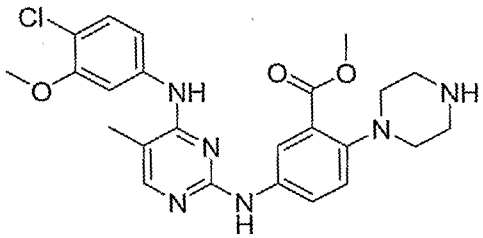

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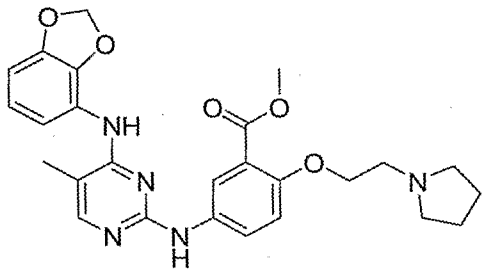

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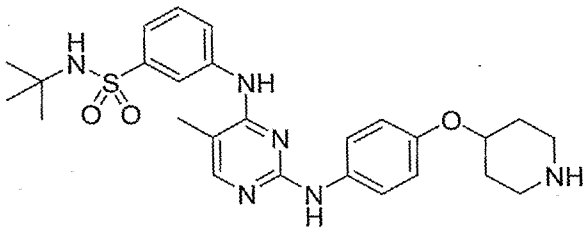

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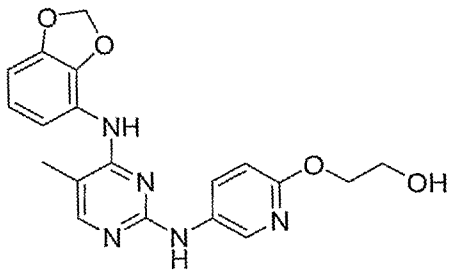

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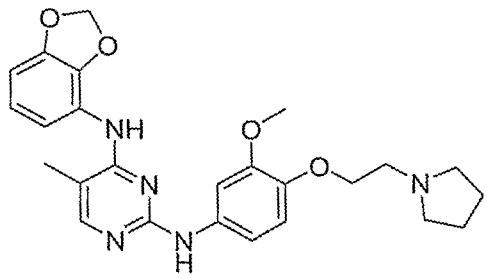

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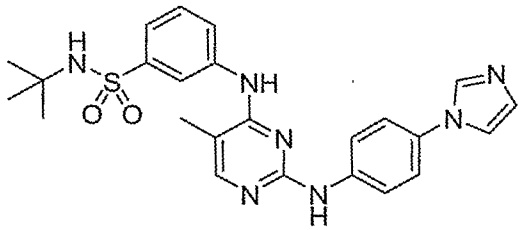

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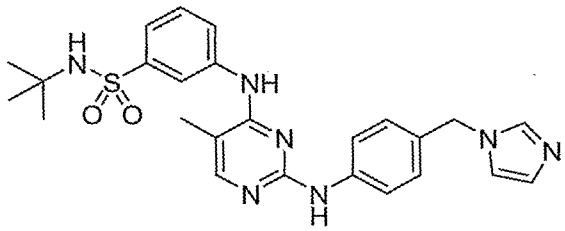

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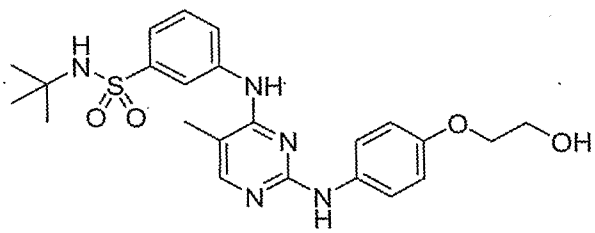

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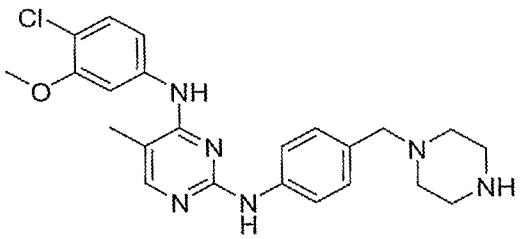

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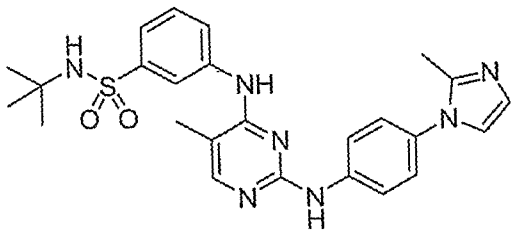

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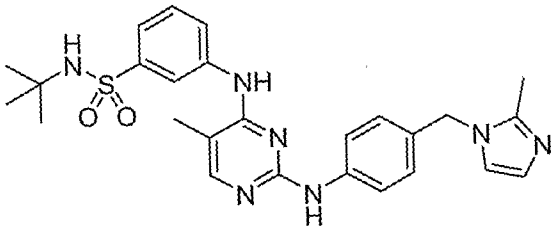

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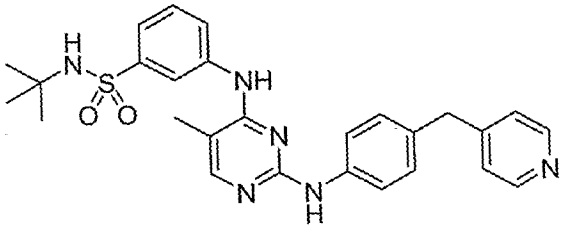

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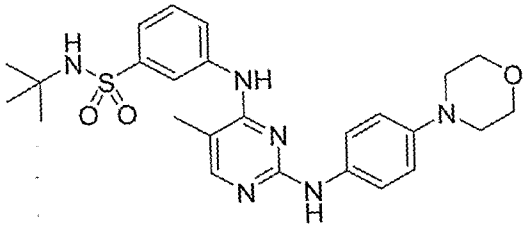

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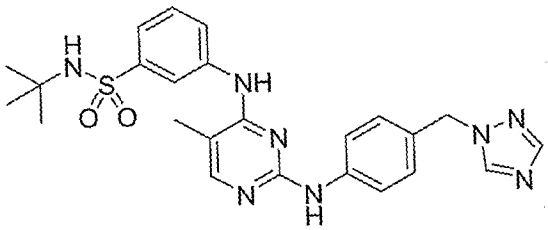

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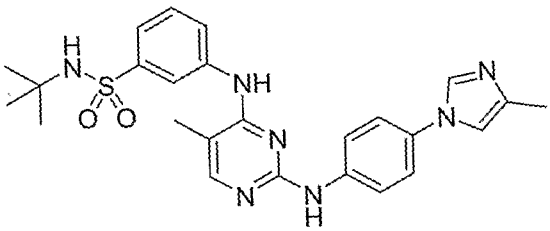

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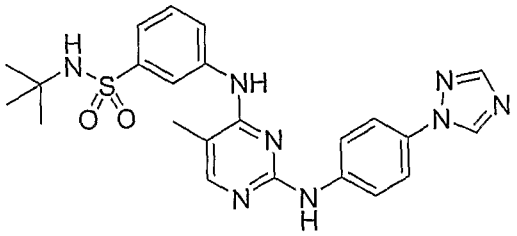

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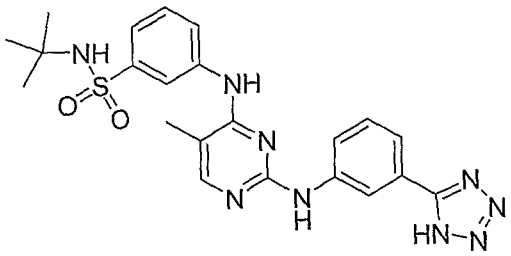

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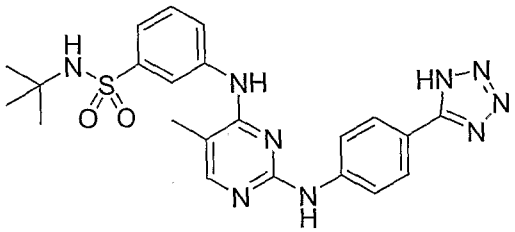

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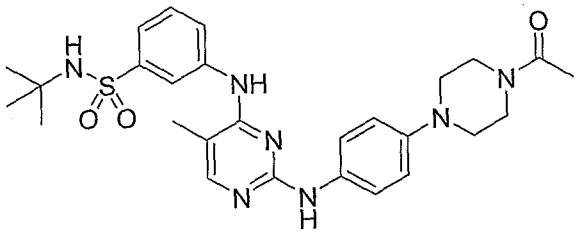

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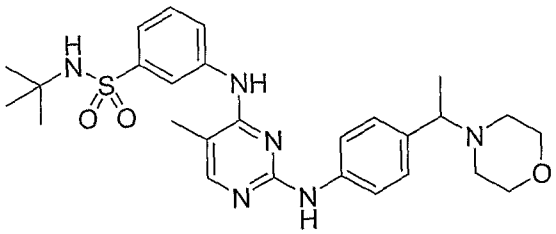

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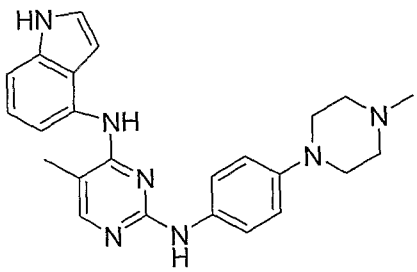

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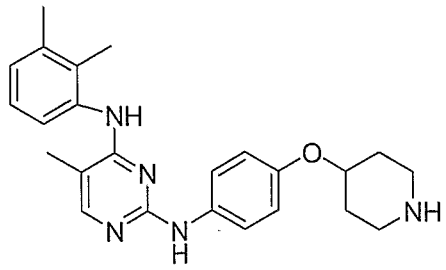

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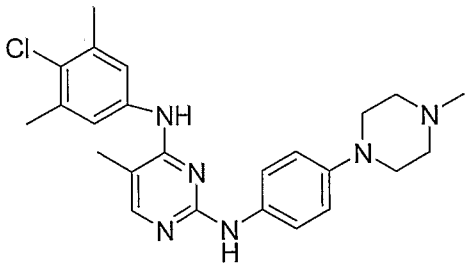

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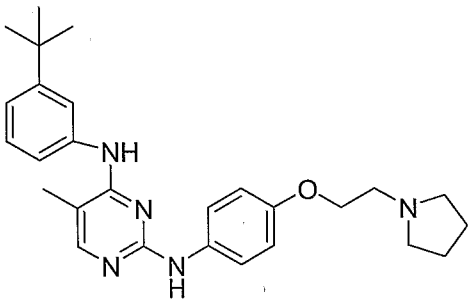

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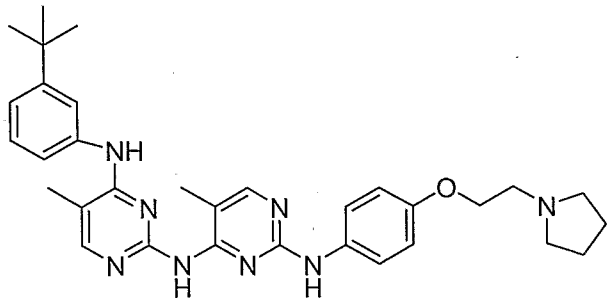

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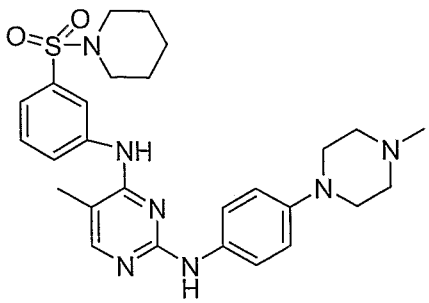

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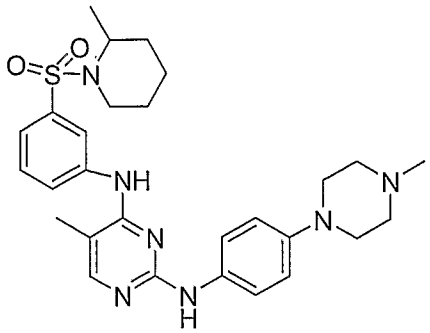

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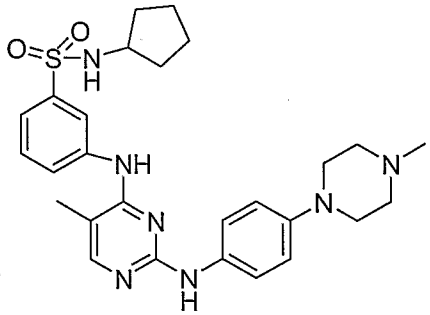

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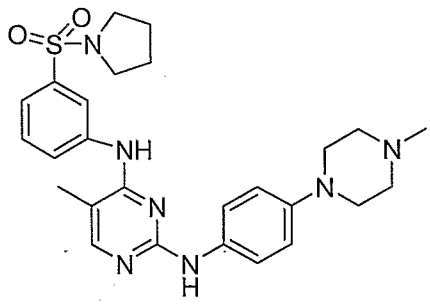

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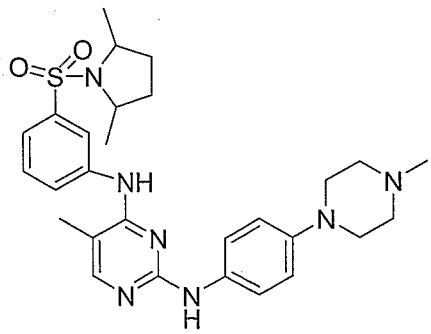

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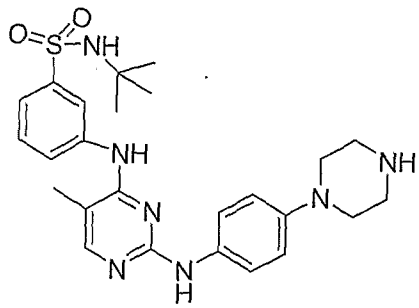

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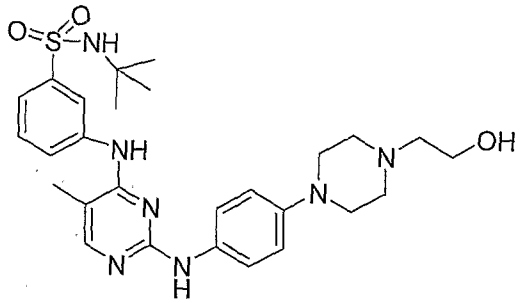

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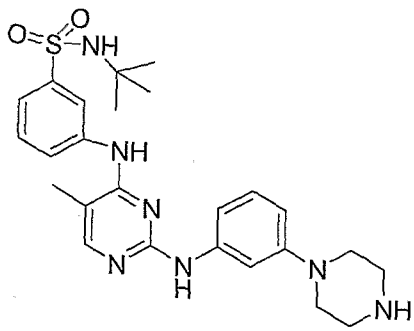

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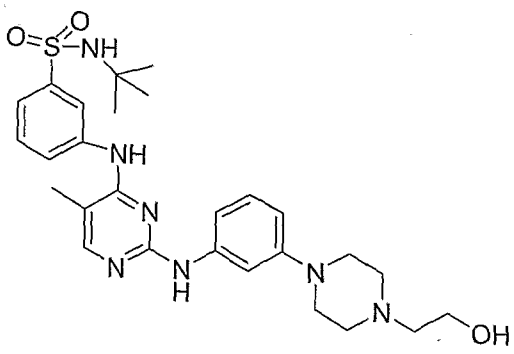

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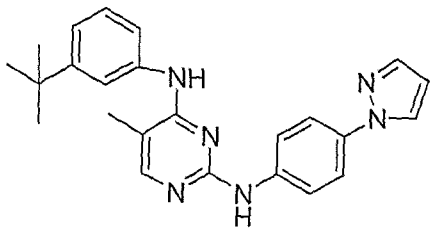

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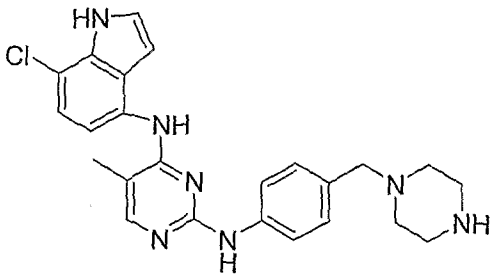

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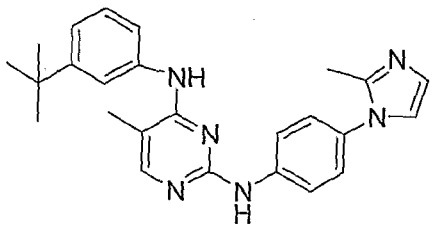

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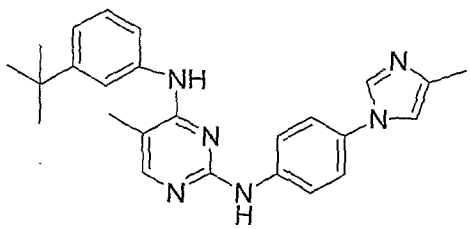

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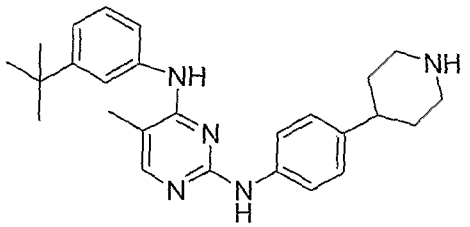

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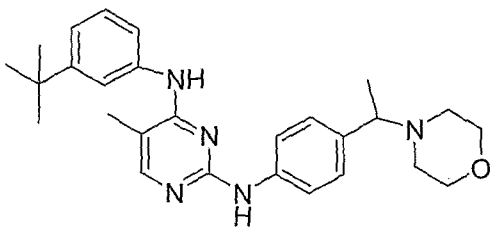

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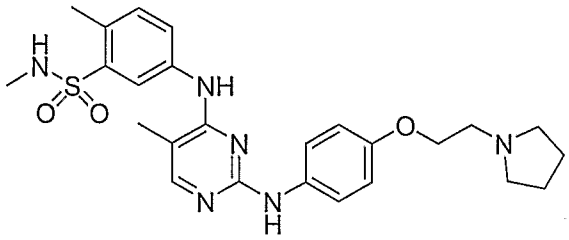

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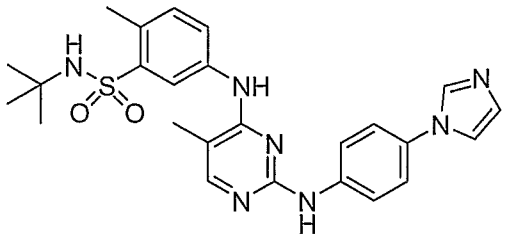

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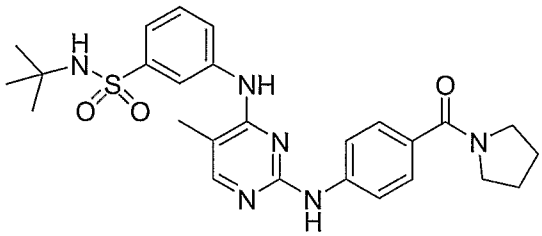

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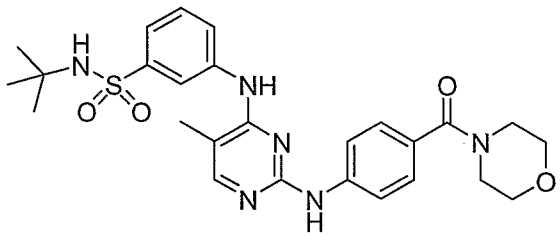

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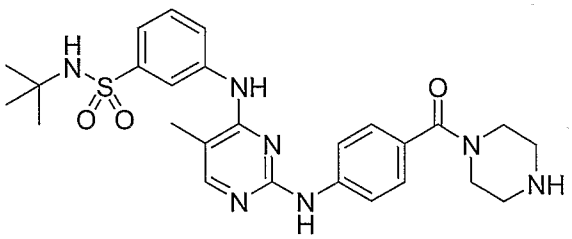

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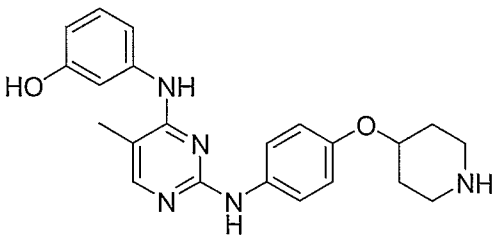

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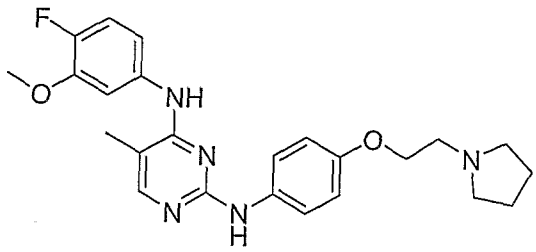

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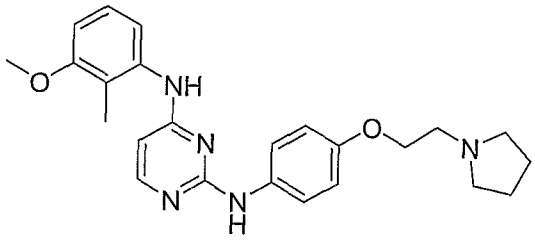

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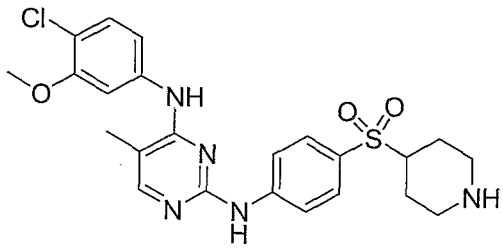

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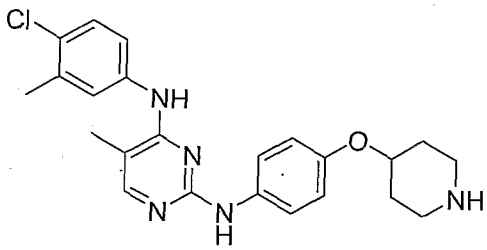

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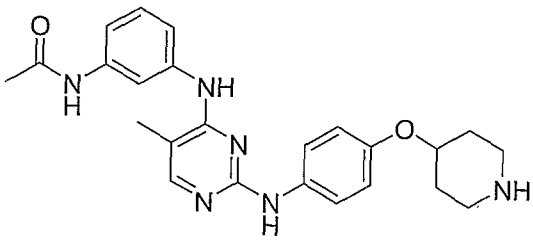

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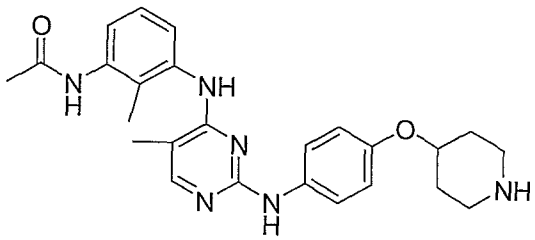

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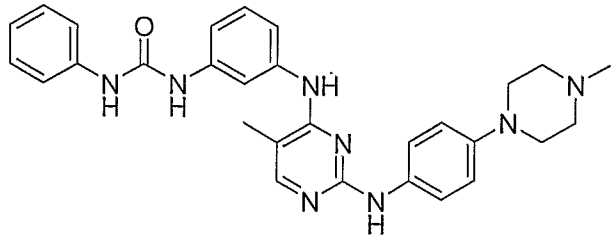

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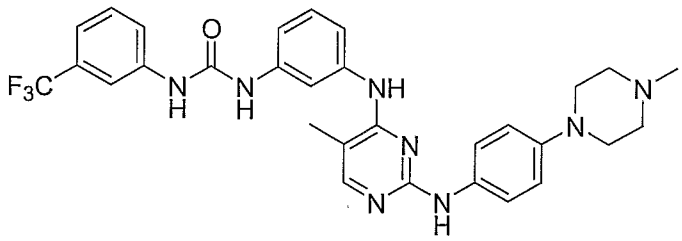

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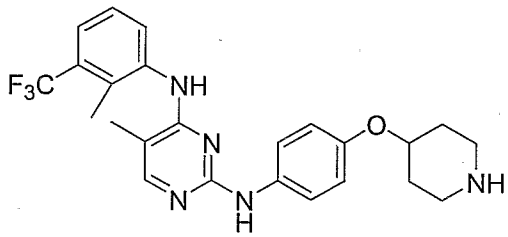

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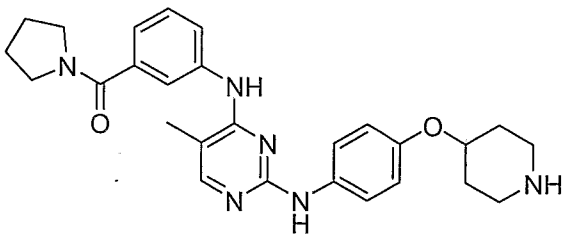

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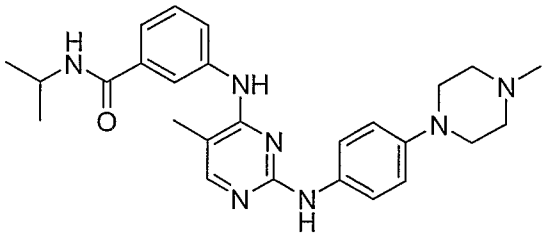

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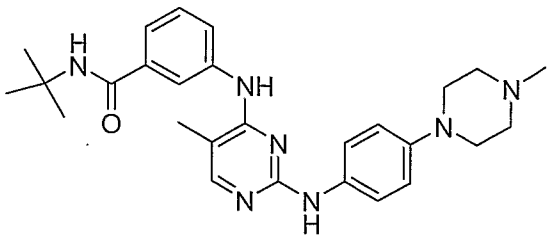

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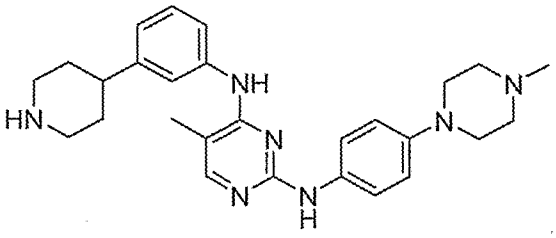

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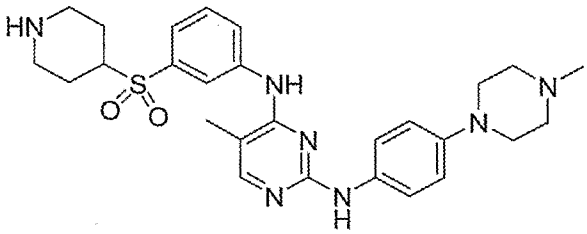

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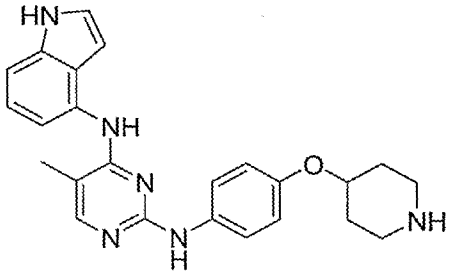

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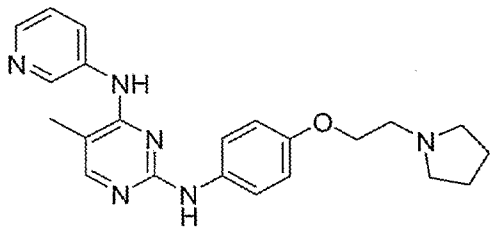

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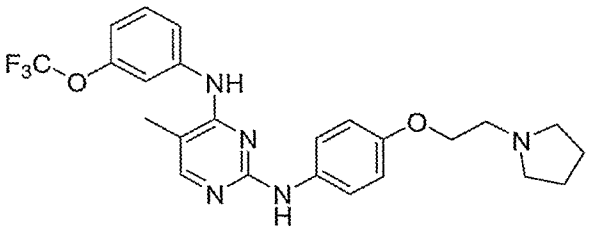

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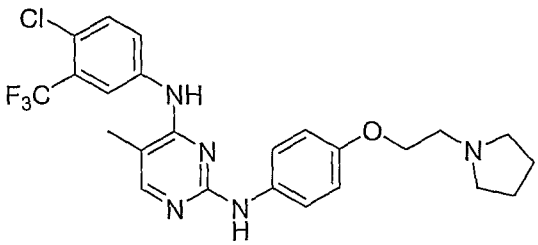

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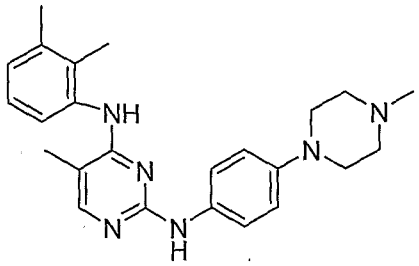

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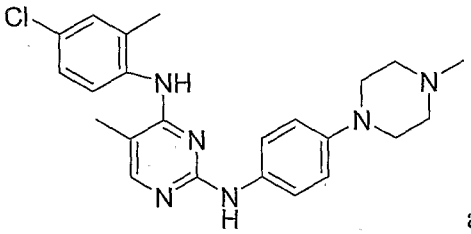

and

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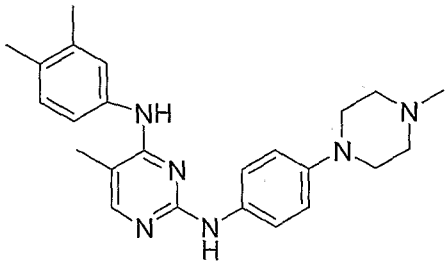


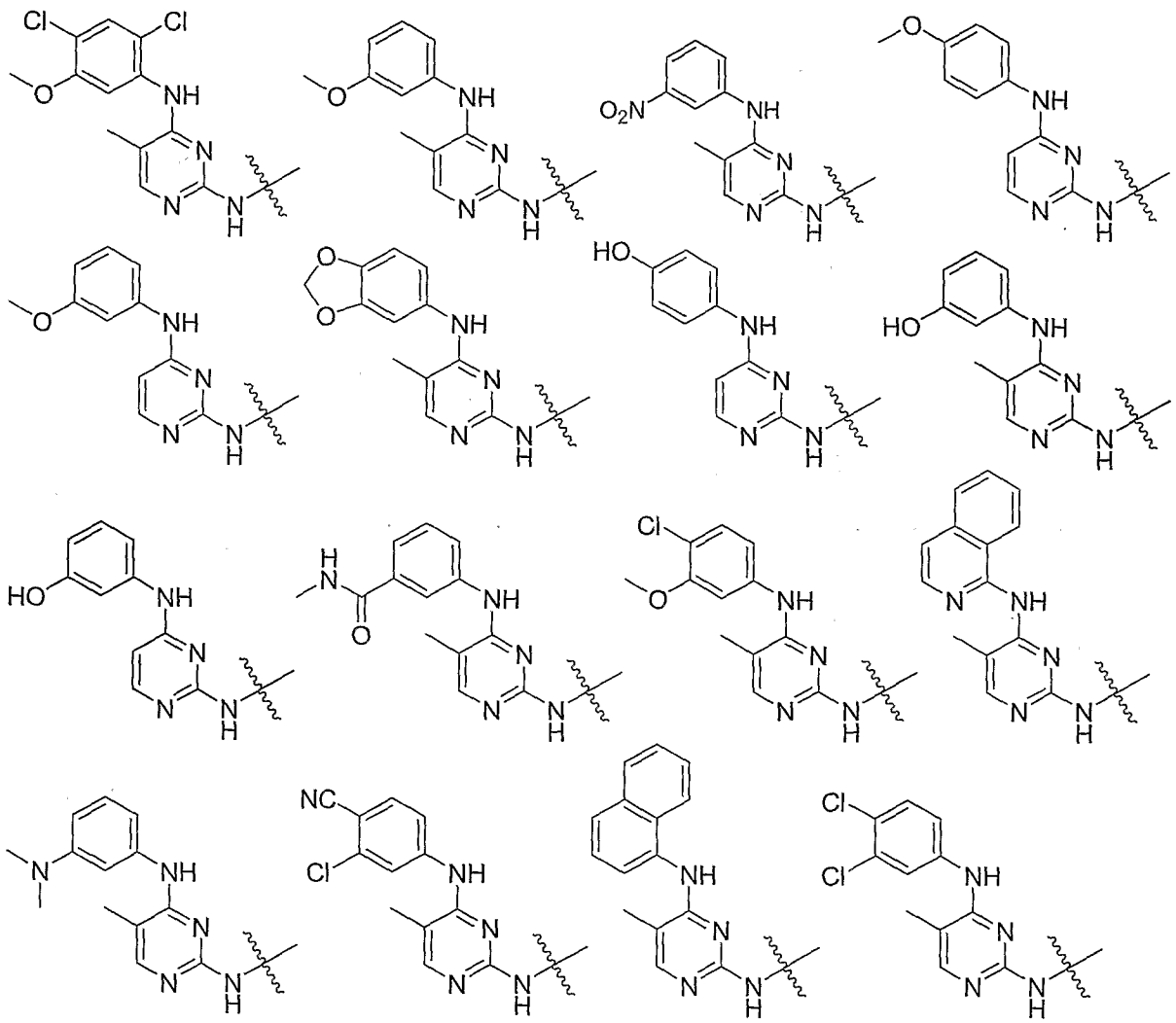
CLXII

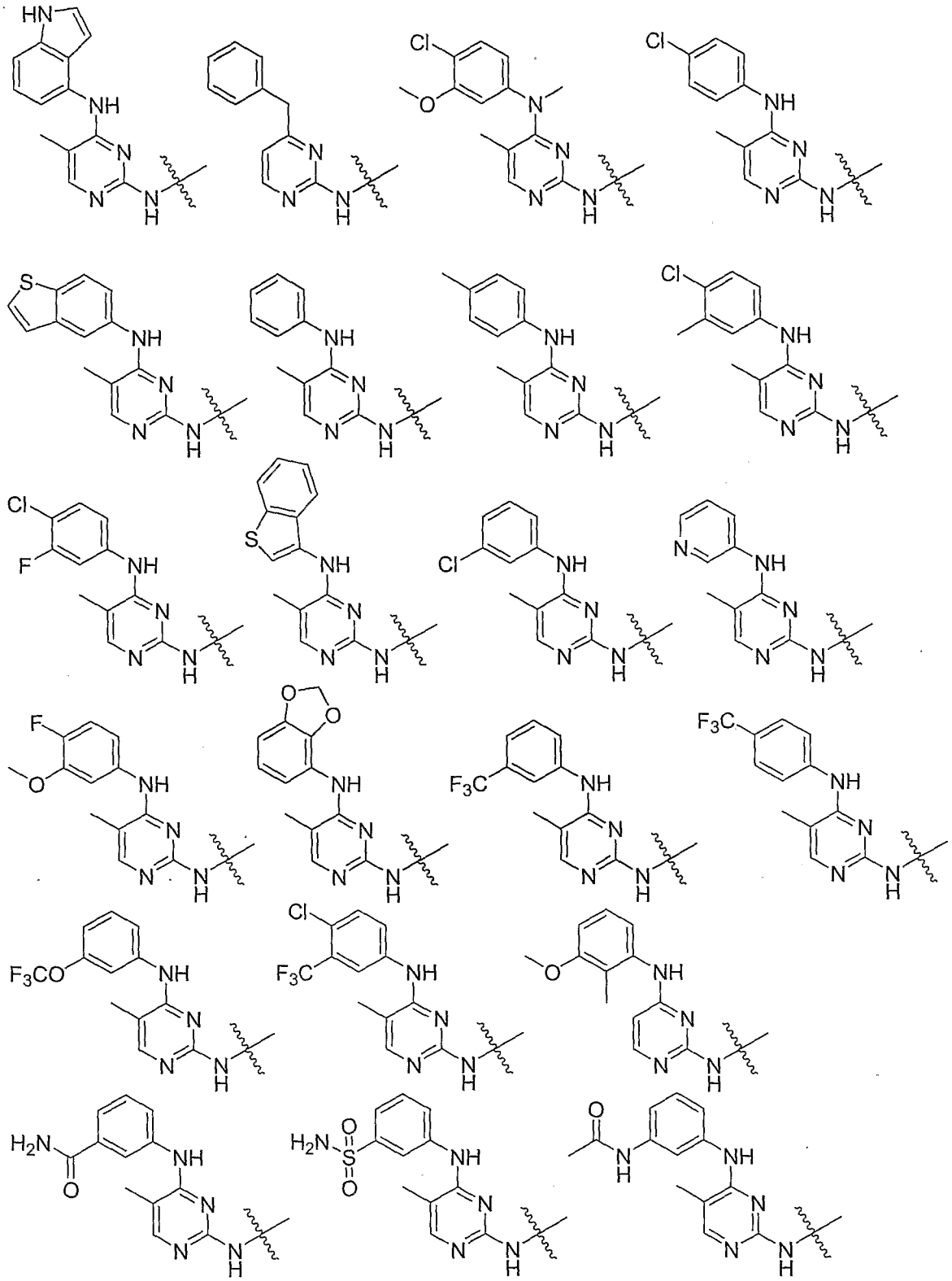
[0056] According to another embodiment of the invention, compounds having the general structure (Z):

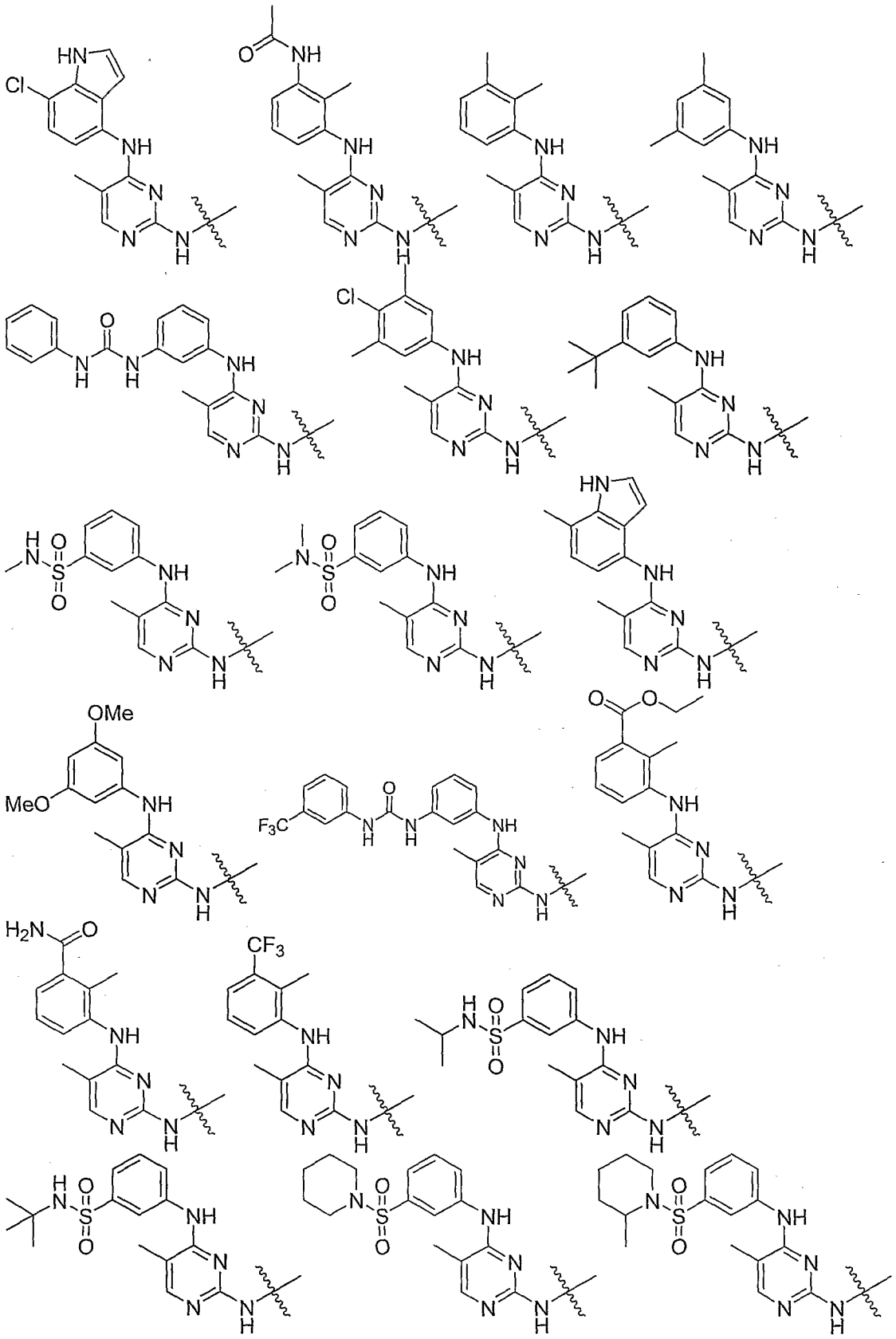
B-C (Z)

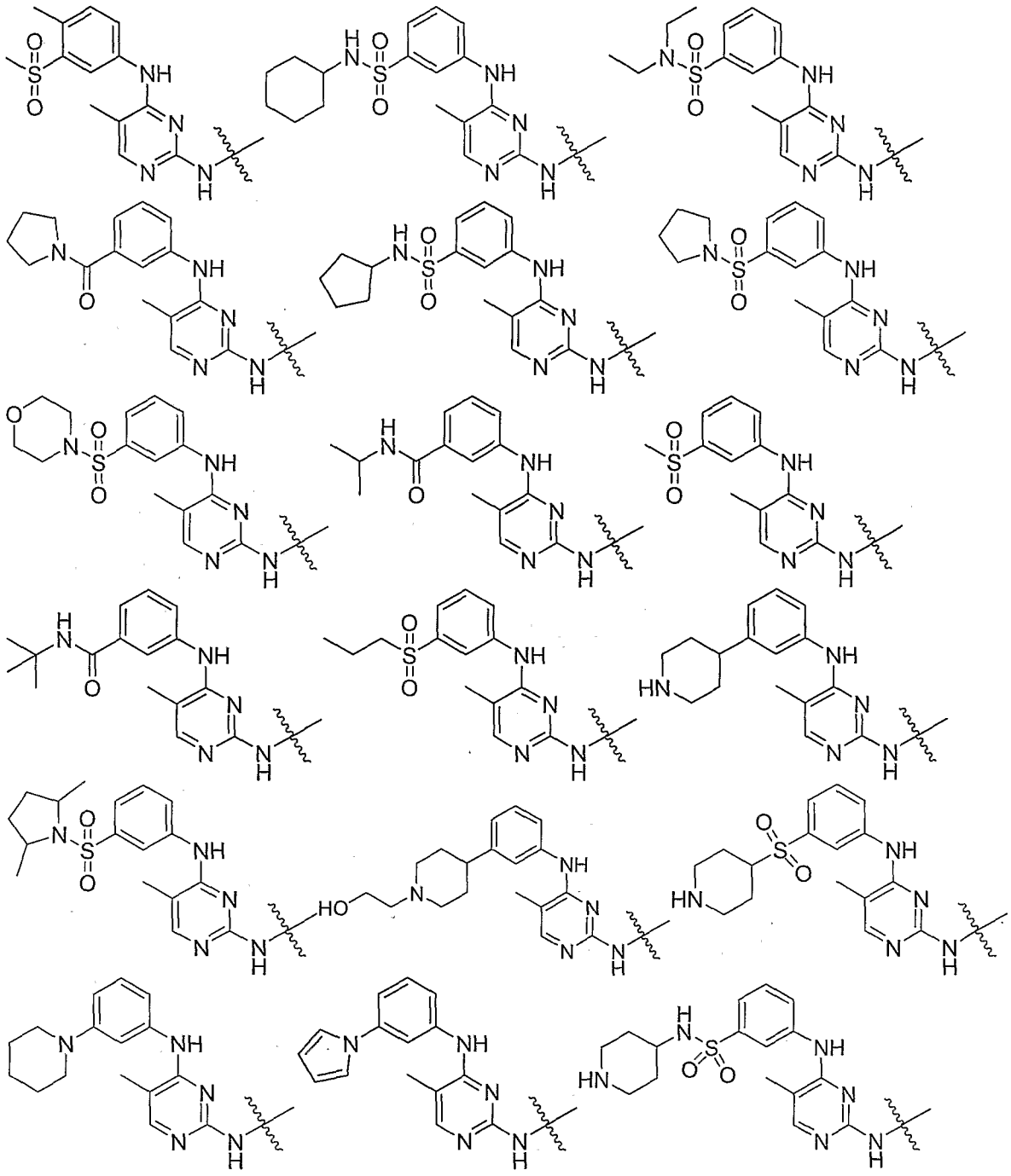
are provided for treatment of various diseases, disorders, and pathologies.

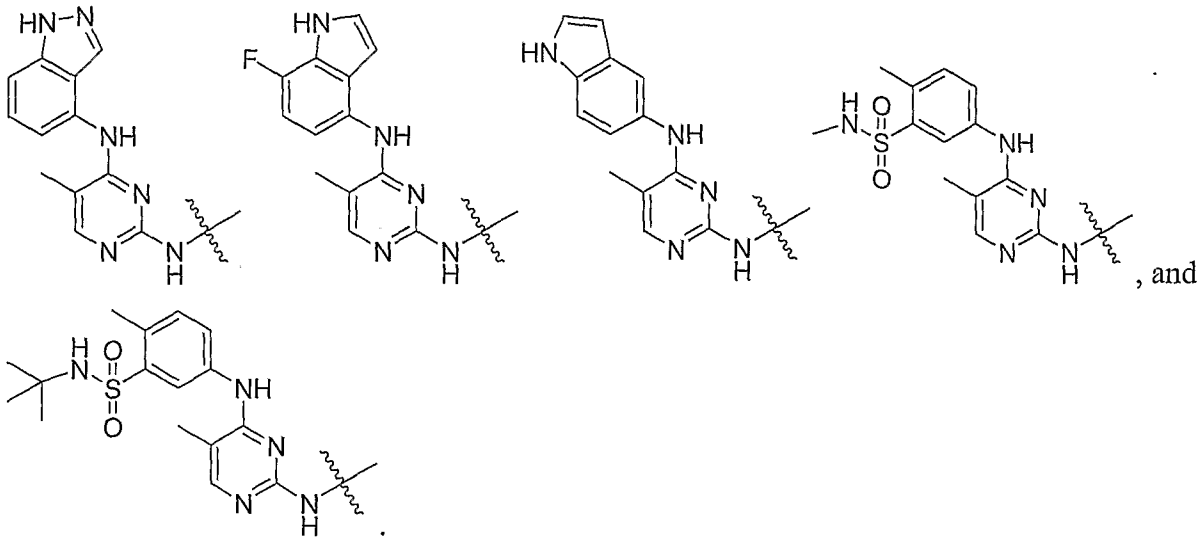
[0057] The general structure (Z) includes two chemically connected moieties B and C. The moiety B in the general structure (Z) includes any moiety selected from the following group:











, and

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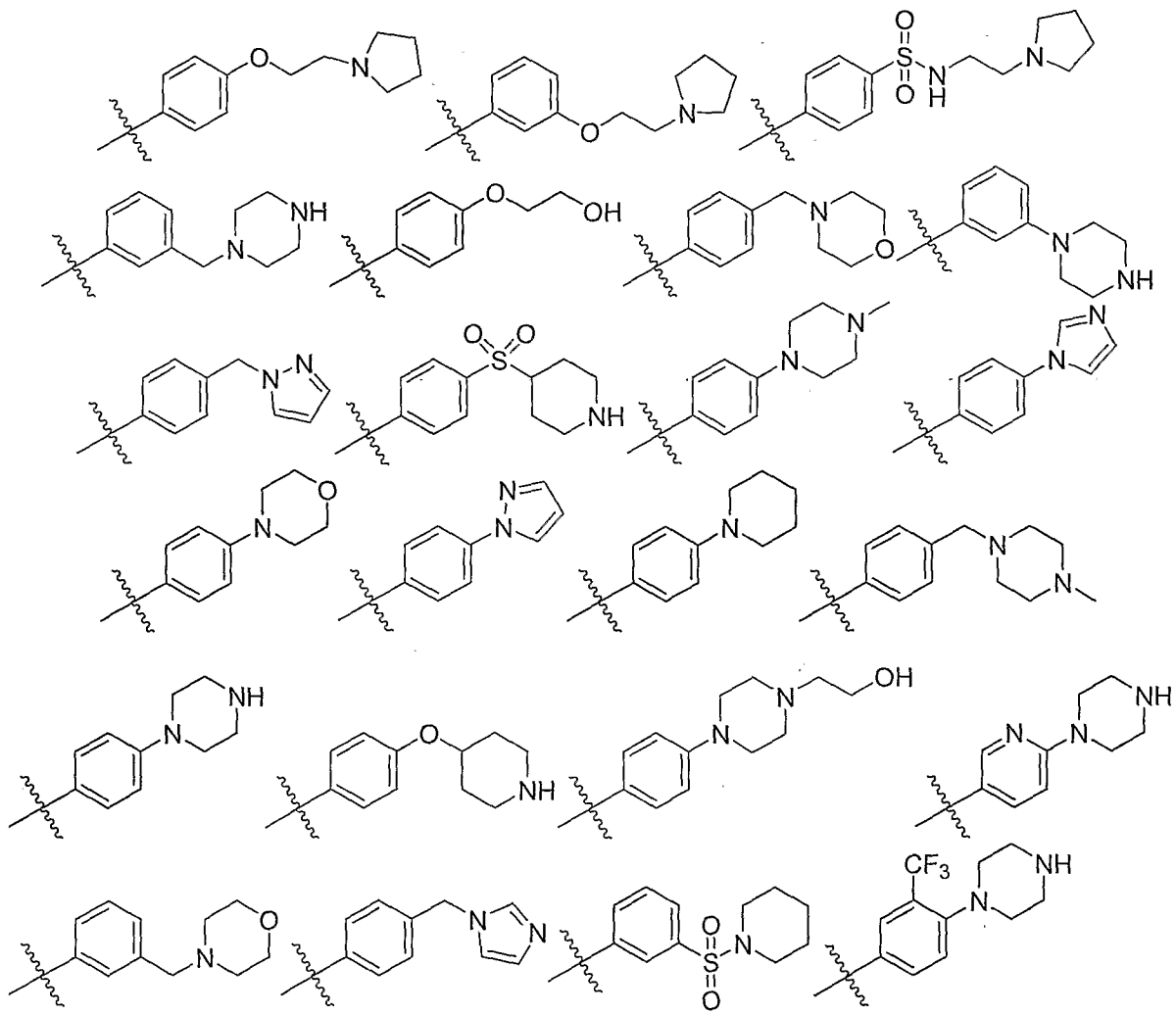
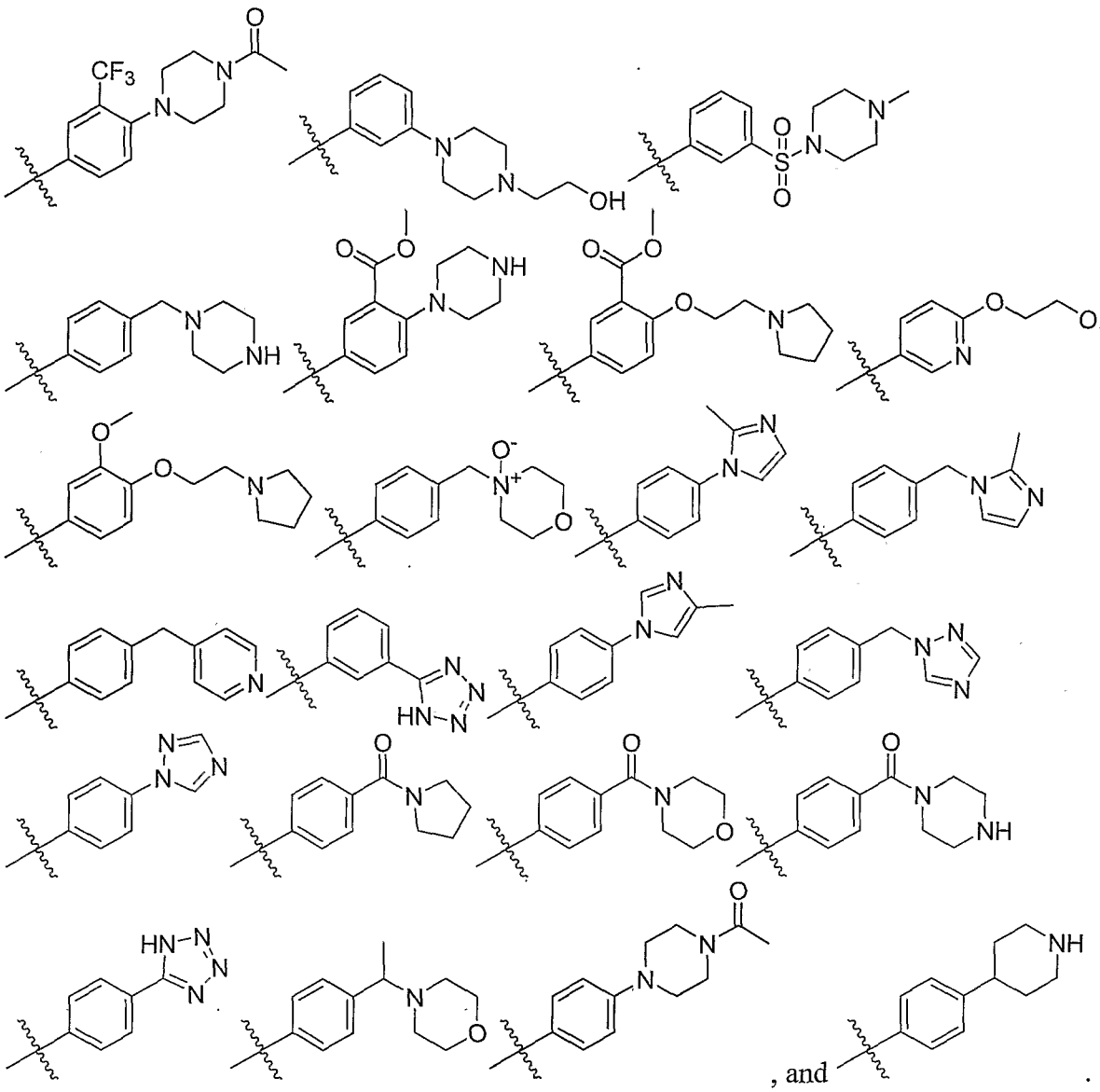
[0058] The moiety C in the structure (Z), above, includes any moiety selected from the following group:





, and .

[0059] The compounds and methods of the present invention, or pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers thereof, either when administered alone or in combination with other agents (e.g., chemotherapeutic agents or protein therapeutic agents described below) are useful in treating a variety of disorders, including, but not limited to, for example, myeloproliferative disorders, proliferative diabetic retinopathy and other angiogenic-associated disorders including solid tumors and other types of cancer, eye disease, inflammation, psoriasis, and a viral infection. The kinds of cancer that can be treated include, but are not limited to, an alimentary/gastrointestinal tract cancer, colon cancer, liver cancer, skin cancer, breast cancer, ovarian cancer, prostate cancer, lymphoma, leukemia (including acute myelogenous leukemia and chronic myelogenous leukemia), kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer or brain cancer.

[0060] Some examples of the diseases and disorders that can be treated also include ocular neovascularia ztion, infantile haemangiomas; organ hypoxia, vascular hyperplasia, organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type 1 diabetes and complications from diabetes, inflammatory disease, acute pancreatitis, chronic pancreatitis, asthma, allergies, adult respiratory distress syndrome, cardiovascular disease, liver disease, other blood disorders, asthma, rhinitis, atopic, dermatitits, autoimmune thryroid disorders, ulerative colitis, Crohn's disease, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, conditions associated with cytokines, and other autoimmune diseases including glomerulonephritis,, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopy (e.g., allergic asthma, atopic dermatitis, or allergic rhinitis), chronic active hepatitis, myasthenia graivs, multiple scleroiss, inflammatory bowel disease, graft vs host disease, neurodegenerative diseases including motor neuron disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral scelerosis, Huntington's disease, cerebral ischemia, or neurodegenerative disease caused by traumatic injury, strike, gluatamate neurtoxicity or hypoxia; ischemic/reperfusion injury in stroke, myocardial ischemica, renal ischemia, heart attacks, cardiac hypertrophy, atherosclerosis and arteriosclerosis, organ hyoxia, and platelet aggregation.

[0061] Examples of some additional diseases and disorders that can be treated also include cell mediated hypersensitivity (allergic contact dermatitis, hypersensitivity pneumonitis), rheumatic diseases (e.g., systemic lupus erythematosus (SLE), juvenile arthritis, Sjogren's Syndrome, scleroderma, polymyositis, ankylosing spondylitis, psoriatic arthritis), viral diseases (Epstein Barr Virus, Hepatitis B, Hepatitis C, HIV, HTLV1, Vaicella-Zoster Virus, Human Papilloma Virus), food allergy, cutaneous inflammation, and immune suppression induced by solid tumors.

[0062] Embodiments of the present invention also provide articles of manufacture that can include a packaging material and a pharmaceutical composition contained within the packaging material. The packaging material can comprise a label which indicates that the pharmaceutical composition can be used for treatment of one or more disorders identified above.

[0063] The pharmaceutical composition can include a compound according to the present invention. In addition to a compound of the present invention, the pharmaceutical may also contain other therapeutic agents, and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques known in the art of pharmaceutical formulation.

[0064] Thus, in one embodiment, the invention provides a pharmaceutical composition including a therapeutic agent and a compound of the invention. The compound is present in a concentration effective to treat, for example, cancer or to treat another disease or disorder described above.

[0065] The compounds of the invention may be formulated into therapeutic compositions as natural or salt forms. Pharmaceutically acceptable non-toxic salts include the base addition salts (formed with free carboxyl or other anionic groups) which may be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino-ethanol, histidine, procaine, and the like. Such salts may also be formed as acid addition salts with any free cationic groups and will generally be formed with inorganic acids such as, for example, hydrochloric, sulfuric, or phosphoric acids, or organic acids such as acetic, citric, p-toluenesulfonic, methanesulfonic acid, oxalic, tartaric, mandelic, and the like.

[0066] Salts of the invention can include amine salts formed by the protonation of an amino group with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like. Salts of the invention can also include amine salts formed by the protonation of an amino group with suitable organic acids, such as p-toluenesulfonic acid, acetic acid, methanesulfonic acid and the like. Additional excipients which are contemplated for use in the practice of the present invention are those available to those of ordinary skill in the art, for example, those found in the United States Pharmacopeia Vol. XXII and National Formulary Vol. XVII, U.S. Pharmacopeia Convention, Inc., Rockville, MD (1989), the relevant contents of which is incorporated herein by reference. In addition, polymorphs of the invention compounds are included in the present invention.

[0067] Pharmaceutical compositions of the invention may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, intrathecal, or intracisternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds may also be administered liposomally.

[0068] In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

[0069] The pharmaceutical compositions for the administration of the compounds of this embodiment, either alone or in combination with other therapeutic agents, may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

[0070] Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for control release.

[0071] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0072] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. Also useful as a solubilizer is polyethylene glycol, for example. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or *n*-propyl, *p*-

hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0073] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0074] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0075] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[0076] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a parenterally-acceptable diluent or solvent or cosolvent or complexing agent or dispersing agent or excipient or combination thereof, for example 1,3-butanediol, polyethylene glycols, polypropylene glycols, ethanol or other alcohols, povidones, various brands of TWEEN surfactant, sodium dodecyl sulfate, sodium deoxycholate, dimethylacetamide, polysorbates, poloxamers, cyclodextrins, lipids, and excipients such as inorganic salts (e.g., sodium chloride), buffering agents (e.g., sodium citrate, sodium phosphate), and sugars (e.g., saccharose and dextrose). Among the acceptable vehicles and solvents that may be employed are water, dextrose solutions, Ringer's solutions and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be

employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0077] Depending on the condition being treated, these pharmaceutical compositions may be formulated and administered systemically or locally. Techniques for formulation and administration may be found in the latest edition of "Remington's Pharmaceutical Sciences" (Mack Publishing Co, Easton Pa.). Suitable routes may, for example, include oral or transmucosal administration; as well as parenteral delivery, including intramuscular, subcutaneous, intramedullary, intrathecal, intraventricular, intravenous, intraperitoneal, or intranasal administration. For injection, the pharmaceutical compositions of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. For tissue or cellular administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0078] The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0079] For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles).

[0080] In one embodiment, the invention compounds are administered in combination with an anti-inflammatory agent, antihistamines, chemotherapeutic agent, immunomodulator, therapeutic antibody or a protein kinase inhibitor, e.g., a tyrosine kinase inhibitor, to a subject in need of such treatment. While not wanting to be limiting, chemotherapeutic agents include antimetabolites, such as methotrexate, DNA cross-linking agents, such as cisplatin/carboplatin; alkylating agents, such as canbusil; topoisomerase I inhibitors such as dactinomicin; microtubule inhibitors such as taxol (paclitaxol), and the like. Other chemotherapeutic agents include, for example, a vinca alkaloid, mitomycin-type antibiotic, bleomycin-type antibiotic, antifolate, colchicine, demecoline, etoposide, taxane, anthracycline antibiotic, doxorubicin, daunorubicin, carminomycin, epirubicin, idarubicin, mithoxanthrone, 4-dimethoxy-daunomycin, 11-deoxydaunorubicin, 13-deoxydaunorubicin, adriamycin-14-benzoate, adriamycin-14-octanoate, adriamycin-14-naphthaleneacetate, amsacrine, carmustine, cyclophosphamide, cytarabine, etoposide, lovastatin, melphalan, topetecan, oxalaplatin, chlorambucil, methtrexate, lomustine, thioguanine, asparaginase, vinblastine, vindesine, tamoxifen, or mechlorethamine. While not wanting to be limiting, therapeutic antibodies include antibodies directed against the HER2 protein, such as trastuzumab; antibodies directed against growth factors or growth factor receptors, such as bevacizumab, which targets vascular endothelial growth factor, and OSI-774, which targets epidermal growth factor; antibodies targeting integrin receptors, such as Vitaxin (also known as MEDI-522), and the like. Classes of anticancer agents suitable for use in compositions and methods of the present invention include, but are not limited to: 1) alkaloids, including, microtubule inhibitors (e.g., Vincristine, Vinblastine, and Vindesine, etc.), microtubule stabilizers (e.g., Paclitaxel [Taxol], and Docetaxel, Taxotere, etc.), and chromatin function inhibitors, including, topoisomerase inhibitors, such as, epipodophyllotoxins (e.g., Etoposide [VP-16], and Teniposide [VM-26], etc.), and agents that target topoisomerase I (e.g., Camptothecin and Isirinotecan [CPT-11], etc.); 2) covalent DNA-binding agents [alkylating agents], including, nitrogen mustards (e.g., Mechlorethamine, Chlorambucil, Cyclophosphamide, Ifosphamide, and Busulfan [Myleran], etc.), nitrosoureas (e.g., Carmustine, Lomustine, and Semustine, etc.), and other alkylating agents (e.g., Dacarbazine, Hydroxymethylmelamine, Thiotepa, and Mitocycin, etc.); 3) noncovalent DNA-binding agents [antitumor antibiotics], including, nucleic acid inhibitors (e.g., Dactinomycin [Actinomycin D], etc.), anthracyclines (e.g., Daunorubicin [Daunomycin, and Cerubidine], Doxorubicin [Adriamycin], and Idarubicin [Idamycin], etc.), anthracenediones (e.g.,

anthracycline analogues, such as, [Mitoxantrone], etc.), bleomycins (Blenoxane), etc., and plicamycin (Mithramycin), etc.; 4) antimetabolites, including, antifolates (e.g., Methotrexate, Folex, and Mexate, etc.), purine antimetabolites (e.g., 6-Mercaptopurine [6-MP, Purinethol], 6-Thioguanine [6-TG], Azathioprine, Acyclovir, Ganciclovir, Chlorodeoxyadenosine, 2-Chlorodeoxyadenosine [CdA], and 2'-Deoxycoformycin [Pentostatin], etc.), pyrimidine antagonists (e.g., fluoropyrimidines [e.g., 5-fluorouracil (Adrucil), 5-fluorodeoxyuridine (FdUrd) (Floxuridine)] etc.), and cytosine arabinosides (e.g., Cytosar [ara-C] and Fludarabine, etc.); 5) enzymes, including, L-asparaginase; 6) hormones, including, glucocorticoids, such as, antiestrogens (e.g., Tamoxifen, etc.), nonsteroidal antiandrogens (e.g., Flutamide, etc.), and aromatase inhibitors (e.g., anastrozole [Arimidex], etc.); 7) platinum compounds (e.g., Cisplatin and Carboplatin, etc.); 8) monoclonal antibodies conjugated with anticancer drugs, toxins, and/or radionuclides, etc.; 9) biological response modifiers (e.g., interferons [e.g., IFN-.alpha., etc.] and interleukins [e.g., IL-2, etc.], etc.); 10) adoptive immunotherapy; 11) hematopoietic growth factors; 12) agents that induce tumor cell differentiation (e.g., all-trans-retinoic acid, etc.); 13) gene therapy techniques; 14) antisense therapy techniques; 15) tumor vaccines; 16) therapies directed against tumor metastases (e.g., Batimistat, etc.); and 17) inhibitors of angiogenesis.

[0081] The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions. Examples of other therapeutic agents include the following: cyclosporins (e.g., cyclosporin A), CTLA4-Ig, antibodies such as ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, agents blocking the interaction between CD40 and gp39, such as antibodies specific for CD40 and/or gp39 (i.e., CD154), fusion proteins constructed from CD40 and gp39 (CD40Ig and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG), cholesterol biosynthesis inhibitors such as HMG CoA reductase inhibitors (lovastatin and simvastatin), non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen and cyclooxygenase inhibitors such as rofecoxib, steroids such as prednisone or dexamethasone, gold compounds, antiproliferative agents such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil, cytotoxic drugs such as azathioprine and cyclophosphamide, TNF-a inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or Rapamune) or derivatives thereof.

[0082] Other agents that may be administered in combination with invention compounds include protein therapeutic agents such as cytokines, immunomodulatory agents and antibodies. As used herein the term "cytokine" encompasses chemokines, interleukins, lymphokines, monokines, colony stimulating factors, and receptor associated proteins, and functional fragments thereof. As used herein, the term "functional fragment" refers to a polypeptide or peptide which possesses biological function or activity that is identified through a defined functional assay.

[0083] The cytokines include endothelial monocyte activating polypeptide II (EMAP-II), granulocyte-macrophage-CSF (GM-CSF), granulocyte-CSF (G-CSF), macrophage-CSF (M-CSF), IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-12, and IL-13, interferons, and the like and which is associated with a particular biologic, morphologic, or phenotypic alteration in a cell or cell mechanism.

[0084] When other therapeutic agents are employed in combination with the compounds of the present invention they may be used for example in amounts as noted in the Physician Desk Reference (PDR) or as otherwise determined by one having ordinary skill in the art.

[0085] In the treatment or prevention of conditions which involve cellular proliferation, an appropriate dosage level can generally be between about 0.01 and about 1000 mg per 1 kg of patient body weight per day which can be administered in single or multiple doses. For example, the dosage level can be between about 0.01 and about 250 mg/kg per day; more narrowly, between about 0.5 and about 100 mg/kg per day. A suitable dosage level can be between about 0.01 and about 250 mg/kg per day, between about 0.05 and about 100 mg/kg per day, or between about 0.1 and about 50 mg/kg per day, or about 1.0 mg/kg per day. For example, within this range the dosage can be between about 0.05 and about 0.5 mg/kg per day, or between about 0.5 and about 5 mg/kg per day, or between about 5 and about 50 mg/kg per day. For oral administration, the compositions can be provided in the form of tablets containing between about 1.0 and about 1,000 mg of the active ingredient, for example, about 1.0, about 5.0, about 10.0, about 15.0, about 20.0, about 25.0, about 50.0, about 75.0, about 100.0, about 150.0, about 200.0, about 250.0, about 300.0, about 400.0, about 500.0, about 600.0, about 750.0, about 800.0, about 900.0, and about 1,000.0 mg of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds can be administered on a regimen of 1 to 4 times per day, such as once or

twice per day. There may be a period of no administration followed by another regimen of administration.

[0086] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0087] Compounds of the present invention can be used, alone or in combination with an effective amount of a therapeutic antibody (or therapeutic fragment thereof), a chemotherapeutic or an immunotoxic agent, for treatment of tumors. Illustrative examples of chemotherapeutic agents that can be used for this purpose include doxorubicin, docetaxel, or taxol. It should be further understood that the invention includes combination therapy including a compound of the invention, including but not limited to vasculostatic agents, such as tyrosine, serine or threonine kinase inhibitors, and any chemotherapeutic agent or therapeutic antibody.

C. Examples

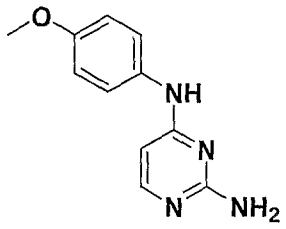
[0088] The following examples are provided to further illustrate the advantages and features of the present invention, but are not intended to limit the scope of the invention.

EXAMPLE 1. General Methods

[0089] All experiments were performed under anhydrous conditions (i.e. dry solvents) in an atmosphere of argon, except where stated, using oven-dried apparatus and employing standard techniques in handling air-sensitive materials. Aqueous solutions of sodium bicarbonate ($NaHCO_3$) and sodium chloride (brine) were saturated. Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualization by ultraviolet and/or anisaldehyde, potassium permanganate or phosphomolybdic acid dips. Reverse-phase HPLC chromatography was carried out on Gilson 215 liquid handler equipped with Waters *SymmetryShield*™ RP18 7μm (40 x 100mm) Prep-Pak cartridge. Mobile phase consisted of standard acetonitrile (ACN) and DI Water, each with 0.1% TFA added. Purification was carried out at a flow rate of 40mL/ min. NMR spectra: ^1H Nuclear magnetic

resonance spectra were recorded at 500 MHz. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, dd = doublet of doublets, m = multiplet, br s = broad singlet), coupling constant (J/Hz) and integration. Coupling constants were taken directly from the spectra and are uncorrected. Low resolution mass spectra: Electrospray (ES+) ionization was used. The protonated parent ion (M+H) or fragment of highest mass is quoted. Analytical gradient consisted of 10% ACN in water ramping up to 100% ACN over 5 min unless otherwise stated.

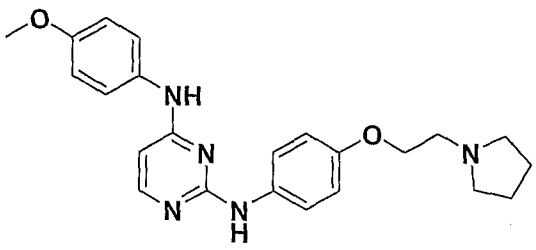
EXAMPLE 2. N^4-(4-Methoxy-phenyl)-pyrimidine-2,4-diamine (Intermediate 1)



1

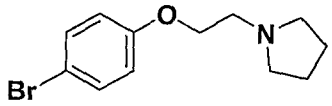
[0090] A mixture of 4-chloro-pyrimidin-2-ylamine (0.30 g, 2.3 mmol) and 4-methoxy-phenylamine (0.30 g, 2.4 mmol) were suspended in acetic acid (10 mL) and heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (20 mL) and neutralized to pH~7 with 7M of NaOH solution. The resulting solution was extracted with EtOAc (30 mL) and the organic layer separated. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by flash chromatography on silica gel (hexane to EtOAc) to afford the title intermediate **1** (0.23 g, 45%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): 3.69 (s, 3H), 5.84 (d, J = 5.8 Hz, 1H), 6.79 (d, J = 9.1 Hz, 2H), 7.63 (d, J = 9.1 Hz, 2H), 7.78 (d, J = 5.8 Hz, 1H), 8.65 (s, 1H); MS (ESI+): *m/z* 217 $(M+H)^+$.

EXAMPLE 3. N^4-(4-Methoxy-phenyl)-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine (Compound I)



I

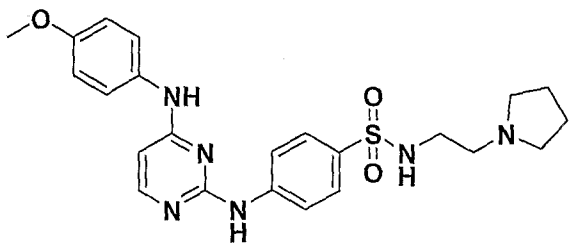
[0091] To synthesize compound **I**, intermediate **1** described above and intermediate **2** were used. Intermediate **2**, 1-[2-(4-bromo-phenoxy)-ethyl]-pyrrolidine, shown below is available commercially, and was used as received.



(2)

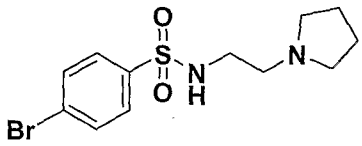
[0092] A suspension of intermediate **1** (74 mg, 0.34 mmol), intermediate **2** (0.10 g, 0.37 mmol), $Pd(OAc)_2$ (5 mg, 0.022 mmol), Xantphos (26 mg, 0.05 mmol) and potassium *tert*-butoxide (80 mg, 0.71 mmol) in dioxane/DMF (3/1; 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC to afford the title compound **I** (20 mg of TFA salt, 11%) as a brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): 1.80–1.95 (m, 2H), 1.95–2.10 (m, 2H), 3.05–3.20 (m, 2H), 3.55–3.65 (m, 4H), 3.77 (s, 3H), 4.29 (t, J = 4.9 Hz, 2H), 6.30 (d, J = 6.8 Hz, 1H), 6.96 (d, J = 8.3 Hz, 2H), 6.98 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 7.89 (d, J = 6.2 Hz, 1H), 9.87 (br s, 1H), 10.22 (br s, 1H), 10.44 (br s, 1H); MS (ESI+): *m/z* 406 $(M+H)^+$.

EXAMPLE 4. 4-[4-(4-Methoxy-phenylamino)-pyrimidin-2-ylamino]-*N*-(2-pyrrolidin-1-yl-ethyl)-benzenesulfonamide (Compound II)



II

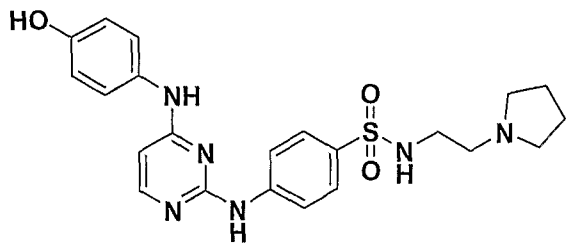
[0093] To synthesize compound **II**, intermediate **1** described above and intermediate **3** were used. Intermediate **3**, 4-bromo-N-(2-pyrrolidin-1-yl-ethyl)-benzenesulfonamide, the formula of which is shown below, was synthesized from 4-bromophenylsulfonylchloride and 2-aminoethylpyrrolidine, using commonly known synthetic techniques.



3

[0094] A suspension of intermediate **1** described above (70 mg, 0.32 mmol), intermediate **3** (0.12 g, 0.36 mmol), $Pd(OAc)_2$ (5 mg, 0.022 mmol), Xantphos (26 mg, 0.05 mmol) and potassium *tert*-butoxide (80 mg, 0.71 mmol) in dioxane/DMF (3/1; 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC to afford the title compound **II** (0.16 g of TFA salt, 85%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): 1.80–1.95 (m, 2H), 1.95–2.05 (m, 2H), 2.95–3.05 (m, 4H), 3.23 (q, J = 5.8 Hz, 2H), 3.50–3.60 (m, 2H), 3.79 (s, 3H), 6.41 (d, J = 6.8 Hz, 1H), 6.99 (d, J = 8.9 Hz, 2H), 7.43 (d, J = 8.9 Hz, 2H), 7.71 (d, J = 8.6 Hz, 2H), 7.85–7.95 (m, 2H), 7.96 (t, J = 6.1 Hz, 1H), 8.02 (d, J = 6.2 Hz, 1H), 9.64 (br s, 1H), 10.21 (br s, 1H), 10.71 (br s, 1H); MS (ESI+): *m/z* 469 $(M+H)^+$.

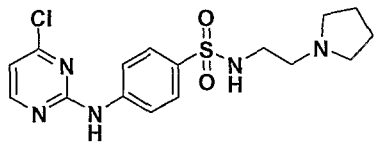
EXAMPLE 5. 4-[4-(4-Hydroxy-phenylamino)-pyrimidin-2-ylamino]-*N*-(2-pyrrolidin-1-yl-ethyl)-benzenesulfonamide (Compound III)



III

[0095] To a solution of compound **II** described above (50 mg, 0.09 mmol) in DCM (6 mL) at room temperature was added BBr_3 (0.1 mL) and the mixture stirred at room temperature for 2.5 h. The reaction was quenched with saturated $NaHCO_3$ solution until the pH~7 and the mixture extracted with EtOAc (30 mL). The organic layer was separated and washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated and the resulting solid re-dissolved in minimum of EtOAc. Hexane was added until solid crushed out and the title compound **III** was filtered as a white solid (25 mg, 64%) without further purification. ^{1}H NMR (500 MHz, DMSO-d_6): 1.55–1.65 (m, 4H), 2.30–2.40 (m, 4H), 2.43 (t, J = 7.0 Hz, 2H), 2.82 (t, J = 6.6 Hz, 2H), 6.20 (d, J = 5.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 5.5 Hz, 1H), 8.93 (s, 1H), 9.08 (br s, 1H), 9.70 (s, 1H); MS (ESI+): *m/z* 455 $(M+H)^+$.

EXAMPLE 6. 4-(4-Chloro-pyrimidin-2-ylamino)-*N*-(2-pyrrolidin-1-yl-ethyl)-benzenesulfonamide (Intermediate 4)

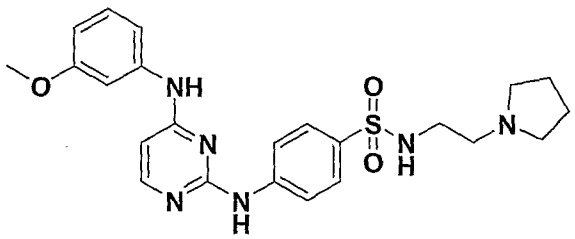


4

[0096] A mixture of 4-chloro-pyrimidin-2-ylamine (1.0 g, 7.8 mmol), above-described intermediate **3** (2.6 g, 7.8 mmol), $Pd(OAc)_2$ (90 mg, 0.40 mmol), Xantphos (0.50 g, 0.86 mmol) and potassium *tert*-butoxide (2.2 g, 20 mmol) were suspended in dioxane (30 mL) and heated at reflux under the argon atmosphere for 16 h. The mixture was poured into water (30 mL) and extracted with EtOAc (60 mL). The organic layer was separated and washed with

brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by flash chromatography on silica gel (DCM to 25% MeOH/DCM) to afford the title intermediate **4** (0.15 g, 5%) as a brown solid. MS (ESI+): *m/z* 382 $(M+H)^+$.

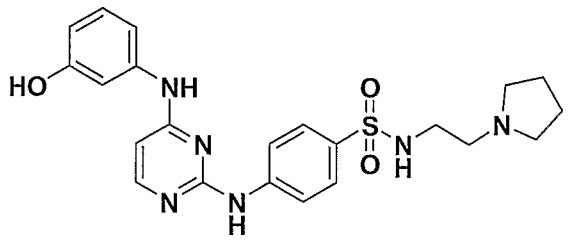
EXAMPLE 7. 4-[4-(3-Methoxy-phenylamino)-pyrimidin-2-ylamino]-*N*-(2-pyrrolidin-1-yl-ethyl)-benzenesulfonamide (Compound IV)



IV

[0097] A mixture of the above described intermediate **4** (0.10 g, 0.26 mmol) and 3-methoxy-phenylamine (0.05 mL, 0.45 mmol) were suspended in acetic acid (6 mL) and heated at 100 °C for 1.5 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (20 mL) and neutralized to pH~7. The resulting solution was extracted with EtOAc (30 mL) and the organic layer separated. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by HPLC to afford the title compound **IV** (55 mg of TFA salt, 36%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6): 1.80–1.90 (m, 2H), 1.95–2.05 (m, 2H), 2.95–3.05 (m, 4H), 3.24 (q, J = 6.0 Hz, 2H), 3.50–3.60 (m, 2H), 3.73 (s, 3H), 6.40 (d, J = 6.3 Hz, 1H), 6.68 (d, J = 7.3 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.30 (s, 1H), 7.72 (d, J = 8.9 Hz, 2H), 7.91 (t, J = 6.1 Hz, 1H), 7.95 (d, J = 8.7 Hz, 2H), 8.10 (d, J = 6.2 Hz, 1H), 9.59 (br s, 1H), 9.87 (br s, 1H), 10.38 (br s, 1H); MS (ESI+): *m/z* 469 $(M+H)^+$.

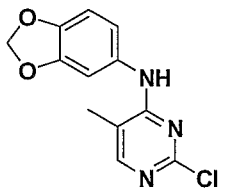
EXAMPLE 8. 4-[4-(3-Hydroxy-phenylamino)-pyrimidin-2-ylamino]-*N*-(2-pyrrolidin-1-yl-ethyl)-benzenesulfonamide (Compound V)



V

[0098] To a solution of the above-described compound **IV** (30 mg, 0.05 mmol) in DCM (6 mL) at room temperature was added BBr_3 (0.1 mL) and the mixture stirred at room temperature for 2.5 h. The reaction was quenched with saturated $NaHCO_3$ solution until the pH~7 and the mixture extracted with EtOAc (30 mL). The organic layer was separated and washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated and the residue purified by HPLC to afford the title compound **V** (13 mg of TFA salt, 46%) as an off white solid. ^1H NMR (500 MHz, DMSO-d_6): 1.80–1.90 (m, 2H), 1.95–2.05 (m, 2H), 2.95–3.05 (m, 4H), 3.20–3.30 (m, 2H), 6.39 (d, J = 6.3 Hz, 1H), 6.53 (d, J = 7.2 Hz, 1H), 7.01 (d, J = 9.2 Hz, 1H), 7.09 (s, 1H), 7.14 (t, J = 8.1 Hz, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.90 (t, J = 6.2 Hz, 1H), 7.97 (d, J = 8.8 Hz, 2H), 8.08 (d, J = 6.4 Hz, 1H), 9.48 (br s, 1H), 9.57 (br s, 1H), 9.86 (br s, 1H), 10.41 (br s, 1H); MS (ESI+): *m/z* 455 $(M+H)^+$.

EXAMPLE 9. Benzo[1,3]dioxol-5-yl-(2-chloro-5-methyl-pyrimidin-4-yl)-amine (Intermediate 5)

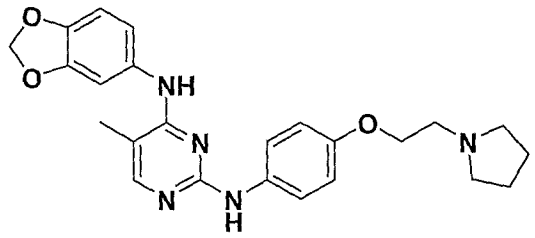


5

[0099] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.30 g, 2.1 mmol), 5-bromo-benzo[1,3]dioxole (0.45 g, 2.2 mmol), $Pd(OAc)_2$ (30 mg, 0.13 mmol), Xantphos (0.15 g, 0.26 mmol) and potassium *tert*-butoxide (0.45 g, 4.0 mmol) were suspended in dioxane (15 mL) and heated at reflux under the argon atmosphere for 16 h. The reaction mixture was

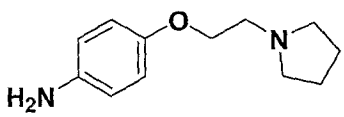
cooled to room temperature and diluted with DCM (20 mL). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane to 50% EtOAc/hexane) to afford the title intermediate **5** (0.10 g, 18%) as a white solid. MS (ESI+): *m/z* 264 $(M+H)^+$.

EXAMPLE 10. N^4-Benzo[1,3]dioxol-5-yl-5-methyl-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine (Compound VI)



VI

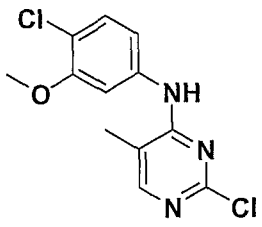
[0100] To synthesize compound **VI**, intermediate **5** described above and intermediate **6** were used. Intermediate **6**, 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine, the formula of which is shown below, was synthesized in two steps, first by alkylation of 4-nitrophenol using 2-chloroethylpyrrolidine, followed by reduction to yield the aniline derivative.



6

[0101] Commonly known synthetic techniques were used to synthesize intermediate **6**. A mixture of the above-described intermediate **5** (90 mg, 0.34 mmol), intermediate **6** (95 mg, 0.46 mmol), $Pd_2(dba)_3$ (20 mg, 0.02 mmol), Xantphos (30 mg, 0.05 mmol) and cesium carbonate (0.30 g, 0.9 mmol) were suspended in dioxane (10 mL) and heated at reflux under the argon atmosphere for 20 h. The reaction mixture was cooled to room temperature and diluted with DCM (20 mL). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound **VI** (40 mg of TFA salt, 21%) as a brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): 1.85–1.95 (m, 2H), 1.95–2.05 (m, 2H), 2.13 (s, 3H), 3.10–3.20 (m, 2H), 4.26 (t, J = 5.0 Hz, 2H), 6.07 (s, 2H), 6.90–7.00 (m, 4H), 7.19 (s, 1H), 7.37 (d, J = 9.0 Hz, 2H), 7.84 (s, 1H), 9.60 (br s, 1H), 9.89 (br s, 1H), 10.32 (br s, 1H); MS (ESI+): *m/z* 434 $(M+H)^+$.

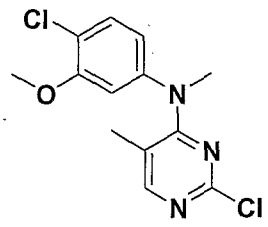
EXAMPLE 11. (4-Chloro-3-methoxy-phenyl)-(2-chloro-5-methyl-pyrimidin-4-yl)-amine (Intermediate 7)



7

[0102] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.50 g, 3.5 mmol), 4-bromo-1-chloro-2-methoxy-benzene (0.65 mL, 4.8 mmol), $Pd_2(dba)_3$ (0.17 g, 0.19 mmol), Xantphos (0.22 g, 0.38 mmol) and cesium carbonate (2.3 g, 7.1 mmol) were suspended in dioxane (20 mL) and heated at reflux under the argon atmosphere for 5 h. The reaction mixture was cooled to room temperature and diluted with DCM (30 mL). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane to 40% EtOAc/hexane) to afford the title intermediate **7** (0.55 g, 55%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): 2.18 (s, 3H), 3.85 (s, 3H), 7.35 (dd, J = 8.6 Hz, J = 2.3 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 2.3 Hz, 1H), 8.09 (d, J = 0.9 Hz, 1H), 8.91 (s, 1H); MS (ESI+): *m/z* 284 $(M+H)^+$.

EXAMPLE 12. (4-Chloro-3-methoxy-phenyl)-(2-chloro-5-methyl-pyrimidin-4-yl)-methyl-amine (Intermediate 8)

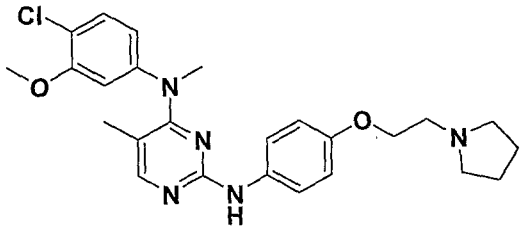


8

[0103] A suspension of intermediate **7** (0.50 g, 1.8 mmol) and sodium hydride (60% in mineral oil, 0.15 g, 3.8 mmol) in THF (10 mL) was stirred under the argon atmosphere at 0 °C for 5 min. Methyl iodide (0.15 mL, 2.4 mmol) was syringed at the same temperature to the above mixture. The resulting solution was stirred from 0 °C to room temperature over 15 min and further stirred at room temperature for additional 17 h. The reaction was quenched

with water (10 mL) and then extracted with EtOAc (30 mL). The organic layer was separated and washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated and the residue purified by flash chromatography on silica gel (hexane to 20% EtOAc/hexane) to afford the title intermediate **8** (0.20 g, 38%) as a white solid. MS (ESI+): *m/z* 298 $(M+H)^+$.

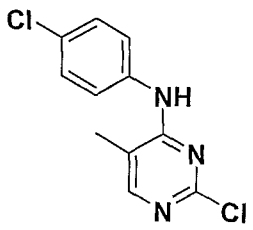
EXAMPLE 13. N^2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N^4-(4-chloro-3-methoxyphenyl)-N^4,5-dimethylpyrimidine-2,4-diamine (Compound VII)



VII

[0104] A mixture of intermediate **8** (0.15 g, 0.49 mmol) and intermediate **6** (0.15 g, 0.73 mmol), each of which intermediates is described above, were suspended in acetic acid (8 mL) and heated at 100 °C for 17 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (15 mL) and neutralized to pH~7 with 7M of NaOH solution. The resulting solution was extracted with EtOAc (30 mL) and the organic layer separated. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by HPLC to afford the title compound **VII** (0.14 g of TFA salt, 49%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6): 1.85–1.95 (m, 2H), 2.00–2.10 (m, 2H), 3.08–3.18 (m, 2H), 3.46 (s, 3H), 3.55–3.65 (m, 4H), 3.85 (s, 3H), 4.27 (t, J = 5.0 Hz, 2H), 6.86 (d, J = 7.4 Hz, 1H), 7.01 (d, J = 9.0 Hz, 2H), 7.15 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.9 Hz, 2H), 7.83 (s, 1H), 9.85 (br s, 1H), 10.04 (br s, 1H), 10.32 (br s, 1H); MS (ESI+): *m/z* 468 $(M+H)^+$.

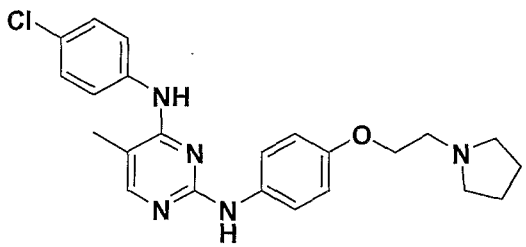
EXAMPLE 14. (2-Chloro-5-methyl-pyrimidin-4-yl)-(4-chloro-phenyl)-amine (Intermediate 9)



9

[0105] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.30 g, 2.1 mmol), 1-bromo-4-chloro-benzene (0.60 g, 3.1 mmol), $Pd_2(dba)_3$ (95 mg, 0.10 mmol), Xantphos (0.12 g, 0.20 mmol) and cesium carbonate (1.3 g, 4.0 mmol) were suspended in dioxane (20 mL) and heated at reflux under the argon atmosphere for 4 h. The reaction mixture was cooled to room temperature and diluted with DCM (20 mL). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane to 30% EtOAc/hexane) to afford the title intermediate **9** (0.15 g, 28%) as a pale yellow solid. MS (ESI+): *m/z* 254 $(M+H)^+$.

EXAMPLE 15. N^4-(4-Chloro-phenyl)-5-methyl-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine (Compound VIII)

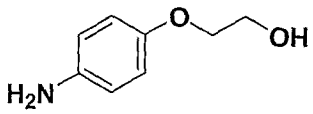


VIII

[0106] A mixture of the above-described intermediates **9** (0.15 g, 0.60 mmol) and **6** (0.20 g, 0.97 mmol) was suspended in acetic acid (8 mL) and heated at 100 °C for 6 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (15 mL) and neutralized to pH~7 with 7M of NaOH solution. The resulting brown solid was filtered and further purified by HPLC to afford the title compound **VIII** (38 mg of TFA salt, 12%) as a brown oil. ^{1}H NMR (500 MHz, DMSO-

d_6): 1.80–1.95 (m, 2H), 2.00–2.10 (m, 2H), 2.15 (s, 3H), 3.10–3.20 (m, 2H), 3.55–3.65 (m, 4H), 3.77 (s, 3H), 4.28 (t, J = 5.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 7.38 (d, J = 8.9 Hz, 2H), 7.42 (d, J = 8.9 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.90 (s, 1H), 9.48 (br s, 1H), 9.84 (br s, 1H), 10.10 (br s, 1H); MS (ESI+): *m/z* 424 $(M+H)^+$.

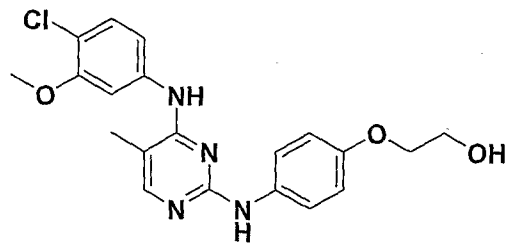
EXAMPLE 16. 2-(4-Amino-phenoxy)-ethanol (Intermediate 10)



10

[0107] A solution of 2-(4-nitro-phenoxy)-ethanol (2.1 g, 12 mmol) in MeOH (30 mL) was flushed with argon and then charged with Pd/C (10% by wt). The mixture was evacuated under house vacuum and then refilled with hydrogen from hydrogen balloon. The cycle was repeated again and the mixture stirred at room temperature for 2 h. The heterogeneous reaction mixture was filtered through a pad of Celite, washed with MeOH and concentrated *in vacuo* to furnish the title intermediate **10** (1.8 g, 99%) as a brown solid. MS (ESI+): *m/z* 154 $(M+H)^+$.

EXAMPLE 17. 2-{4-[4-(4-Chloro-3-methoxy-phenylamino)-5-methyl-pyrimidin-2-ylamino]-phenoxy}-ethanol (Compound IX)

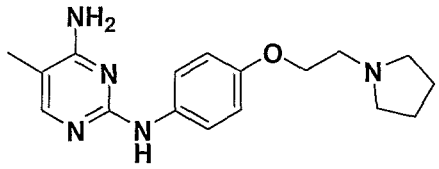


IX

[0108] A suspension of the above described intermediates **7** (50 mg, 0.17 mmol), **10** (40 mg, 0.26 mmol), $Pd_2(dba)_2$ (8 mg, 0.01 mmol), Xantphos (10 mg, 0.02 mmol) and cesium carbonate (0.13 g, 0.40 mmol) in dioxane (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by flash chromatography on silica gel

(hexane to EtOAc) to afford the title compound **IX** (14 mg, 21%) as a light brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): 2.10 (s, 3H), 3.69 (t, J = 5.3 Hz, 2H), 3.75 (s, 3H), 3.92 (t, J = 5.1 Hz, 2H), 4.83 (t, J = 5.6 Hz, 1H), 6.78 (d, J = 9.0 Hz, 2H), 7.29 (d, J = 8.5 Hz, 1H), 7.43 (dd, J = 8.6 Hz, J = 2.2 Hz, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.52 (d, J = 9.0 Hz, 2H), 7.88 (s, 1H), 8.31 (s, 1H), 8.80 (s, 1H); MS (ESI+): *m/z* 401 $(M+H)^+$.

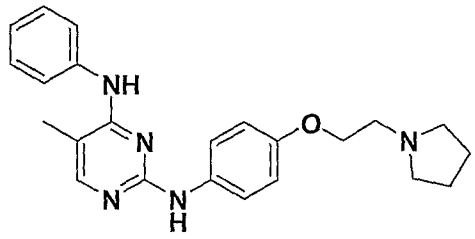
EXAMPLE 18. 5-Methyl-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine (Intermediate 11)



11

[0109] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.13 g, 0.87 mmol) and the above described intermediate **6** (0.30 g, 1.5 mmol) were suspended in acetic acid (8 mL) and heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (15 mL) and neutralized to pH~7 with 7M of NaOH solution. The resulting solid was filtered (30 mg) and washed with ether. The filtrate was extracted with EtOAc (30 mL) and the organic layer separated. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated to afford the additional solid (0.2 g), which were combined with the first batch and afforded the title intermediate **11** (0.23 g, 85%) as a light brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): 1.65–1.70 (m, 4H), 1.89 (s, 3H), 2.74 (t, J = 6.0 Hz, 2H), 3.98 (t, J = 6.1 Hz, 2H), 6.30 (s, 2H), 6.78 (d, J = 9.1 Hz, 2H), 7.62 (d, J = 9.1 Hz, 2H), 7.64 (s, 1H), 8.50 (s, 1H); MS (ESI+): *m/z* 314 $(M+H)^+$.

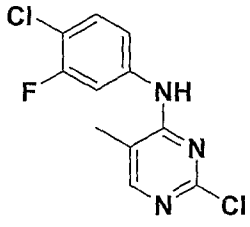
EXAMPLE 19. 5-Methyl-N^4-phenyl-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine (Compound X)



X

[0110] A suspension of the above-described intermediate **11** (25 mg, 0.08 mmol), bromobenzene (0.05 mL, 0.50 mmol), $Pd_2(dba)_2$ (5 mg, 0.006 mmol), Xantphos (10 mg, 0.02 mmol) and cesium carbonate (70 mg, 0.21 mmol) in dioxane (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by flash chromatography on silica gel (DCM to 30% MeOH/DCM) to afford the title compound **X** (10 mg, 32%) as a light brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): 1.65–1.72 (m, 4H), 2.10 (s, 3H), 2.48–2.58 (m, 4H), 2.75–2.82 (m, 2H), 4.00 (t, J = 5.9 Hz, 2H), 6.77 (d, J = 9.0 Hz, 2H), 7.04 (t, J = 7.3 Hz, 1H), 7.32 (t, J = 7.9 Hz, 2H), 7.54 (d, J = 9.0 Hz, 2H), 7.71 (d, J = 7.8 Hz, 2H), 7.84 (s, 1H), 8.20 (s, 1H), 8.76 (s, 1H); MS (ESI+): *m/z* 390 $(M+H)^+$.

EXAMPLE 20. (4-Chloro-3-fluoro-phenyl)-(2-chloro-5-methyl-pyrimidin-4-yl)-amine (Intermediate 12)

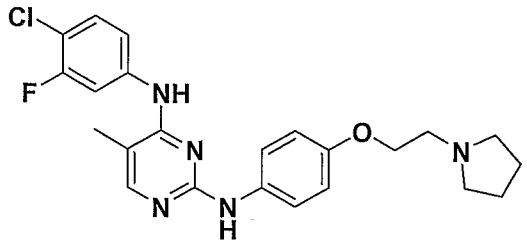


12

[0111] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.50 g, 3.5 mmol), 4-Bromo-1-chloro-2-fluoro-benzene (1.0 g, 4.8 mmol), $Pd_2(dba)_3$ (0.16 g, 0.17 mmol), Xantphos (0.20 g, 0.34 mmol) and cesium carbonate (2.3 g, 7.0 mmol) were suspended in

dioxane (25 mL) and heated at reflux under the argon atmosphere for 15 h. The reaction mixture was cooled to room temperature and diluted with DCM (30 mL). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane to 40% EtOAc/hexane) to afford the title intermediate **12** (0.75 g, 80%) as an off white solid. MS (ESI+): *m/z* 272 $(M+H)^+$.

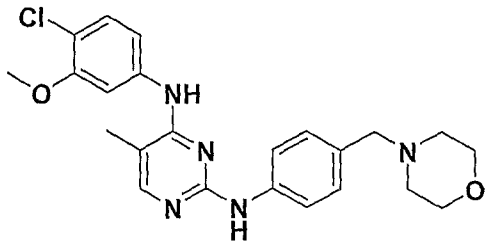
EXAMPLE 21. N^4-(4-Chloro-3-fluoro-phenyl)-5-methyl- N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine (Compound XI)



XI

[0112] A mixture of the above-described intermediates **12** (0.20 g, 0.74 mmol) and **6** (0.20 g, 0.97 mmol) was suspended in acetic acid (8 mL) and heated at 100 °C for 6 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (15 mL) and neutralized to pH~7 with 7M of NaOH solution. The resulting solution was extracted with EtOAc (30 mL) and the organic layer separated. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by flash chromatography on silica gel (DCM to 30% MeOH/DCM) to afford the title compound **XI** (90 mg, 28%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6): 1.65–1.71 (m, 4H), 2.10 (s, 3H), 2.45–2.55 (m, 4H), 2.77 (t, J = 6.0 Hz, 2H), 4.01 (t, J = 6.0 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 7.44 (t, J = 8.8 Hz, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.55 (dd, J = 8.9 Hz, J = 2.0 Hz, 1H), 7.91 (s, 1H), 8.07 (dd, J = 12.5 Hz, J = 2.0 Hz, 1H), 8.43 (s, 1H), 8.90 (s, 1H); MS (ESI+): *m/z* 442 $(M+H)^+$.

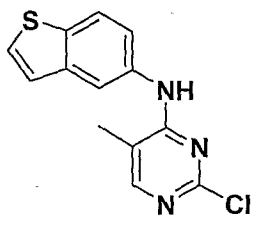
EXAMPLE 22. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N^2-(4-morpholin-4-ylmethyl-phenyl)-pyrimidine-2,4-diamine (Compound XII)



XII

[0113] A suspension of the above-described intermediate **7** (50 mg, 0.17 mmol), 4-morpholin-4-ylmethyl-phenylamine (50 mg, 0.26 mmol), $Pd_2(dba)_2$ (8 mg, 0.009 mmol), Xantphos (10 mg, 0.02 mmol) and cesium carbonate (0.13 g, 0.40 mmol) in dioxane (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC to afford the title compound **XII** (40 mg of TFA salt, 43%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): 2.16 (s, 3H), 3.05–3.15 (m, 2H), 3.10–3.20 (m, 2H), 3.60–3.70 (m, 2H), 3.90–4.00 (m, 2H), 4.28 (s, 2H), 4.01 (t, J = 6.0 Hz, 2H), 7.25–7.35 (m, 3H), 7.35–7.41 (m, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.98 (s, 1H), 9.10 (br s, 1H), 9.86 (br s, 1H), 9.95 (br s, 1H); MS (ESI+): *m/z* 440 $(M+H)^+$.

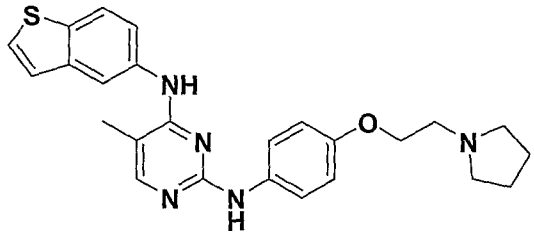
EXAMPLE 23. Benzo[*b*]thiophen-5-yl-(2-chloro-5-methyl-pyrimidin-4-yl)-amine (Intermediate 13)



13

[0114] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.30 g, 2.1 mmol), 5-bromo-benzo[*b*]thiophene (0.6 g, 2.8 mmol), $Pd_2(dba)_3$ (95 mg, 0.10 mmol), Xantphos (0.12 g, 0.20 mmol) and cesium carbonate (1.3 g, 4.0 mmol) was suspended in dioxane (25 mL) and heated at reflux under the argon atmosphere for 3 h. The reaction mixture was cooled to room temperature and diluted with DCM (30 mL) . The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane to 30% EtOAc/hexane) to afford the title intermediate **13** (0.23 g, 40%) as a white solid. MS (ESI+): *m/z* 276 $(M+H)^+$.

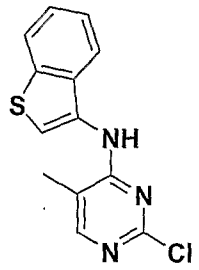
EXAMPLE 24. N^4-Benzo[*b*]thiophen-5-yl-5-methyl-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine (Compound XIII)



XIII

[0115] A mixture of the above-described intermediates **13** (0.23 g, 0.83 mmol) and **6** (0.35 g, 1.7 mmol) were suspended in acetic acid (8 mL) and *heated* at 100 °C for 1 d. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (15 mL) and neutralized to pH~7 with 7M of NaOH solution. The resulting solution was extracted with EtOAc (30 mL) and the organic layer separated. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by flash chromatography on silica gel (DCM to 15% MeOH/DCM) to afford the title compound **XIII** (0.13 g, 35%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6): 1.65–1.75 (m, 4H), 2.12 (s, 3H), 2.50–2.62 (m, 4H), 2.75–2.85 (m, 2H), 3.99 (t, J = 5.9 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 5.4 Hz, 1H), 7.51 (d, J = 9.1 Hz, 2H), 7.61 (dd, J = 8.7 Hz, J = 2.0 Hz, 1H), 7.74 (d, J = 5.4 Hz, 1H), 7.85 (d, J = 0.8 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H), 8.29 (d, J = 1.7 Hz, 1H), 8.34 (s, 1H), 8.76 (s, 1H); MS (ESI+): *m/z* 446 $(M+H)^+$.

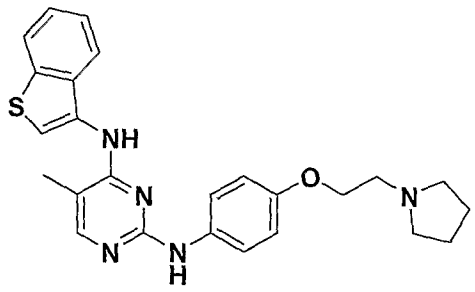
EXAMPLE 25. Benzo[*b*]thiophen-3-yl-(2-chloro-5-methyl-pyrimidin-4-yl)-amine (Intermediate 14)



14

[0116] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.30 g, 2.1 mmol), 3-bromo-benzo[*b*]thiophene (0.6 g, 2.8 mmol), $Pd_2(dba)_3$ (95 mg, 0.10 mmol), Xantphos (0.12 g, 0.20 mmol) and cesium carbonate (1.3 g, 4.0 mmol) were suspended in dioxane (25 mL) and heated at reflux under the argon atmosphere for 3 h. The reaction mixture was cooled to room temperature and diluted with DCM (30 mL). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane to 30% EtOAc/hexane) to afford the title intermediate **14** (65 mg, 11%) as a yellow solid. MS (ESI+): *m/z* 276 $(M+H)^+$.

EXAMPLE 26. N^4-Benzo[*b*]thiophen-3-yl-5-methyl-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine (Compound XIV)

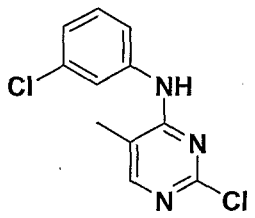


XIV

[0117] A mixture of the above-described intermediates **14** (50 mg, 0.18 mmol) and **6** (0.10 g, 0.48 mmol) was suspended in acetic acid (8 mL) and heated at 100 °C for 15 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (10 mL) and neutralized to pH~7 with 7M of NaOH

solution. The resulting solution was extracted with EtOAc (20 mL) and the organic layer separated. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by flash chromatography on silica gel (DCM to 15% MeOH/DCM) to afford the title compound **XIV** (10 mg, 13%) as an off white solid. ^{1}H NMR (500 MHz, DMSO-d_6): 1.70–1.80 (m, 4H), 2.19 (s, 3H), 2.65–2.80 (m, 4H), 2.85–3.00 (m, 2H), 3.98–4.03 (m, 2H), 6.63 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.6 Hz, 2H), 7.38–7.45 (m, 2H), 7.79–7.83 (m, 1H), 7.87 (s, 1H), 7.90–8.03 (m, 1H), 8.33 (s, 1H), 8.78 (s, 1H); MS (ESI+): *m/z* 446 $(M+H)^+$.

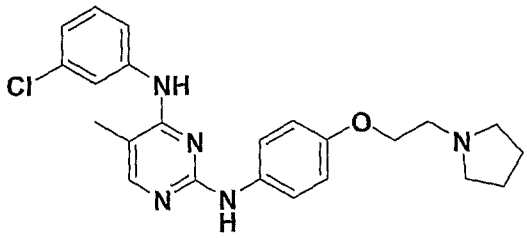
EXAMPLE 27. (2-Chloro-5-methyl-pyrimidin-4-yl)-(3-chloro-phenyl)-amine (Intermediate 15)



15

[0118] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.30 g, 2.1 mmol), 1-bromo-3-chloro-benzene (0.60 g, 3.1 mmol), $Pd_2(dba)_3$ (95 mg, 0.10 mmol), Xantphos (0.12 g, 0.20 mmol) and cesium carbonate (1.3 g, 4.0 mmol) was suspended in dioxane (20 mL) and heated at reflux under the argon atmosphere for 4 h. The reaction mixture was cooled to room temperature and diluted with DCM (20 mL). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane to 40% EtOAc/hexane) to afford the title intermediate **15** (0.30 g, 56%) as a pale yellow solid. MS (ESI+): *m/z* 254 $(M+H)^+$.

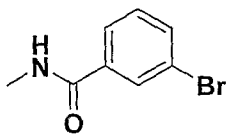
EXAMPLE 28. N^4-(3-Chloro-phenyl)-5-methyl-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine (Compound XV)



XV

[0119] A mixture of the above-described intermediates **15** (0.15 g, 0.59 mmol) and **6** (0.25 g, 1.2 mmol) was suspended in acetic acid (8 mL) and heated at 100 °C for 21 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (15 mL) and neutralized to pH~7 with 7M of NaOH solution. The resulting solution was extracted with EtOAc (30 mL) and the organic layer separated. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by flash chromatography on silica gel (DCM to 10% MeOH/DCM) to afford the title compound **XV** (60 mg, 24%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): 1.65–1.72 (m, 4H), 2.10 (s, 3H), 2.50–2.60 (m, 4H), 2.78–2.83 (m, 2H), 4.01 (t, J = 5.9 Hz, 2H), 6.81 (d, J = 9.1 Hz, 2H), 7.05–7.08 (m, 1H), 7.32 (t, J = 8.1 Hz, 1H), 7.52 (d, J = 9.0 Hz, 2H), 7.71 (d, J = 8.3 Hz, 1H), 7.85 (t, J = 2.1 Hz, 1H), 7.89 (d, J = 0.7 Hz, 1H), 8.33 (s, 1H), 8.86 (s, 1H); MS (ESI+): *m/z* 424 $(M+H)^+$.

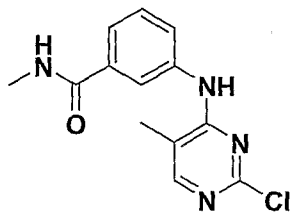
EXAMPLE 29. 3-Bromo-*N*-methyl-benzamide (Intermediate 16)



16

[0120] A solution of 3-bromo-benzoyl chloride (2.93 g, 13.3 mmol, 1 eq) in 30mL THF was stirred vigorously and treated with 2.0M methylamine in THF (15 mL, 29.4 mmol, 2.2 eq). A white precipitate was observed and the reaction was allowed to stir for 20 minutes. Reaction was then poured onto ethyl acetate (100 mL) and washed with water (2 x 150 mL) and brine (1 x 150 mL). Organic phase cut from aqueous phase and dried over sodium sulfate, filtered and evaporated to afford the title intermediate **16** as a white powder. (2.29g, 82% yield).

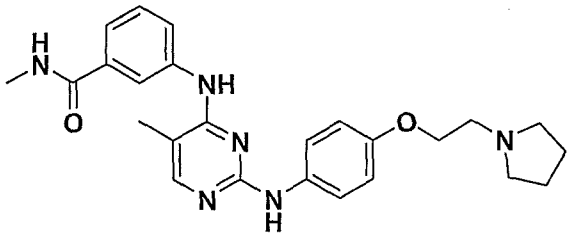
EXAMPLE 30. 3-(2-Chloro-5-methyl-pyrimidin-4-ylamino)-*N*-methyl-benzamide (Intermediate 17)



17

[0121] In a dry 50 mL round bottom flask, 2-chloro-5-methyl-pyrimidin-4-ylamine (0.3 g, 2.09 mmol, 1 equiv), 3-bromo-N-methyl-benzamide (0.489g, 2.29 mmol, 1.1 equiv), cesium carbonate (2.04 g, 6.27 mmol, 3 equiv), 4,5-bis(diphenylphosphino)-9,9-dimethyl xanthene (0.242 g, 0.418 mmol, 0.2 equiv) and tris(dibenzylideneacetone) dipalladium (0.191 g, 0.209 mmol, 0.1 equiv) were combined. Reactants were diluted with dioxane (20 mL), flushed with argon and outfitted with reflux condenser. Reaction was heated to reflux for 16 hours. Reaction was then transferred into centrifuge tube, spun down, decanted and evaporated. Resulting yellow solids were diluted with DCM and adsorbed onto silica gel. Chromatography (gradient of 50% ethyl acetate in hexanes up to 100% ethyl acetate) afforded the title intermediate **17** as a pale yellow powder (0.25 g, 43% yield). MS (ESI+): 277.01 (M+H), r.t. = 1.92 min.

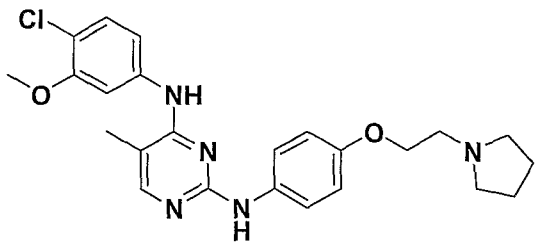
EXAMPLE 31. *N*-Methyl-3-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-ylamino}-benzamide TFA salt (Compound XVI)



XVI

[0122] The above-described intermediate 17 (0.068 g, 0.246 mmol, 1 eq), 4-(2-Pyrrolidin-1-yl-ethoxy)-phenylamine (0.061 g, 0.296 mmol, 1.2 eq), cesium carbonate (0.241 g, 0.74 mmol, 3 equiv), 4,5-bis(diphenylphosphino)-9,9-dimethyl xanthene (0.029 g, 0.05 mmol, 0.2 equiv) and tris(dibenzylideneacetone) dipalladium (0.023 g, 0.025 mmol, 0.1 equiv) were combined in 15ml microwave vessel. Reactants were then diluted with 7 ml dioxane and microwaved for 15 minutes at 160 °C. Reaction vessel was then spun down, decanted and evaporated to dryness. HPLC purification afforded the TFA salt of the title product **XVI** (0.084 g, 76%). MS (ESI+): 447.20 (M+H), r.t. = 1.53 min. ^{1}H NMR (DMSO-d_6): δ 1.87-1.91 (m, 2H), 2.02-2.06 (m, 2H), 2.16 (s, 3H), 2.79 (d, J=4.6 Hz, 3H), 3.11-3.15 (m, 2H), 3.57-3.61 (m, 5H), 4.23 (t, J=5.0 Hz, 3H), 6.84 (d, J=8.8 Hz, 2H), 7.34 (d, J=8.9 Hz, 2H), 7.47 (t, J=7.9 Hz, 1H), 7.68-7.70 (m, 2H), 7.93 (s, 1H), 8.00 (s, 1H), 8.46-8.47 (m, 1H), 9.80 (bs, 1H), 9.93 (bs, 1H) 10.41 (bs, 1H).

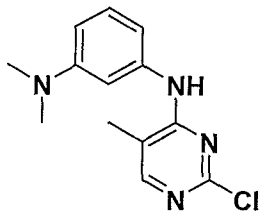
EXAMPLE 32. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine TFA salt (Compound XVII)



XVII

[0123] The above-described intermediate **7** (0.083 g, 0.293 mmol, 1 eq), 4-(2-Pyrrolidin-1-yl-ethoxy)-phenylamine (0.073 g, 0.352 mmol, 1.2 eq), cesium carbonate (0.287 g, 0.879 mmol, 3 equiv), 4,5-bis(diphenylphosphino)-9,9-dimethyl xanthene (0.034 g, 0.059 mmol, 0.2 equiv) and tris(dibenzylideneacetone) dipalladium (0.027 g, 0.029 mmol, 0.1 equiv) were combined in 15ml microwave vessel. Reactants were then diluted with 7 ml dioxane and microwaved for 15 minutes at 160 °C. Reaction vessel was then spun down, decanted and evaporated to dryness. HPLC purification afforded the TFA salt of the title product **XVII** (0.1 g, 75%). MS (ESI+): 454.13 (M+H), r.t. = 1.82 min. ^{1}H NMR (DMSO-d_6): δ 1.87-1.90 (m, 2H), 2.02-2.05 (m, 2H), 2.15 (s, 3H), 3.11-3.14(m, 2H), 3.58-3.61 (m, 5H), 3.70 (s, 3H), 4.26 (t, J=5.0 Hz, 3H), 6.91 (d, J=8.9 Hz, 2H), 7.23 (m, 1H), 7.34-7.4 (m, 4H), 7.93 (s, 1H), 9.63 (bs, 1H), 9.96 (bs, 1H) 10.40 (bs, 1H).

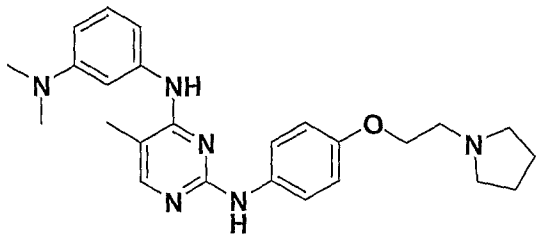
EXAMPLE 33. *N*-(2-Chloro-5-methyl-pyrimidin-4-yl)-*N'*,*N'*-dimethyl-benzene-1,3-diamine (Intermediate 18)



18

[0124] 2-Chloro-5-methyl-pyrimidin-4-ylamine (0.343 g, 2.38 mmol, 1 equiv), (3-bromo-phenyl)-dimethyl-amine (0.524g, 2.62 mmol, 1.1 equiv), cesium carbonate (2.3 g, 7.15 mmol, 3 equiv), 4,5-bis(diphenylphosphino)-9,9-dimethyl xanthene (0.276 g, 0.476 mmol, 0.2 equiv) and tris(dibenzylideneacetone) dipalladium (0.218 g, 0.238 mmol, 0.1 equiv) were combined in 30ml microwave vessel. Reactants were then diluted with 12ml dioxane and microwaved for 25 minutes at 160 °C. Reaction vessel was then spun down, decanted and evaporated to dryness. Resulting solids were diluted with DCM and adsorbed onto silica gel. Chromatography (gradient of 0% methanol in DCM up to 25% methanol in DCM) afforded the title intermediate **18** as orange solid (0.184 g, 29% yield). MS (ESI+): 263.02 (M+H), r.t. = 1.72 min.

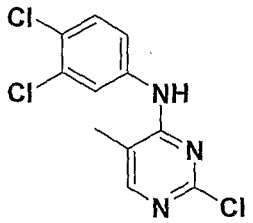
EXAMPLE 34. N^4-(3-Dimethylamino-phenyl)-5-methyl-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine TFA salt (Compound XVIII)



XVIII

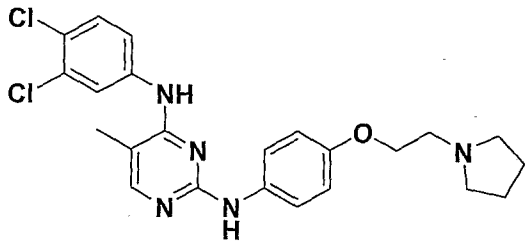
[0125] The above-described intermediate **18** (0.092 g, 0.35 mmol, 1 eq), 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (0.087 g, 0.42 mmol, 1.2 eq), cesium carbonate (0.343 g, 1.05 mmol, 3 equiv), 4,5-bis(diphenyl phosphino)-9,9-dimethyl xanthene (0.041 g, 0.0702 mmol, 0.2 equiv) and tris(dibenzylideneacetone) dipalladium (0.032 g, 0.035 mmol, 0.1 equiv) were combined in a 15 ml microwave vessel. Reactants were then diluted with 7ml dioxane and microwaved for 15 minutes at 160 °C. Reaction vessel was then spun down, decanted and evaporated to dryness. HPLC purification provided the TFA salt of the title compound **XVIII** (0.035 g, 23%). MS (ESI+): 433.21 (M+H), r.t. = 1.52 min. ^{1}H NMR (DMSO-d_6): δ 1.87-1.90 (m, 2H), 2.03-2.06 (m, 2H), 2.15 (s, 3H), 2.87 (s, 6H), 3.12-3.15 (m, 2H), 3.57-3.60 (m, 4H), 3.70 (s, 3H), 4.25 (t, J=5.0 Hz, 3H), 6.34 (dd, J=8.4 Hz, J=2.3 Hz, 1H), 6.82-6.90 (m, 4H), 7.20 (t, J=8.0 Hz, 1H), 7.39 (d, J=9.1 Hz, 2H), 7.85 (s, 1H), 9.63 (bs, 1H), 9.90 (bs, 1H) 10.39 (bs, 1H).

EXAMPLE 35. (2-Chloro-5-methyl-pyrimidin-4-yl)-(3,4-dichloro-phenyl)-amine (Intermediate 19)



[0126] 2-chloro-5-methyl-pyrimidin-4-ylamine (0.408 g, 2.83 mmol, 1 equiv), 4-Bromo-1,2-dichloro-benzene (0.704 g, 3.12 mmol, 1.1 equiv), cesium carbonate (2.8 g, 8.49 mmol, 3 equiv), 4,5-bis(diphenylphosphino)-9,9-dimethyl xanthene (0.328 g, 0.57 mmol, 0.2 equiv) and tris(dibenzylideneacetone) dipalladium (0.26 g, 0.283 mmol, 0.1 equiv) were combined in 30ml microwave vessel. Reactants were then diluted with 12ml dioxane and microwaved for 25 minutes at 160 °C. Reaction vessel was then spun down, decanted and evaporated to dryness. Resulting solids were diluted with DCM and adsorbed onto silica gel. Chromatography (gradient of 15% ethyl acetate in hexanes up to 80% ethyl acetate in hexanes) afforded the title intermediate **19** as a pale yellow powder (0.366 g, 45% yield). MS (ESI+): 287.97 (M+H), r.t. = 3.12 min.

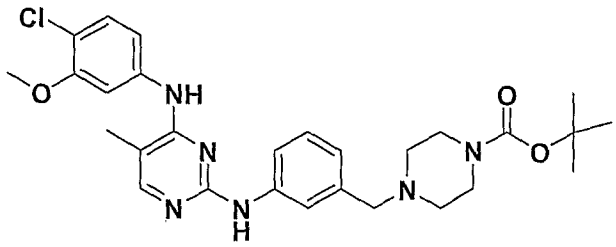
EXAMPLE 36. N^4-(3,4-Dichloro-phenyl)-5-methyl-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine TFA salt (Compound XIX)



XIX

[0127] The above-described intermediate **19** (0.09 g, 0.313 mmol, 1 eq), 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (0.078 g, 0.376 mmol, 1.2 eq), cesium carbonate (0.307 g, 0.941 mmol, 3 equiv), 4,5-bis(diphenylphosphino)-9,9-dimethyl xanthene (0.036 g, 0.063 mmol, 0.2 equiv) and tris(dibenzylideneacetone) dipalladium (0.029 g, 0.0314 mmol, 0.1 equiv) were combined in 15ml microwave vessel. Reactants were then diluted with 7ml dioxane and microwaved for 15 minutes at 160 °C. Reaction vessel was then spun down, decanted and evaporated to dryness. HPLC purification provided the TFA salt of the title compound **XIX** (0.056 g, 39%). MS (ESI+): 458.1 (M+H), r.t. = 1.93 min. ^{1}H NMR (DMSO-d_6): δ 1.87-1.91 (m, 2H), 2.03-2.06 (m, 2H), 2.14 (s, 3H), 3.12-3.15 (m, 3H), 3.57-3.60 (m, 4H), 4.26 (t, J=5.0 Hz, 2H), 6.97 (d, J=9.0 Hz, 1H), 7.40 (d, J=9 Hz, 2H), 7.60 (s, 2H), 7.97 (d, J=15.35 Hz, 2H), 9.46 (bs, 1H), 9.89 (bs, 1H) 10.17 (bs, 1H).

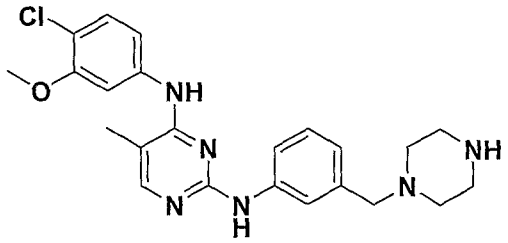
EXAMPLE 37. 4-{3-[4-(4-Chloro-3-methoxy-phenylamino)-5-methyl-pyrimidin-2-ylamino]-benzyl}-piperazine-1-carboxylic acid *tert*-butyl ester (Intermediate 20)



20

[0128] (4-Chloro-3-methoxy-phenyl)-(2-chloro-5-methyl-pyrimidin-4-yl)-amine (0.092 g, 0.325 mmol, 1 eq), 4-(3-amino-benzyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.114 g, 0.39 mmol, 1.2 eq), cesium carbonate (0.318 g, 0.975 mmol, 3 equiv), 4,5-bis(diphenylphosphino)-9,9-dimethyl xanthene (0.038 g, 0.065 mmol, 0.2 equiv) and tris(dibenzylideneacetone) dipalladium (0.03 g, 0.0325 mmol, 0.1 equiv) were combined in a 15 ml microwave vessel. Reactants were then diluted with 7ml dioxane and microwaved for 15 minutes at 160 °C. Reaction vessel was then spun down, decanted and evaporated to dryness. HPLC purification afforded the TFA salt of the title intermediate **20** (0.075 g, 43%). MS (ESI+): 539.32 (M+H), r.t. = 2.09 min.

EXAMPLE 38. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N^2-(3-piperazin-1-ylmethyl-phenyl)-pyrimidine-2,4-diamine TFA salt (Compound XX)

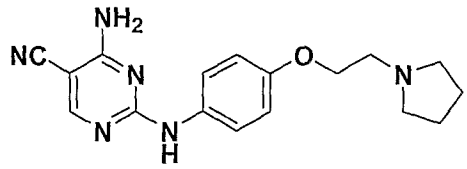


XX

[0129] A stirring solution of the above-described intermediate **20** (0.075 g, 0.14 mmol, 1 eq) in DCM (6ml) was treated with TFA (2ml). After 2h, reaction solvents were evaporated and resulting residue triturated with ether to afford the title compound **XX** as white, hygroscopic solids, TFA salt. (0.05 g, 82%). MS (ESI+): 439.13 (M+H), r.t. = 1.67 min. ^{1}H NMR (DMSO-d_6): δ 2.17 (s, 3H), 2.89 (bs, 4H), 3.2 (bs, 4H), 3.68 (s, 3H), 3.82 (bs, 3H),

7.16-7.20 (m, 2H), 7.28 (t, J=7.7 Hz, 1H), 7.33 (d, J=2.3Hz, 1H), 7.39 (s, 1H), 7.42 (d, J=8.5 Hz, 1H), 7.49-7.51 (m, 1H), 7.98 (s, 1H), 8.87 (bs, 1H), 9.79 (bs, 1H) 10.57 (bs, 1H).

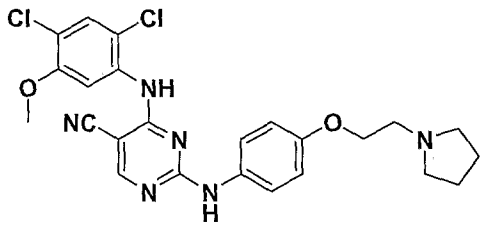
EXAMPLE 39. 2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenylamino)-4-aminopyrimidine-5-carbonitrile (Intermediate 21)



21

[0130] To a solution of 2,4-diaminopyrimidine-5-carbonitrile (135 mg, 1.00 mmol) in 1,4-dioxane (20 mL) was added 1-(2-(4-bromophenoxy)ethyl)pyrrolidine (270 mg, 1.0 mmol), Cs_2CO_3 (1.3 g, 4.0 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 174 mg, 0.3 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 100 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed until 5 mL and hexane (50 mL) was added, the solid was collected by filtration. The crude product was purified by HPLC and afforded the title intermediate **21** (32 mg, 10%).

EXAMPLE 40. 4-(2,4-Dichloro-5-methoxyphenylamino)-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl-amino)pyrimidine-5-carbonitrile (Compound XXI)

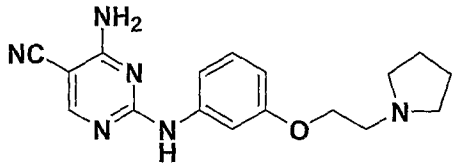


XXI

[0131] To a solution of the above-described intermediate **21** (32 mg, 0.1 mmol) in 1,4-dioxane (10 mL) was added 1-bromo-2,4-dichloro-5-methoxybenzene (28 mg, 0.11 mmol), Cs_2CO_3 (97 mg, 0.3mmol), $Pd_2(dba)_3$ (7 mg, 0.0074 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 13 mg, 0.022 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 50 mL).

The organic solution was separated and dried (Na_2SO_4). The solvent was removed in vacuo. The crude product was purified by chromatograph (SiO_2/ CH_2Cl_2, then CH_2Cl_2 : MeOH : $NH_3.H_2O$ = 100 : 10 : 1) and afforded the title compound **XXI** (35 mg, 67%). ^{1}H NMR (500 MHz, DMSO-d^6): 1.88-1.90 (m, 2H); 2.00-2.03 (m, 2H); 3.07-3.11 (m, 2H); 3.54-3.56 (m, 4H); 3.81 (s, 3H); 4.25 (br, 2H); 6.68 (br, 2H); 7.32 (br, 2H); 7.33 (s, 1H); 7.75 (s, 1H); 8.50 (s, 1H); 9.73 (br, 1H); 9.94 (br, 1H); 10.60 (br, 1H). MS (EI): 499.0.

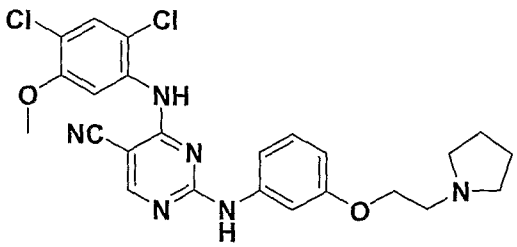
EXAMPLE 41. 2-(3-(2-(Pyrrolidin-1-yl)ethoxy)phenylamino)-4-aminopyrimidine-5-carbonitrile (Intermediate 22)



22

[0132] To a solution of 2,4-diaminopyrimidine-5-carbonitrile (145 mg, 1.07 mmol) in 1,4-dioxane (20 mL) was added 1-(2-(3-bromophenoxy)ethyl)pyrrolidine (290 mg, 1.07 mmol), Cs_2CO_3 (1.43 g, 4.4 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 174 mg, 0.3 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 100 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed until 5 mL and hexane (50 mL) was added, the solid was collected by filtration. The crude product was purified by HPLC and afforded the title intermediate **22** (55 mg, 16%).

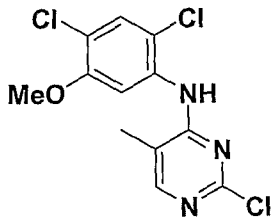
EXAMPLE 42. 4-(2,4-Dichloro-5-methoxyphenylamino)-2-(3-(2-(pyrrolidin-1-yl)ethoxy)phenyl-amino)pyrimidine-5-carbonitrile (Compound XXII)



XXII

[0133] To a solution of the above-described intermediate **22** (50 mg, 0.15 mmol) in 1,4-dioxane (10 mL) was added 1-bromo-2,4-dichloro-5-methoxybenzene (44 mg, 0.17 mmol), Cs_2CO_3 (200 mg, 0.62 mmol), $Pd_2(dba)_3$ (14 mg, 0.015 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 27 mg, 0.05 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 50 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed in vacuo. The crude product was purified by HPLC and afforded the title compound **XXII** (6 mg, 8%). ^{1}H NMR (500 MHz, DMSO-d^6): 1.87-1.89 (m, 2H); 1.90-2.03 (m, 2H); 3.04-3.08 (m, 2H); 3.52-3.56 (m, 4H); 3.80 (s, 3H); 4.23 (br, 2H); 6.62 (d, J = 6.4 Hz, 2H); 6.97 (br, 1H); 7.14 (br, 2H); 7.34 (s, 1H); 7.74 (s, 1H); 8.54 (s, 1H); 9.70 (br, 1H); 9.95 (br, 1H); 10.83 (br, 1H). MS (EI): 499.0.

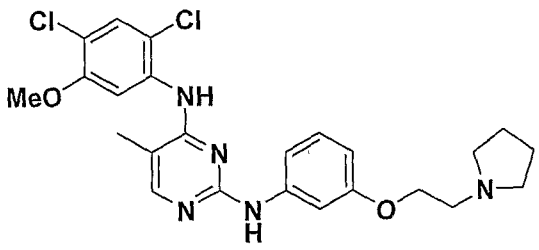
EXAMPLE 43. 2-Chloro-N-(2,4-dichloro-5-methoxyphenyl)-5-methylpyrimidin-4-amine (Intermediate 23)



23

[0134] To a solution of 2-chloro-5-methylpyrimidin-4-amine (44.8 mg, 0.31 mmol) in 1,4-dioxane (20 mL) was added 1-bromo-2,4-dichloro-5-methoxybenzene (96 mg, 0.37 mmol), Cs_2CO_3 (408 mg, 1.25 mmol), $Pd_2(dba)_3$ (37 mg, 0.04 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 70 mg, 0.12 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 100 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed in vacuo. The crude product was used for next reaction without purification.

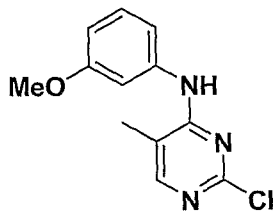
EXAMPLE 44. N^2-(3-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N^4-(2,4-dichloro-5-methoxyphenyl)-5-methylpyrimidine-2,4-diamine (Compound XXIII)



XXIII

[0135] To a solution of the above-described intermediate **23** in 1,4-dioxane (10 mL) was added 3-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (77.3 mg, 0.38 mmol), Cs_2CO_3 (488 mg, 1.25 mmol), $Pd_2(dba)_3$ (28 mg, 0.03 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 53 mg, 0.09 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 50 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed in vacuo. The crude product was purified by HPLC and afforded the title compound **XXIII** (25 mg, 15%). ^{1}H NMR (500 MHz, DMSO-d^6): 1.87-1.89 (m, 2H); 1.90-2.03 (m, 2H); 2.18 (s, 3H); 3.04-3.08 (m, 2H); 3.52-3.56 (m, 4H); 3.80 (s, 3H); 4.24 (t, J = 5.0 Hz, 2H); 6.71 (d, J = 7.65 Hz, 1H); 6.91 (s, 1H); 6.96 (d, J = 8.5 Hz, 1H); 7.02 (t, J = 8.2 Hz, 1H); 7.37 (s, 1H); 7.83 (s, 1H); 8.02 (s, 1H); 10.09 (br, 1H); 10.66 (br, 1H); 10.82 (br, 1H). MS (EI): 488.2.

EXAMPLE 45. 2-Chloro-*N*-(3-methoxyphenyl)-5-methylpyrimidin-4-amine (Intermediate 24)

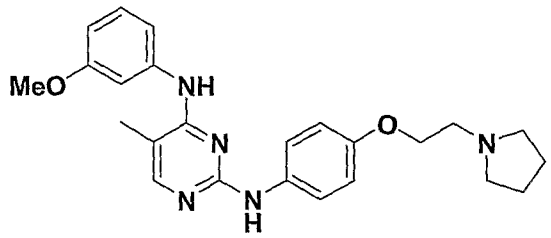


24

[0136] To a solution of 2-chloro-5-methylpyrimidin-4-amine (320 mg, 2.23 mmol) in 1,4-dioxane (40 mL) was added 1-bromo-3-methoxybenzene (458.5 mg, 2.45 mmol), Cs_2CO_3 (2.9 g, 8.9 mmol), $Pd_2(dba)_3$ (201 mg, 0.22 mmol), and 4,5-bis(diphenylphosphino)-9,9-

dimethyxanthene (Xant Phos, 382 mg, 0.66 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 100 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed until 5 mL and hexane (100 mL) was added, the solid was collected by filtration. The crude product, the title intermediate **24** (500 mg, 90%), was used for next reaction without further purification.

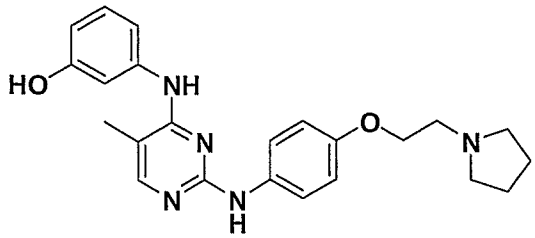
EXAMPLE 46. N^2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N^4-(3-methoxyphenyl)-5-methyl-pyrimidine-2,4-diamine (Compound XXIV)



XXIV

[0137] To a solution of the above-described intermediate **24** (240 mg, 0.96 mmol) in 1,4-dioxane (20 mL) was added 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (200 mg, 0.96 mmol), Cs_2CO_3 (1.3 mg, 4.0 mmol), $Pd_2(dba)_3$ (82 mg, 0.09 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 156 mg, 0.27 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 50 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed in vacuo. The crude product was purified by HPLC and afforded the title compound **XXIV** (85 mg, 20%). ^1H NMR (500 MHz, DMSO-d^6): 1.89-1.91 (m, 2H); 1.98-2.05 (m, 2H); 2.16 (s, 3H); 3.07-3.12 (m, 2H); 3.52-3.56 (m, 4H); 3.73 (s, 3H); 4.33 (t, J = 4.5 Hz, 2H); 6.83-6.85 (m, 1H); 6.91 (d, J = 8.8 Hz, 2H); 7.17 (s, 1H); 7.34 (d, J = 8.8 Hz, 2H); 7.41 (t, J = 7.7 Hz, 1H); 7.56 (d, J = 7.7 Hz, 1H); 7.89 (s, 1H); 9.75 (s, 1H); 10.51 (s, 1H); 10.96 (br, 1H). MS (EI): 420.2.

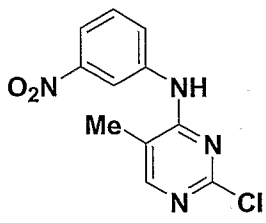
EXAMPLE 47. 3-(2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenylamino)-5-methylpyrimidin-4-ylamino)-phenol (Compound XXV)



XXV

[0138] To a solution of the above-described compound **XXIV** (50 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (10 mL) was added 1.0 M BBr_3 in CH_2Cl_2 (0.3 mL, 0.3 mmol). The mixture was stirred for 3 h at room temperature. The saturated $NaHCO_3$ (20 mL) was added and organic layer was separated. The aqueous was extracted with CH_2Cl_2 (3 x 10 mL). Combined organic solution was dried (Na_2SO_4). The product was purified by HPLC and afforded the title compound **XXV** (17 mg, 35%) as yellow solid. ^{1}H NMR (500 MHz, DMSO-d^6): 1.89 (br, 2H); 2.00 (br, 2H); 2.14 (s, 3H); 3.09 (br, 2H); 3.42 (br, 4H); 4.33 (br, 2H); 6.72 (d, J = 7.1 Hz, 1H); 6.91 (d, J = 8.4 Hz, 2H); 6.96 (d, J = 7.6 Hz, 1H); 7.00 (s, 1H); 7.18 (t, J = 8.0 Hz, 1H); 7.38 (d, J = 8.6 Hz, 2H); 7.88 (s, 1H); 9.70 (s, 1H); 9.74 (s, 1H); 10.55 (s, 1H); 11.09 (br, 1H). MS (EI): 406.2.

EXAMPLE 48. 2-Chloro-5-methyl-*N*-(3-nitrophenyl)pyrimidin-4-amine (Intermediate 25)

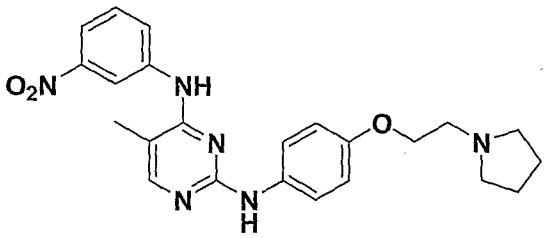


25

[0139] To a solution of 2-chloro-5-methylpyrimidin-4-amine (232 mg, 1.61 mmol) in 1,4-dioxane (40 mL) was added 1-bromo-3-nitrobenzene (359 mg, 1.78 mmol), Cs_2CO_3 (2.1 g, 6.4 mmol), $Pd_2(dba)_3$ (146 mg, 0.16 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 278 mg, 0.48 mmol). The mixture was heated under reflux for

4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 100 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed until 5 mL and hexane (100 mL) was added, the solid was collected by filtration. The crude product, the title intermediate **25**, was used for next reaction without further purification.

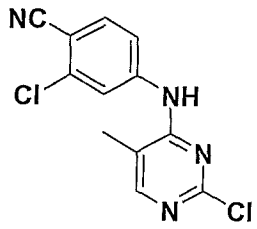
EXAMPLE 49. N^2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-5-methyl-N^4-(3-nitrophenyl)pyrimidine-2,4-diamine (Compound XXVI)



XXVI

[0140] To a solution of the above-described intermediate **25** in 1,4-dioxane (40 mL) was added 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (367 mg, 1.78 mmol), Cs_2CO_3 (2.1 g, 6.4 mmol), $Pd_2(dba)_3$ (146 mg, 0.16 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 218 mg, 0.48 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 50 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed in vacuo. The crude product was purified by HPLC and afforded the title compound **XXVI** (51 mg, 7%). ^{1}H NMR (500 MHz, DMSO-d^6): 1.89-1.92 (m, 2H); 1.98-2.05 (m, 2H); 2.21 (s, 3H); 3.10-3.12 (m, 2H); 3.52-3.57 (m, 4H); 4.33 (t, J = 4.8 Hz, 2H); 6.90 (d, J = 8.9 Hz, 2H); 7.32 (d, J = 8.9 Hz, 2H); 7.67 (t, J = 8.2 Hz, 1H); 7.99 (s, 1H); 7.56 (dd, J = 8.4 Hz, J = 1.8 Hz, 1H); 8.09 (d, J = 7.4 Hz, 1H); 8.45 (s, 1H); 10.14 (s, 1H); 10.60 (s, 1H); 11.17 (br, 1H). MS (EI): 435.2.

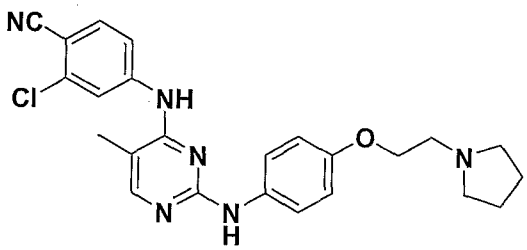
EXAMPLE 50. 4-(2-Chloro-5-methylpyrimidin-4-ylamino)-2-chlorobenzonitrile (Intermediate 26)



26

[0141] To a solution of 2-chloro-5-methylpyrimidin-4-amine (144 mg, 1.0 mmol) in 1,4-dioxane (20 mL) was added 4-bromo-2-chlorobenzonitrile (217 mg, 1.0 mmol), Cs_2CO_3 (1.3 g, 4.0 mmol), $Pd_2(dba)_3$ (91 mg, 0.1 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 173 mg, 0.3 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 100 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed until 5 mL and hexane (100 mL) was added, the solid was collected by filtration. The crude product, the title intermediate **26**, was used for next reaction without further purification.

EXAMPLE 51. 4-(2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)-5-methylpyrimidin-4-ylamino)-2-chlorobenzonitrile (Compound XXVII)

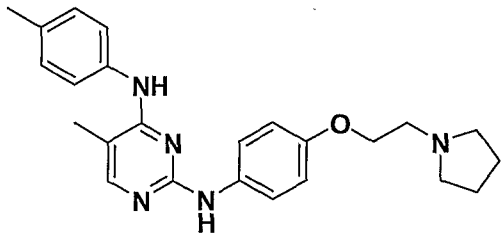


XXVII

[0142] To a solution of the above-described intermediate **26** (140 mg, 0.5 mmol) in 1,4-dioxane (20 mL) was added 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (113 mg, 0.55 mmol), Cs_2CO_3 (660 mg, 2.0 mmol), $Pd_2(dba)_3$ (46 mg, 0.05 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 87 mg, 0.15 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 50 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed in vacuo.

The crude product was purified by HPLC and afforded the title compound **XXVII** (11.5 mg, 5%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d^6): 1.89-1.92 (m, 2H); 1.98-2.05 (m, 2H); 2.20 (s, 3H); 3.08-3.13 (m, 2H); 3.56-3.59 (m, 4H); 4.36 (t, J = 4.9 Hz, 2H); 7.03 (d, J = 9.0 Hz, 2H); 7.40 (d, J = 9.0 Hz, 2H); 7.87 (br, 1H); 7.92 (d, J = 8.6 Hz, 1H); 8.03 (s, 1H); 8.16 (s, 1H); 9.82 (br, 1H); 10.37 (br, 1H); 10.90 (br, 1H). MS (EI): 449.1.

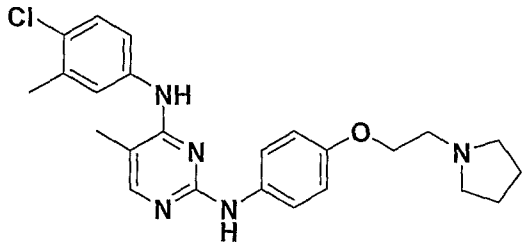
EXAMPLE 52. N^2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-5-methyl-N^4-p-tolylpyrimidine-2,4-diamine (Compound XXVIII)



XXVIII

[0143] To a solution of the above-described intermediate **11** (50 mg, 0.16 mmol) in 1,4-dioxane (20 mL) was added 1-bromo-4-methylbenzene (28 mg, 0.16 mmol), Cs_2CO_3 (210 mg, 0.64 mmol), $Pd_2(dba)_3$ (10 mg, 0.01 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 18 mg, 0.03 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off. The solvent was removed in vacuo. The crude product was purified by HPLC and afforded the title compound **XXVIII** (15.7 mg, 6%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d^6): 1.85-1.89 (m, 2H); 1.96-2.01 (m, 2H); 2.12 (s, 3H); 2.31 (s, 3H); 3.04-3.08 (m, 2H); 3.51-3.55 (m, 4H); 4.32 (br, 2H); 6.89 (br, 2H); 7.18 (br, 2H); 7.31 (br, 2H); 7.41 (br, 2H); 7.84 (s, 1H); 9.71 (s, 1H); 10.46 (s, 1H); 11.13 (br, 1H). MS (EI): 404.2.

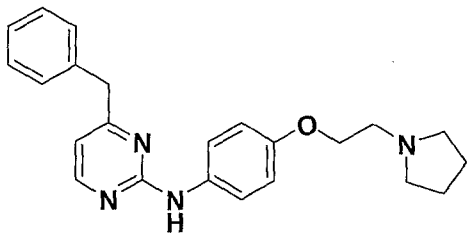
EXAMPLE 53. N^2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N^4-(4-chloro-3-methylphenyl)-5-methylpyrimidine-2,4-diamine (Compound XXIX)



XXIX

[0144] To a solution of the above-described intermediate **11** (80 mg, 0.25 mmol) in 1,4-dioxane (20 mL) was added 4-bromo-1-chloro-2-methylbenzene (63 mg, 0.30 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), $Pd_2(dba)_3$ (18 mg, 0.02 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 36 mg, 0.06 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off. The solvent was removed in vacuo. The crude product was purified by HPLC and afforded the title compound **XXIX** (17.5 mg, 15%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d^6): 1.85-1.89 (m, 2H); 1.96-2.01 (m, 2H); 2.12 (s, 3H); 2.25 (s, 3H); 3.04-3.08 (m, 2H); 3.51-3.55 (m, 4H); 4.32 (br, 2H); 6.91 (br, 2H); 7.04 (br, 1H); 7.31 (br, 1H); 7.41 (br, 2H); 7.58 (s, 1H); 7.89 (br, 1H); 9.75 (s, 1H); 10.54 (s, 1H); 11.13 (br, 1H). MS (EI): 438.1.

EXAMPLE 54. *N*-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-4-benzyl-5-methylpyrimidin-2-amine (Compound XXX)

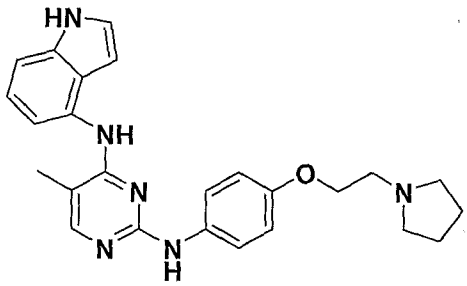


XXX

[0145] To a solution of 4-benzyl-2-chloropyrimidine (286 mg, 1.4 mmol) in 1,4-dioxane (20 mL) was added 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (288 mg, 1.4 mmol), Cs_2CO_3 (1.82 g, 5.6 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 173 mg, 0.3 mmol). The mixture was heated under reflux for 4

h under Ar. The solid was filtered off. The solvent was removed in vacuo. The crude product was purified by HPLC and afforded the title compound **XXX** (42 mg, 10%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d^6): 1.89 (br, 2H); 2.00 (br, 2H); 3.09 (br, 2H); 3.54 (br, 4H); 4.31 (br, 2H); 6.71 (d, J = 5.0 Hz, 1H); 6.93 (d, J = 8.8 Hz, 2H); 7.24 (m, 1H); 7.32 (m, 4H); 7.62 (d, J = 8.8 Hz, 2H); 8.32 (d, J = 5.0 Hz, 1H); 9.66 (s, 1H); 10.92 (br, 1H). MS (EI): 375.2.

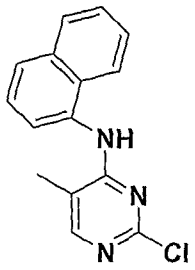
EXAMPLE 55. 4-((1*H*-indol-4-yl)methyl)-*N*-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-5-methylpyrimidin-2-amine (Compound XXXI)



XXXI

[0146] To a solution of the above-described intermediate **11** (460 mg, 1.46 mmol) in 1,4-dioxane (20 mL) was added 4-bromo-1*H*-indole (288 mg, 1.46 mmol), Cs_2CO_3 (1.95 g, 6.0 mmol), $Pd_2(dba)_3$ (128 mg, 0.14 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 243 mg, 0.42 mmol). The mixture was heated under reflux for overnight under Ar. The solid was filtered off. The solvent was removed in vacuo. The crude product was purified by HPLC and afforded the title compound **XXXI** (66 mg, 10%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d^6): 1.87 (br, 2H); 1.98-2.05 (m, 2H); 2.21 (s, 3H); 3.15 (br, 2H); 3.52 (br, 2H); 3.69 (br, 2H); 4.24 (br, 2H); 6.33 (s, 1H); 6.60 (br, 2H); 6.82 (br, 1H); 6.92 (br, 1H); 7.02 (br, 2H); 7.16 (br, 1H); 7.26 (br, 1H); 7.43 (m, 1H); 7.88 (m, 1H); 10.11 (s, 1H); 11.40 (s, 1H). MS (EI): 429.1.

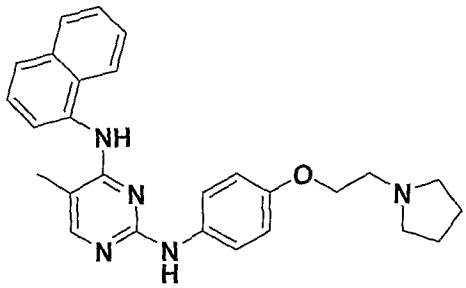
EXAMPLE 56. 2-Chloro-5-methyl-*N*-(naphthalen-1-yl)pyrimidin-4-amine (Intermediate 27)



27

[0147] To a solution of 2-chloro-5-methylpyrimidin-4-amine (144 mg, 1.0 mmol) in 1,4-dioxane (40 mL) was added 1-bromonaphthalene (227 mg, 1.1 mmol), Cs_2CO_3 (1.3 g, 4.0 mmol), $Pd_2(dba)_3$ (91 mg, 0.1 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 183 mg, 0.3 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 100 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed until 5 mL and hexane (100 mL) was added, the solid was collected by filtration. The crude product, the title intermediate **27**, was used for next reaction without further purification.

EXAMPLE 57. *N*-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-5-methyl-4-(naphthalen-1-yl)pyrimidin-2-amine (Compound XXXII)

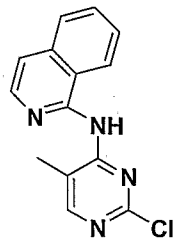


XXXII

[0148] To a solution of the above-described intermediate **27** (235 mg, 0.87 mmol) in 1,4-dioxane (20 mL) was added 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (183 mg, 0.87 mmol), Cs_2CO_3 (1.3 g, 4.0 mmol), $Pd_2(dba)_3$ (46 mg, 0.05 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 87 mg, 0.15 mmol). The mixture was heated under reflux

for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 50 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed in vacuo. The crude product was purified by HPLC and afforded the title compound **XXXII** (89 mg, 21%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d^6): 1.88-1.90 (m, 2H); 1.97-2.03 (m, 2H); 2.30 (s, 3H); 3.03-3.08 (m, 2H); 3.50-3.53 (m, 4H); 4.21 (t, J = 4.9 Hz, 2H); 6.50 (d, J = 7.2 Hz, 2H); 6.82 (d, J = 8.6 Hz, 2H); 7.54 (d, J = 7.8 Hz, 2H); 7.57-7.61 (m, 1H); 7.63 (t, J = 7.4 Hz, 1H); 7.89 (d, J = 8.3 Hz, 2H); 7.95 (s, 1H); 8.02 (d, J = 8.3 Hz, 1H); 8.08 (d, J = 7.7 Hz, 1H); 10.37 (s, 1H); 10.43 (s, 1H); 10.93 (br, 1H). MS (EI): 440.1.

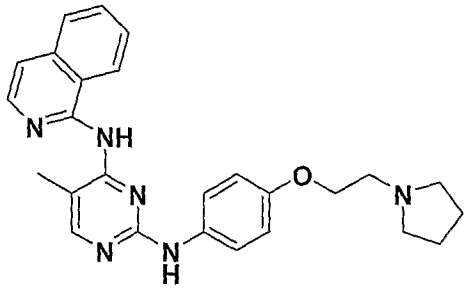
EXAMPLE 58. 1-(2-Chloro-5-methylpyrimidin-4-yl)isoquinoline (Intermediate 28)



28

[0149] To a solution of 2-chloro-5-methylpyrimidin-4-amine (144 mg, 1.0 mmol) in 1,4-dioxane (40 mL) was added 1-chloroisoquinoline (164 mg, 1.0 mmol), Cs_2CO_3 (1.3 g, 4.0 mmol), $Pd_2(dba)_3$ (91 mg, 0.1 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 183 mg, 0.3 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 100 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed until 5 mL and hexane (100 mL) was added, the solid was collected by filtration. The crude product, the title intermediate **28**, was used for next reaction without further purification.

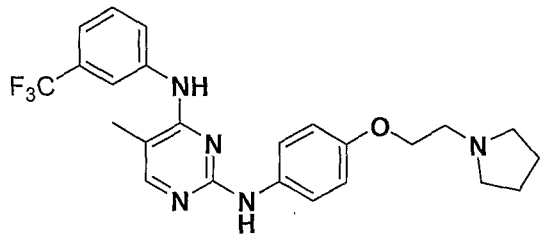
EXAMPLE 59. *N*-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-4-(isoquinolin-1-yl)-5-methylpyrimidin-2-amine (Compound XXXIII)



XXXIII

[0150] To a solution of the above-described intermediate **28** (90 mg, 0.33 mmol) in 1,4-dioxane (20 mL) was added 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (76 mg, 0.37 mmol), Cs_2CO_3 (391 mg, 1.2 mmol), $Pd_2(dba)_3$ (28 mg, 0.03 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xant Phos, 52 mg, 0.09 mmol). The mixture was heated under reflux for 4 h under Ar. The solid was filtered off and the filtrate washed with brine (1 x 50 mL). The organic solution was separated and dried (Na_2SO_4). The solvent was removed in vacuo. The crude product was purified by HPLC and afforded the title compound **XXXIII** (21 mg, 15%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d^6): 1.64-1.70 (m, 6H); 2.23 (s, 3H); 2.78 (t, J = 5.9 Hz, 2H); 4.04 (t, J = 5.9 Hz, 2H); 6.38 (d, J = 7.2 Hz, 1H); 6.93 (d, J = 9.0 Hz, 2H); 6.97 (d, J = 7.2 Hz, 1H); 7.45 (br, 1H); 7.57 (d, J = 8.8 Hz, 1H); 7.58-7.62 (m, 1H); 7.70-7.78 (m, 2H); 8.04 (s, 1H); 8.75 (d, J = 8.1 Hz, 1H); 9.06 (s, 1H); 9.19 (s, 1H). MS (EI): 441.2.

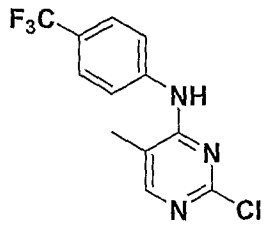
EXAMPLE 60. N^2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N^4-(3-(trifluoromethyl)phenyl)-5-methylpyrimidine-2,4-diamine (Compound XXXIV)



XXXIV

[0151] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (143 mg, 1.0 mmol), 1-bromo-3-(trifluoromethyl)benzene (225 mg, 1.0 mmol), $Pd_2(dba)_3$ (9.0 mg, 0.01 mmol), Xantphos (12 mg, 0.02 mmol) and cesium carbonate (650 mg, 2.0 mmol) were suspended in dioxane (15 mL) and heated at reflux under the argon atmosphere for 15 h. The reaction mixture was cooled to room temperature and diluted with DCM (30 mL). The mixture was filtered and the filtrate concentrated *in vacuo* . The residue on purification using HPLC gave N^4-(3-(trifluoromethyl)phenyl)-5-methylpyrimidine-2,4-diamine as an off white solid (192 mg, 67%). MS (ESI+): *m/z* 288 $(M+H)^+$. A mixture of N^4-(3-(trifluoromethyl)phenyl)-5-methylpyrimidine-2,4-diamine (28.7 mg, 0.1 mmol) and 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (22 mg, 0.12 mmol) were dissolved in acetic acid (5 mL) and heated under microwave at 150 °C for 10 min. The mixture was cooled to room temperature and acetic acid removed under reduced pressure. The residue was purified by HPLC to afford the title compound **XXXIV** as brown solid (16 mg, 35%). ^1H NMR (500 MHz, DMSO-d_6): 1.65–1.71 (m, 4H), 2.11 (s, 3H), 2.45–2.55 (m, 4H), 2.74 (t, J = 6.0 Hz, 2H), 3.98 (t, J = 6.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H), 7.35 (d, J = 5.1Hz, 1H), 7.45-7.57 (m, 3H), 7.9-7.97 (m, 2H), 8.20 (d, J = 7.6 Hz, 1H), 8.41(s, 1H), 8.85 (s, 1H), *m/z* 458 $(M+H)^+$.

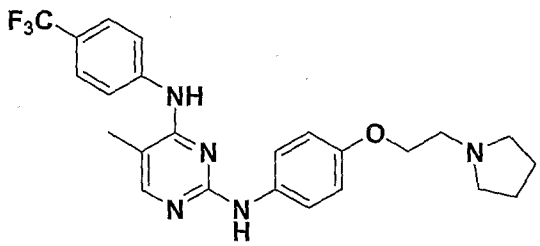
EXAMPLE 61. 2-chloro-*N*-(4-(trifluoromethyl)phenyl)-5-methylpyrimidin-4-amine (Intermediate 29)



29

[0152] A suspension of 2-chloro-5-methylpyrimidin-4-amine (159 μL, 1.2 mmol), 1-bromo-4-(trifluoromethyl)benzene (150 mg, 1.0 mmol), potassium *tert*-butoxide (224 mg, 2.0 mmol), Xantphos (120 mg, 0.2 mmol), and palladium acetate (26 mg, 0.1 mmol) was sealed in a microwave reaction tube and irradiated at 160 °C for 15 min. The mixture was allowed to cool to room temperature, the solids were filtered using DCM to rinse, and the solution was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane to EtOAc) to afford the title intermediate **29** (128.7 mg, 43%) as a white solid. MS (ESI+): *m/z* 288 $(M+H)^+$.

EXAMPLE 62. N^2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N^4-(4-(trifluoromethyl)phenyl)-5-methylpyrimidine-2,4-diamine (Compound XXXV)

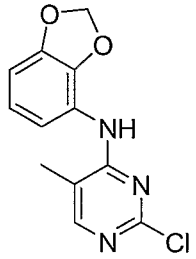


XXXV

[0153] A mixture of the above-described intermediates **29** (128 mg, 0.5 mmol) and **6** (212 mg, 1.0 mmol) were suspended in acetic acid (5 mL) and heated at 75 °C for 18 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was basified with sat., aq $NaHCO_3$ (50 mL) and extracted with DCM (2x50 mL). The organic layer was concentrated *in vacuo* and the crude product purified by reverse phase flash chromatography on C18 (water to CH_3CN, 0.1% TFA). The aqueous

fractions were neutralized with sat, aq $NaHCO_3$ and extracted with EtOAc. The organics were concentrated *in vacuo* and the residue taken up in DCM. HCl in dioxane was added along with ether and the resulting solid filtered to afford the hydrochloride salt of the title compound **XXXV** (166 mg, 70%) as a grey solid. ^{1}H NMR (500 MHz, DMSO-d_6): 1.80–1.95 (m, 2H), 1.95–2.10 (m, 2H), 2.19 (s, 3H), 3.05–3.20 (m, 2H), 3.55–3.65 (m, 6H), 4.33 (t, J = 4.7 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.94 (s, 1H), 9.92 (br s, 1H), 10.44 (br s, 1H), 10.85 (br s, 1H); MS (ESI+): *m/z* 458.5 $(M+H)^+$.

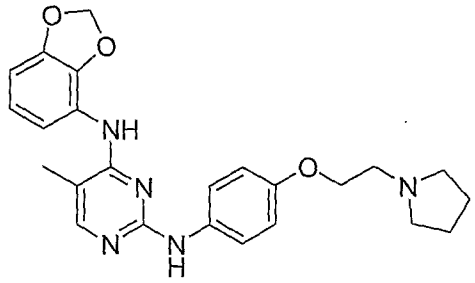
EXAMPLE 63. Benzo[1,3]dioxol-4-yl-(2-chloro-5-methyl-pyrimidin-4-yl)-amine (Intermediate 30)



30

[0154] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (1.4 g, 9.7 mmol), 4-bromo-benzo[1,3]dioxole (2.0 g, 10 mmol), $Pd_2(dba)_3$ (0.80 g, 0.87 mmol), Xantphos (1.0 g, 1.7 mmol) and cesium carbonate (6.3 g, 19 mmol) was suspended in dioxane (40 mL) and heated at reflux under the argon atmosphere for 5 h. The reaction mixture was cooled to room temperature and diluted with DCM (30 mL). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexanes to 50% EtOAc/hexanes) to afford the title compound (1.0 g, 39%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.13 (s, 3H), 5.99 (s, 2H), 6.80–6.90 (m, 3H), 8.01 (s, 1H), 8.92 (s, 1H). MS (ES+): *m/z* 264 $(M+H)^+$.

EXAMPLE 64. N^4-Benzo[1,3]dioxol-4-yl-5-methyl-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine (Compound XXXVI)

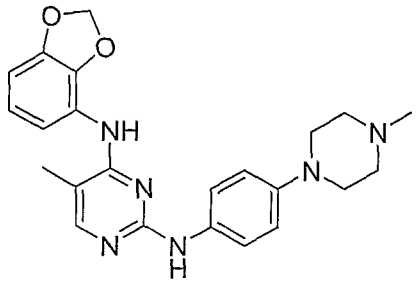


XXXVI

[0155] A mixture of intermediate **30** (0.25 g, 0.95 mmol) and 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (0.40 g, 1.9 mmol) in acetic acid (15 mL) was heated at 100 °C for 20 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (*20* mL) and neutralized to pH~7 with 10% NaOH solution. The resulting solution was extracted with EtOAc (2 x 30 mL) and the organic layer separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by flash chromatography on silica gel (DCM to 20% MeOH/DCM) to afford the title compound (0.14 g, 34%) as a white solid.

[0156] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.65–1.75 (m, 4H), 2.06 (s, 3H), 2.55–2.65 (m, 4H), 2.78–2.88 (m, 2H), 3.98 (t, J = 5.8 Hz, 2H), 5.89 (s, 2H), 6.65 (d, J = 9.0 Hz, 2H), 6.79–6.84 (m, 2H), 6.89 (dd, J = 7.7, 1.7 Hz, 1H), 7.45 (d, J = 9.1 Hz, 2H), 7.81 (s, 1H), 8.23 (s, 1H), 8.73 (s, 1H). MS (ES+): *m/z* 434 $(M+H)^+$.

EXAMPLE 65. N^4-Benzo[1,3]dioxol-4-yl-5-methyl-N^2-[4-(4-methyl-piperazin-1-yl)-phenyl]-pyrimidine-2,4-diamine (Compound XXXVII)

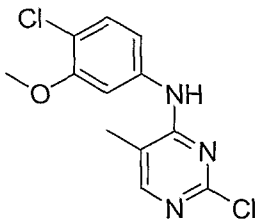


XXXVII

[0157] A mixture of intermediate **30** (0.10 g, 0.38 mmol) and 4-(4-methyl-piperazin-1-yl)-phenylamine (0.12 g, 0.51 mmol) in acetic acid (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 150 °C for 15 min. After cooling to room temperature, the cap was removed and the mixture concentrated. The residue was taken in water (20 mL) and the mixture was neutralized with 10% NaOH solution until solid precipitated. The solid was filtered and then purified by flash chromatography on silica gel (DCM to 15% MeOH/DCM) to afford the title compound (22 mg, 14%) as a light red solid.

[0158] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.06 (s, 3H), 2.21 (s, 3H), 2.44 (t, J = 4.8 Hz, 4H), 2.97 (t, J = 4.9 Hz, 4H), 5.89 (s, 2H), 6.67 (d, J = 9.1 Hz, 2H), 6.80–6.86 (m, 2H), 6.91 (dd, J = 7.6, 1.7 Hz, 1H), 7.41 (d, J = 9.0 Hz, 2H), 7.79 (s, 1H), 8.17 (s, 1H), 8.63 (s, 1H). MS (ES+): *m/z* 419 $(M+H)^+$.

EXAMPLE 66. (4-Chloro-3-methoxy-phenyl)-(2-chloro-5-methyl-pyrimidin-4-yl)-amine (Intermediate 31)



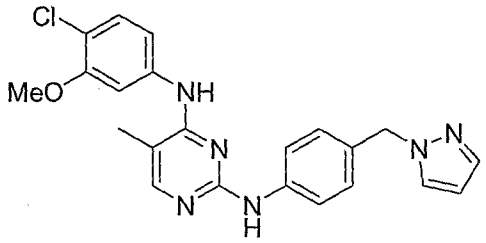
31

[0159] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.50 g, 3.5 mmol), 4-bromo-1-chloro-2-methoxy-benzene (0.65 mL, 4.8 mmol), $Pd_2(dba)_3$ (0.17 g, 0.19 mmol), Xantphos (0.22 g, 0.38 mmol) and cesium carbonate (2.3 g, 7.1 mmol) was suspended in dioxane (20 mL) and heated at reflux under the argon atmosphere for 5 h. The reaction

mixture was cooled to room temperature and diluted with DCM (30 mL). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexanes to 40% EtOAc/hexanes) to afford the title compound (0.55 g, 55%) as a yellow solid.

[0160] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.18 (s, 3H), 3.85 (s, 3H), 7.35 (dd, J = 8.6, 2.3 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 2.3 Hz, 1H), 8.09 (d, J = 0.9 Hz, 1H), 8.91 (s, 1H). MS (ES+): *m/z* 284 $(M+H)^+$.

EXAMPLE 67. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N^2-(4-pyrazol-1-ylmethyl-phenyl)-pyrimidine-2,4-diamine (Compound XXXVIII)



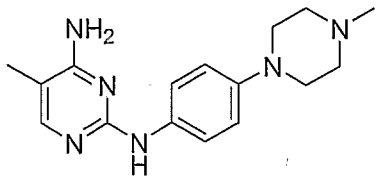
XXXVIII

[0161] A suspension of intermediate **31** (0.20 g, 0.70 mmol), 4-pyrazol-1-ylmethyl-phenylamine (0.14 g, 0.81 mmol), $Pd_2(dba)_3$ (40 mg, 0.044 mmol), Xantphos (50 mg, 0.086 mmol) and cesium carbonate (0.50 g, 1.5 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated $NaHCO_3$ solution (40 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the resulting solid was dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as an off white solid (0.13 g, 44%).

^{1}H NMR (500 MHz, DMSO-d_6): δ 2.11 (s, 3H), 3.74 (s, 3H), 5.22 (s, 2H), 6.25 (t, J = 2.1 Hz, 1H), 7.08 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 9.3 Hz, 1H), 7.40–7.45 (m, 3H), 7.60 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 1.8 Hz, 1H), 7.91 (s, 1H), 8.36 (s, 1H), 9.04 (s, 1H)

MS (ES+): *m/z* 421 $(M+H)^+$.

EXAMPLE 68. 5-Methyl-N^2-[4-(4-methyl-piperazin-1-yl)-phenyl]-pyrimidine-2,4-diamine (Intermediate 32)

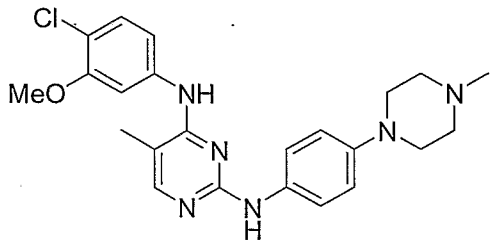


32

[0162] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (1.0 g, 6.9 mmol) and 4-(4-methyl-piperazin-1-yl)-phenylamine (1.5 mL, 7.8 mmol) in acetic acid (15 mL) was heated at 100 °C for 2.5 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (20 mL) and the mixture was neutralized with 10% NaOH solution until solid precipitated. After filtration and washed with water, the title compound was obtained as a grey solid (1.3 g, 63%).

[0163] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.88 (s, 3H), 2.21 (s, 3H), 2.21 (s, 3H), 2.44 (t, J = 4.8 Hz, 4H), 3.00 (t, J = 4.8 Hz, 4H), 6.27 (s, 2H), 6.79 (d, J = 9.0 Hz, 2H), 7.57 (d, J = 9.0 Hz, 2H), 7.63 (s, 1H), 8.42 (s, 1H). MS (ES+): *m/z* 299 $(M+H)^+$.

EXAMPLE 69. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N^2-[4-(4-methyl-piperazin-1-yl)-phenyl]-pyrimidine-2,4-diamine (Compound XXXIX)



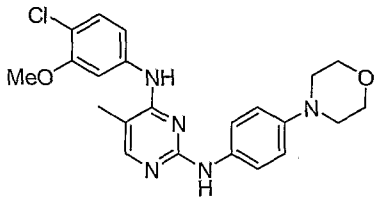
XXXIX

[0164] A suspension of intermediate **32** (0.30 g, 1.0 mmol), 4-bromo-1-chloro-2-methoxy-benzene (0.20 mL, 1.5 mmol), $Pd_2(dba)_3$ (50 mg, 0.055 mmol), Xantphos (65 mg, 0.11 mmol) and cesium carbonate (0.70 g, 2.1 mmol) in dioxane/DMF (3/1, 8 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated $NaHCO_3$ solution (40 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic

layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue triturated in a mixture of EtOAc/hexanes (1/5, 30 mL). After filtration, the title compound was obtained as an off white solid (0.20 g, 46%).

[0165] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.09 (s, 3H), 2.21 (s, 3H), 2.45 (t, J = 4.9 Hz, 4H), 3.02 (t, J = 4.9 Hz, 4H), 3.73 (s, 3H), 6.79 (d, J = 9.1 Hz, 2H), 7.27 (d, J = 8.6 Hz, 1H), 7.42–7.47 (m, 3H), 7.49 (d, J = 2.3 Hz, 1H), 7.86 (s, 1H), 8.28 (s, 1H), 8.72 (s, 1H). MS (ES+): *m/z* 439 $(M+H)^+$.

EXAMPLE 70. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N^2-(4-morpholin-4-yl-phenyl)-pyrimidine-2,4-diamine (Compound XL)

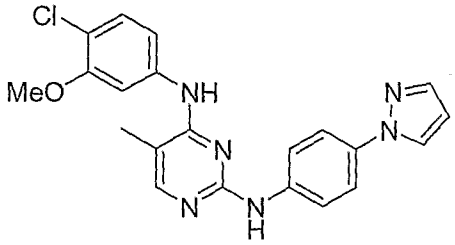


XL

[0166] A mixture of intermediate **31** (0.10 g, 0.35 mmol) and 4-morpholin-4-yl-phenylamine (80 mg, 0.45 mmol) in acetic acid (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the mixture concentrated. The residue was taken in water (20 mL) and the mixture was neutralized with 10% NaOH solution until solid precipitated. The solid was filtered and then purified by flash chromatography on silica gel (DCM to 10% MeOH/DCM) to afford the title compound (55 mg, 37%) as a light brown solid.

[0167] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.10 (s, 3H), 3.00 (t, J = 4.8 Hz, 4H), 3.71–3.76 (m, 7H), 6.80 (d, J = 9.0 Hz, 2H), 7.28 (d, J = 8.6 Hz, 1H), 7.45 (dd, J = 8.7, 2.2 Hz, 1H), 7.47–7.50 (m, 3H), 7.87 (s, 1H), 8.29 (s, 1H), 8.75 (s, 1H). MS (ES+): *m/z* 426 $(M+H)^+$.

EXAMPLE 71. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N^2-(4-pyrazol-1-yl-phenyl)-pyrimidine-2,4-diamine (Compound XLI)

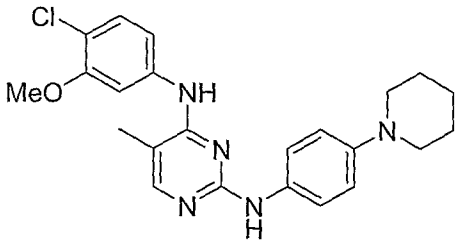


XLI

[0168] A mixture of intermediate **31** (90 mg, 0.32 mmol) and 4-pyrazol-1-yl-phenylamine (70 mg, 0.44 mmol) in acetic acid (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the mixture concentrated. The residue was taken in water (20 mL) and the mixture neutralized with 10% NaOH solution until solid precipitated. The solid was filtered and then purified by HPLC. The corrected fractions were combined and concentrated to afford the title compound (40 mg of TFA salt, 24%) as a white solid.

[0169] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.17 (s, 3H), 3.75 (s, 3H), 6.54 (t, J = 1.9 Hz, 1H), 7.30 (d, J = 6.6 Hz, 1H), 7.39 (d, J = 2.1 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 8.9 Hz, 2H), 7.71 (d, J = 8.9 Hz, 2H), 7.73 (d, J = 1.6 Hz, 1H), 7.93 (s, 1H), 8.41 (d, J = 2.5 Hz, 1H), 9.41 (s, 1H), 10.05 (s, 1H). MS (ES+): *m/z* 407 $(M+H)^+$.

EXAMPLE 72. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N^2-(4-piperidin-1-yl-phenyl)-pyrimidine-2,4-diamine (XLII)



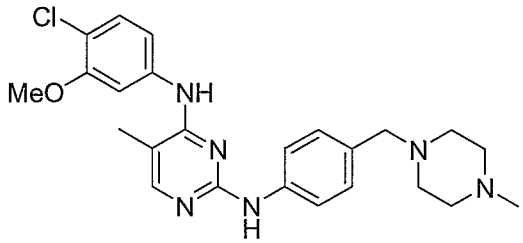
XLII

[0170] A mixture of intermediate **31** (0.11 g, 0.39 mmol) and 4-piperidin-1-yl-phenylamine (90 mg, 0.51 mmol) in acetic acid (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the mixture concentrated. The residue was taken in water (20 mL)

and the mixture neutralized with 10% NaOH solution until solid precipitated. The solid was filtered and then purified by flash chromatography on silica gel (hexanes to 70% EtOAc/hexanes)to afford the title compound (10 mg, 6%) as a light brown solid.

[0171] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.48–1.53 (m, 2H), 1.59–1.65 (m, 4H), 2.09 (s, 3H), 3.00 (t, J = 5.4 Hz, 4H), 3.73 (s, 3H), 6.78 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 8.7 Hz, 1H), 7.40–7.47 (m, 3H), 7.50 (d, J = 2.2 Hz, 1H), 7.86 (s, 1H), 8.28 (s, 1H), 8.71 (s, 1H). MS (ES+): *m/z* 424 $(M+H)^+$.

EXAMPLE 73. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl- N^2-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-pyrimidine-2,4-diamine (XLIII)

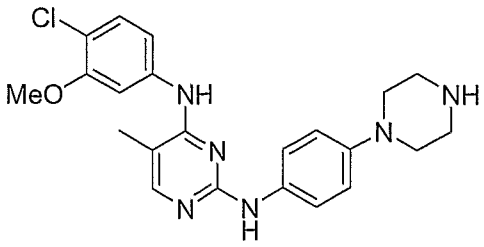


XLIII

[0172] A suspension of intermediate **31** (50 mg, 0.18 mmol), 4-(4-methyl-piperazin-1-ylmethyl)-phenylamine (50 mg, 0.24 mmol), $Pd_2(dba)_3$ (10 mg, 0.011 mmol), Xantphos (13 mg, 0.022 mmol) and cesium carbonate (0.12 g, 0.37 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by flash chromatography on silica gel (DCM to 10% MeOH/DCM)to afford the title compound (35 mg, 44%) as an off white solid.

[0173] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.11 (s, 3H), 2.15 (s, 3H), 2.20–2.45 (m, 8H), 3.35 (s, 2H), 3.75 (s, 3H), 7.07 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 1H), 7.44 (dd, J = 8.7, 2.3 Hz, 1H), 7.47 (d, J = 2.3 Hz, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.91 (s, 1H), 8.36 (s, 1H), 8.98 (s, 1H). MS (ES+): *m/z* 453 $(M+H)^+$.

EXAMPLE 74. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N^2-(4-piperazin-1-yl-phenyl)-pyrimidine-2,4-diamine (Compound XLIV)

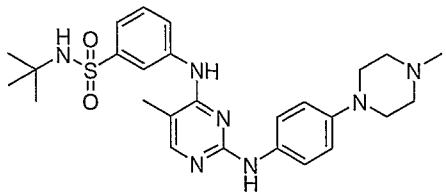


XLIV

[0174] A mixture of intermediate **31** (0.20 g, 0.70 mmol) and 4-(4-amino-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.22 g, 0.79 mmol) in acetic acid (4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 150 °C for 15 min. After cooling to room temperature, the cap was removed and the mixture concentrated. The residue was purified by HPLC and the corrected fractions combined and poured into saturated $NaHCO_3$ solution (40 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the resulting solid dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as an off white solid (0.10 g, 33%).

[0175] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.10 (s, 3H), 3.16 (s, 8H), 3.73 (s, 3H), 6.83 (d, J = 9.0 Hz, 2H), 7.29 (d, J = 8.8 Hz, 1H), 7.44 (dd, J = 8.7, 2.1 Hz, 1H), 7.49–7.52 (m, 3H), 7.88 (s, 1H), 8.32 (s, 1H), 8.81 (s, 1H)
MS (ES+): *m/z* 425 $(M+H)^+$.

EXAMPLE 75. *N-tert*-Butyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound XLV)

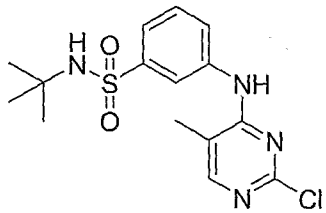


XLV

[0176] A suspension of intermediate **32** (0.30 g, 1.0 mmol), 3-bromo-*N-tert*-butyl-benzenesulfonamide (0.35 g, 1.2 mmol), $Pd_2(dba)_3$ (60 mg, 0.066 mmol), Xantphos (70 mg, 0.12 mmol) and cesium carbonate (0.70 g, 2.1 mmol) in dioxane/DMF (3/1, 8 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated $NaHCO_3$ solution (40 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue triturated in a mixture of EtOAc/hexanes (1/7, 40 mL). After filtration, the title compound was obtained as an off white solid (0.30 g, 59%).

[0177] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.11 (s, 3H), 2.22 (s, 3H), 2.45 (t, J = 4.7 Hz, 4H), 3.02 (t, J = 4.8 Hz, 4H), 6.81 (d, J = 9.1 Hz, 2H), 7.45–7.52 (m, 4H), 7.56 (s, 1H), 7.89 (s, 1H), 8.10–8.16 (m, 2H), 8.51 (s, 1H), 8.70 (s, 1H) MS (ES+): *m/z* 510 $(M+H)^+$.

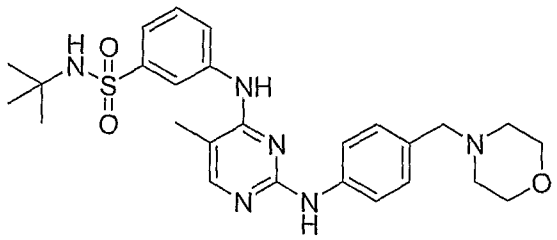
EXAMPLE 76. *N-tert*-Butyl-3-(2-chloro-5-methyl-pyrimidin-4-ylamino)-benzenesulfonamide (Intermediate 33)



33

[0178] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.4 g, 2.8 mmol), 3-bromo-*N-tert*-butyl-benzenesulfonamide (1.0 g, 3.4 mmol), $Pd_2(dba)_3$ (0.17 g, 0.19 mmol), Xantphos (0.2 g, 3.5 mmol) and cesium carbonate (2.0 g, 6.1 mmol) was suspended in dioxane (25 mL) and heated at reflux under the argon atmosphere for 3 h. The reaction mixture was cooled to room temperature and diluted with DCM (30 mL). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc and hexanes added until solid precipitated. After filtration, the title compound (1.2 g, 98%) was obtained as a light brown solid. It was used in the next step without purification. MS (ES+): *m/z* 355 $(M+H)^+$.

EXAMPLE 77. *N-tert*-Butyl-3-[5-methyl-2-(4-morpholin-4-ylmethyl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide (Compound XLVI)

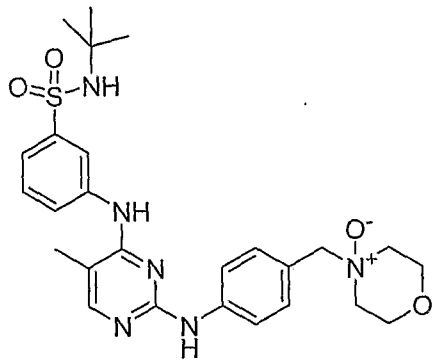


XLVI

[0179] A mixture of intermediate **33** (0.50 g, 1.4 mmol), 4-morpholin-4-ylmethyl-phenylamine (0.35 g, 1.8 mmol), $Pd_2(dba)_3$ (0.10 g, 0.11 mmol), Xantphos (0.12 g, 0.21 mmol) and cesium carbonate (1.0 g, 3.1 mmol) was suspended in dioxane (25 mL) and heated at reflux under the argon atmosphere for 3 h. The reaction mixture was cooled to room temperature and diluted with DCM (30 mL). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC and the corrected fractions combined and poured into saturated $NaHCO_3$ solution (50 mL). The combined aqueous layers were extracted with EtOAc (2 x 50 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the resulting solid dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as an off white solid (0.23 g, 31%).

[0180] ^1H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.13 (s, 3H), 2.28–2.34 (m, 4H), 3.35 (s, 2H), 3.55 (t, J = 4.8 Hz, 4H), 7.10 (d, J = 8.5 Hz, 2H), 7.45–7.52 (m, 2H), 7.57 (s, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.94 (s, 1H), 8.10 (s, 1H), 8.13–8.16 (m, 1H), 8.58 (s, 1H), 8.95 (s, 1H). MS (ES+): *m/z* 511 $(M+H)^+$.

EXAMPLE 78. *N-tert*-Butyl-3-{5-methyl-2-[4-(4-oxy-morpholin-4-ylmethyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound XLVII)

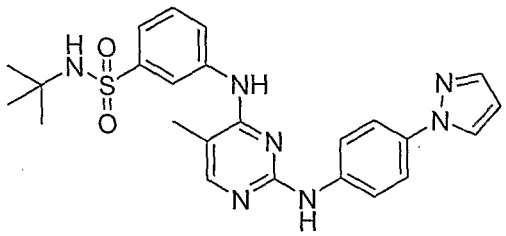


XLVII

[0181] A solution of the above-described compound **XLVI** (30 mg, 0.06 mmol) and 3-chloroperbenzoic acid (77%, 14 mg, 0.06 mmol) in chloroform (30 mL) was strred at room temperature for 1 hour. The solvent was removed by rotovap and the resulting mixture was purified by silica gel with 20% $CH_3OH/CHCl_3$ as an eluent to afford the title compound as an off-white solid (15 mg, 48%).

[0182] ^1H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.14 (s, 3H), 2.71 (d, J = 10.9 Hz, 2H), 3.63 (d, J = 9.9 Hz, 2H), 4.08 (t, J = 11.6 Hz, 2H), 4.28 (s, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 5.0 Hz, 2H), 7.61 (s, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.96 (s, 1H), 8.13 (m, 2H), 8.63 (s, 1H), 9.13 (s, 1H). MS (ES+): *m/z* 527 $(M+H)^+$.

EXAMPLE 79. *N-tert*-Butyl-3-[5-methyl-2-(4-pyrazol-1-yl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide (Compound XLVIII)



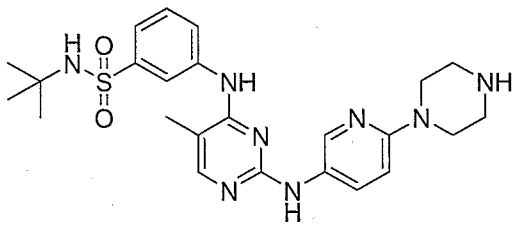
XLVIII

[0183] A mixture of intermediate **33** (0.10 g, 0.28 mmol) and 4-pyrazol-1-yl-phenylamine (50 mg, 0.31 mmol) in acetic acid (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 130 °C for 15 min. After cooling to room temperature, the cap was removed and the mixture concentrated. The residue was taken up in water (20 mL) and neutralized with 10% NaOH solution until solid precipitated. The brown solid was filtered

and then purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the resulting solid dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a white solid (15 mg, 11%).

[0184] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.15 (s, 3H), 6.49 (t, J = 2.2 Hz, 1H), 7.50–7.55 (m, 2H), 7.58 (s, 1H), 7.62 (d, J = 9.1 Hz, 2H), 7.68 (d, J = 1.3 Hz, 1H), 7.77 (d, J = 9.1 Hz, 2H), 7.96 (s, 1H), 8.11 (s, 1H), 8.13–8.16 (m, 1H), 8.33 (d, J = 2.5 Hz, 1H), 8.64 (s, 1H), 9.17 (s, 1H). MS (ES+): *m/z* 478 $(M+H)^+$.

EXAMPLE 80. *N-tert*-Butyl-3-[5-methyl-2-(6-piperazin-1-yl-pyridin-3-ylamino)-pyrimidin-4-ylamino]-benzenesulfonamide (Compound XLIX)

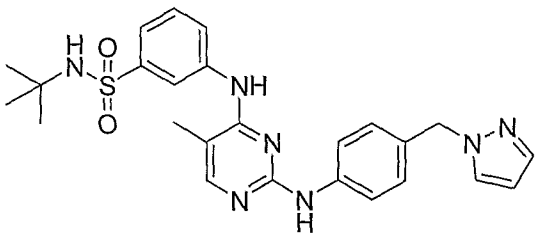


XLIX

[0185] A mixture of intermediate **33** (0.10 g, 0.28 mmol) and 4-(5-amino-pyridin-2-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (90 mg, 0.32 mmol) in acetic acid (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 130 °C for 15 min. After cooling to room temperature, the cap was removed and the mixture concentrated. The residue was dissolved in DCM (5 mL) and 30% TFA/DCM (6 mL) added. The mixture was stirred at room temperature for 1h, concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the resulting solid dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a white solid (10 mg, 7%).

[0186] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.11 (s, 3H), 2.83 (t, J = 5.0 Hz, 4H), 3.28–3.33 (m, 4H), 6.73 (d, J = 9.1 Hz, 1H), 7.40–7.49 (m, 2H), 7.57 (s, 1H), 7.86 (dd, J = 9.1, 2.7 Hz, 1H), 7.88 (s, 1H), 8.10–8.16 (m, 2H), 8.28 (d, J = 2.5 Hz, 1H), 8.53 (s, 1H), 8.72 (s, 1H). MS (ES+): *m/z* 497 $(M+H)^+$.

EXAMPLE 81. *N-tert*-Butyl-3-[5-methyl-2-(4-pyrazol-1-ylmethyl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide (Compund L)

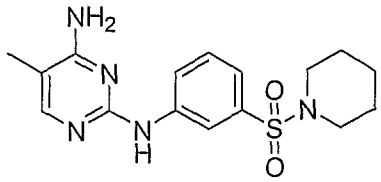


L

[0187] A mixture of intermediate **33** (0.10 g, 0.28 mmol) and 4-pyrazol-1-ylmethyl-phenylamine (50 mg, 0.29 mmol) in acetic acid (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 130 °C for 15 min. After cooling to room temperature, the cap was removed and the mixture concentrated. The residue was purified by HPLC and the corrected fractions combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the resulting solid dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a white solid (12 mg, 9%).

[0188] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.13 (s, 3H), 5.21 (s, 2H), 6.24 (t, J = 1.9 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 7.27–7.50 (m, 3H), 7.56 (s, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 2.1 Hz, 1H), 7.94 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 8.59 (s, 1H), 9.01 (s, 1H). MS (ES+): *m/z* 492 $(M+H)^+$.

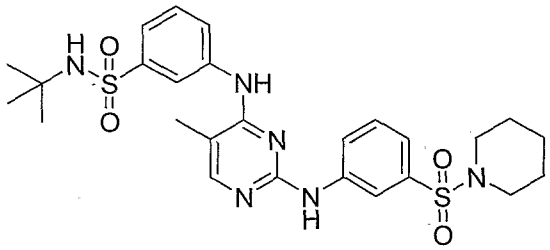
EXAMPLE 82. 5-Methyl-N^2-[3-(piperidine-1-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (Intermediate 34)



34

[0189] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.25 g, 1.74 mmol) and 3-(piperidine-1-sulfonyl)-phenylamine (0.50 g, 2.1 mmol) in acetic acid (4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 130 °C for 15 min. After cooling to room temperature, the cap was removed and the mixture concentrated. The residue was taken in water (20 mL) and pH adjusted to ~9 with 10% NaOH solution. The resulting solution was extracted with EtOAc (2 x 30 mL) and the organic layer separated. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the crude product (~0.6 g) used in the next step without purification. MS (ES+): *m/z* 348 $(M+H)^+$.

EXAMPLE 83. *N-tert*-Butyl-3-{5-methyl-2-[3-(piperidine-1-sulfonyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound LI)



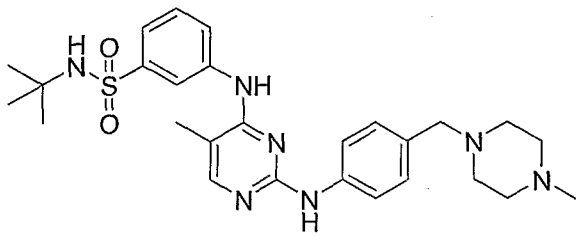
LI

[0190] A suspension of intermediate **34** (0.10 g, 0.29 mmol), 3-bromo-*N-tert*-butyl-benzenesulfonamide (84 mg, 0.29 mmol), $Pd_2(dba)_3$ (15 mg, 0.016 mmol), Xantphos (20 mg, 0.035 mmol) and cesium carbonate (0.18 g, 0.55 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The

filtrate was concentrated and the residue dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a white solid (20 mg, 12%).

[0191] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 1.30–1.40 (m, 2H), 1.50–1.56 (m, 4H), 2.16 (s, 3H), 2.88 (t, J = 5.3 Hz, 4H), 7.17 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.59–7.60 (m, 2H), 7.58 (s, 1H), 8.13 (s, 1H), 7.16 (dd, J = 7.9, 1.9 Hz, 1H), 8.18–8.22 (m, 1H), 8.67 (s, 1H), 9.37 (s, 1H). MS (ES+): *m/z* 559 $(M+H)^+$.

EXAMPLE 84. *N-tert*-Butyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound LII)

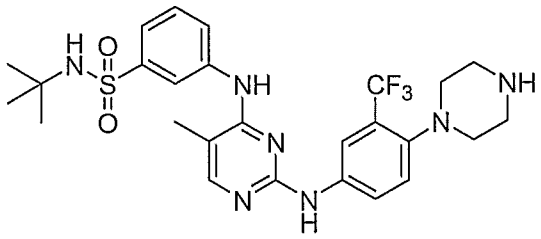


LII

[0192] A suspension of intermediate **33** (0.10 g, 0.28 mmol), 4-(4-methyl-piperazin-1-ylmethyl)-phenylamine (65 mg, 0.32 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.18 g, 0.55 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 170 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a white solid (53 mg, 36%).

[0193] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.13 (s, 3H), 2.15 (s, 3H), 2.20–2.45 (m, 4H), 3.25–3.40 (m, 6H), 7.08 (d, J = 8.6 Hz, 2H), 7.45–7.52 (m, 2H), 7.56 (s, 1H), 7.57 (d, J = 8.6 Hz, 2H), 7.94 (s, 1H), 8.09 (s, 1H), 8.13–8.16 (m, 1H), 8.58 (s, 1H), 8.94 (s, 1H). MS (ES+): *m/z* 524 $(M+H)^+$.

EXAMPLE 85. *N-tert*-Butyl-3-[5-methyl-2-(4-piperazin-1-yl-3-trifluoromethyl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide (Compound LIII)

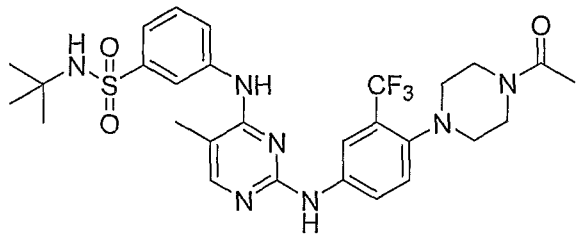


LIII

[0194] A mixture of intermediate **33** (0.10 g, 0.28 mmol), 4-(4-amino-2-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.1 g, 0.29 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.18 g, 0.55 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 170 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM and the filtrate concentrated. The residue was dissolved in DCM (5 mL) and 50% TFA/DCM (6 mL) added. The mixture was stirred at room temperature for 2h, concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the resulting solid dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a white solid (42 mg, 26%).

[0195] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.14 (s, 3H), 2.70–2.75 (m, 4H), 2.80–2.85 (m, 4H), 7.36 (d, J = 8.5 Hz, 2H), 7.45–7.52 (m, 2H), 7.55 (s, 1H), 7.90–8.00 (m, 3H), 8.07 (s, 1H), 8.15 (d, J = 7.6 Hz, 1H), 8.63 (s, 1H), 9.22 (s, 1H) MS (ES+): *m/z* 564 $(M+H)^+$.

EXAMPLE 86. 3-{2-[4-(4-Acetyl-piperazin-1-yl)-3-trifluoromethyl-phenylamino]-5-methyl-pyrimidin-4-ylamino}-*N*-*tert*-butyl-benzenesulfonamide (Compound LIV)

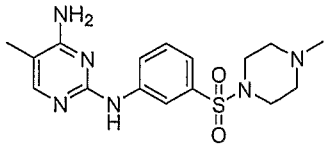


LIV

[0196] A mixture of intermediate **33** (0.10 g, 0.28 mmol), 1-[4-(4-amino-2-trifluoromethyl-phenyl)-piperazin-1-yl]-ethanone (0.1 g, 0.35 mmol), $Pd_2(dba)_3$ (15 mg, 0.016 mmol), Xantphos (20 mg, 0.035 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM and the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the resulting solid dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a white solid (64 mg, 38%).

[0197] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.04 (3, H), 2.14 (s, 3H), 2.73 (t, J = 4.9 Hz, 2H), 2.79 (t, J = 4.7 Hz, 2H), 3.50–3.60 (m, 4H), 7.40 (d, J = 8.7 Hz, 2H), 7.45–7.52 (m, 2H), 7.56 (s, 1H), 7.90–8.00 (m, 3H), 8.07 (s, 1H), 8.14 (d, J = 7.2 Hz, 1H), 8.64 (s, 1H), 9.26 (s, 1H). MS (ES+): *m/z* 606 $(M+H)^+$.

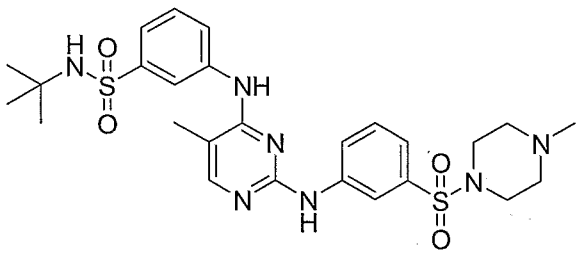
EXAMPLE 87. 5-Methyl-N^2-[3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (Intermediate 35)



35

[0198] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.25 g, 1.74 mmol) and 3-(4-methyl-piperazine-1-sulfonyl)-phenylamine (0.50 g, 2.0 mmol) in acetic acid (4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 130 °C for 15 min. After cooling to room temperature, the cap was removed and the mixture concentrated. The residue was taken in water (20 mL) and pH adjusted to ~9 with 10% NaOH solution. The resulting solution was extracted with EtOAc (2 x 30 mL) and the organic layer separated. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the crude product (~0.42 g) used in the next step without purification. MS (ES+): *m/z* 363 $(M+H)^+$.

EXAMPLE 88. *N-tert*-Butyl-3-{5-methyl-2-[3-(4-methyl-piperazine-1-sulfonyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound LV)



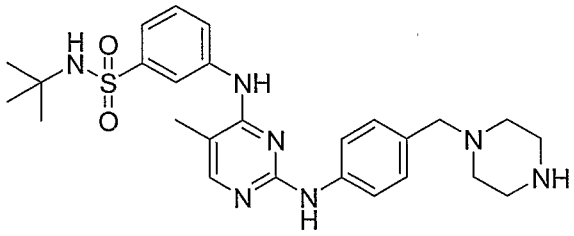
LV

[0199] A suspension of intermediate **35** (0.10 g, 0.28 mmol), 3-bromo-*N-tert*-butyl-benzenesulfonamide (80 mg, 0.27 mmol), $Pd_2(dba)_3$ (15 mg, 0.016 mmol), Xantphos (20 mg, 0.035 mmol) and cesium carbonate (0.18 g, 0.55 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The

filtrate was concentrated and the residue dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a white solid (10 mg, 6%).

[0200] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.13 (s, 3H), 2.16 (s, 3H), 2.33–2.40 (m, 4H), 2.85–2.94 (m, 4H), 7.18 (d, J = 8.1 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.49–7.54 (m, 2H), 7.58 (s, 1H), 8.00–8.03 (m, 2H), 8.13 (s, 1H), 8.15 (dd, J = 8.6, 1.6 Hz, 1H), 8.18–8.23 (m, 1H), 8.66 (s, 1H), 9.38 (s, 1H). MS (ES+): *m/z* 574 $(M+H)^+$.

EXAMPLE 89. *N-tert*-Butyl-3-[5-methyl-2-(4-piperazin-1-ylmethyl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide (Compound LVI)

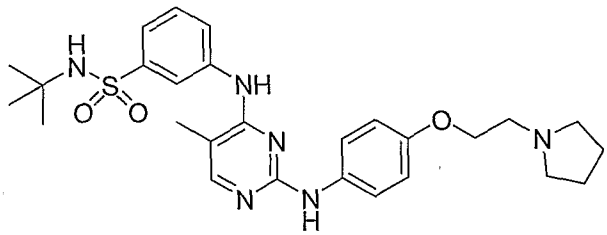


LVI

[0201] A mixture of intermediate **33** (0.10 g, 0.28 mmol), 4-(4-amino-benzyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.1 g, 0.34 mmol), $Pd_2(dba)_3$ (15 mg, 0.016 mmol), Xantphos (20 mg, 0.035 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 170 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM and the filtrate concentrated. The residue was dissolved in DCM (6 mL) and TFA (3 mL) added. The mixture was stirred at room temperature for 1h, concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the resulting solid triturated in hexanes/EtOAc (10/1, 55 mL). After filtration, the title compound was obtained as a white solid (32 mg, 22%).

[0202] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.13 (s, 3H), 2.30–2.40 (m, 4H), 2.85 (t, J = 4.7 Hz, 4H), 3.38 (s, 2H), 7.09 (d, J = 8.5 Hz, 2H), 7.45–7.52 (m, 2H), 7.56 (s, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.94 (s, 1H), 8.10 (s, 1H), 8.13–8.16 (m, 1H), 8.59 (s, 1H), 8.96 (s, 1H). MS (ES+): *m/z* 510 $(M+H)^+$.

EXAMPLE 90. *N-tert*-Butyl-3-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound LVII)

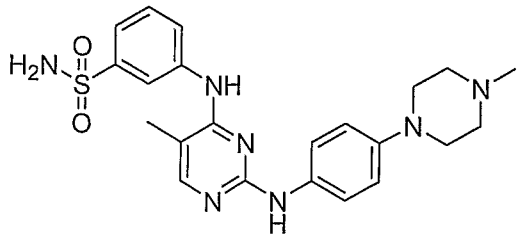


LVII

[0203] A mixture of intermediate **33** (0.10 g, 0.28 mmol) and 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (0.10 g, 0.49 mmol) in acetic acid (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 150 °C for 20 min. After cooling to room temperature, the cap was removed and the mixture concentrated. The residue was purified by HPLC and the corrected fractions combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the resulting solid dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a white solid (40 mg, 27%).

[0204] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 1.65–1.70 (m, 4H), 2.12 (s, 3H), 2.45–2.55 (m, 4H), 2.76 (t, J = 5.8 Hz, 2H), 3.99 (t, J = 6.0 Hz, 2H), 6.79 (d, J = 9.0 Hz, 2H), 7.46–7.53 (m, 4H), 7.56 (s, 1H), 7.90 (s, 1H), 8.10–8.15 (m, 2H), 8.53 (s, 1H), 8.77 (s, 1H). MS (ES+): *m/z* 525 $(M+H)^+$.

EXAMPLE 91. 3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound LVIII)

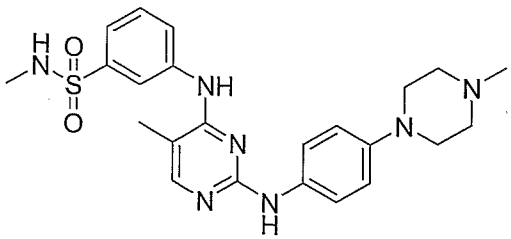


LVIII

[0205] A suspension of intermediate **32** (0.10 g, 0.33 mmol), 3-bromo-benzenesulfonamide (0.10 g, 0.42 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.25 g, 0.77 mmol) in dioxane (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to afford the title compound as a grey solid (10 mg, 7%).

[0206] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.10 (s, 3H), 2.22 (s, 3H), 2.44 (t, J = 4.9 Hz, 4H), 3.03 (t, J = 4.9 Hz, 4H), 6.81 (d, J = 9.0 Hz, 2H), 7.34 (s, 2H), 7.45–7.50 (m, 4H), 7.89 (s, 1H), 8.06 (s, 1H), 8.13–8.18 (m, 1H), 8.54 (s, 1H), 8.70 (s, 1H). MS (ES+): *m/z* 454 $(M+H)^+$.

EXAMPLE 92. *N*-Methyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound LIX)

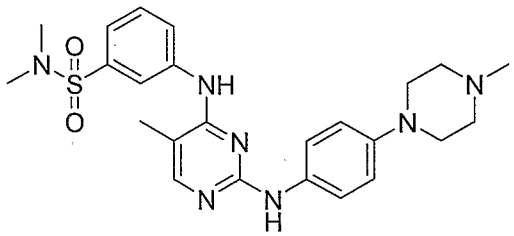


LIX

[0207] A suspension of intermediate **32** (0.10 g, 0.33 mmol), 3-bromo-*N*-methyl-benzenesulfonamide (0.11 g, 0.44 mmol), $Pd_2(dba)_3$ (20 mg, 0.*022* mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.25 g, 0.77 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue triturated in a mixture of DCM/Et_2O (1/5, 30 mL). After filtration, the title compound was obtained as a light brown solid (65 mg, 42%).

[0208] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.11 (s, 3H), 2.23 (s, 3H), 2.44 (d, J = 5.0 Hz, 3H), 2.45–2.50 (m, 4H), 3.03 (t, J = 4.9 Hz, 4H), 6.81 (d, J = 9.1 Hz, 2H), 7.40–7.43 (m, 2H), 7.46 (d, J = 9.1 Hz, 2H), 7.52 (t, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.94 (t, J = 1.8 Hz, 1H), 8.29 (br d, J = 8.3 Hz, 1H), 8.56 (s, 1H), 8.72 (s, 1H). MS (ES+): *m/z* 468 $(M+H)^+$.

EXAMPLE 93. *N,N*-Dimethyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound LX)



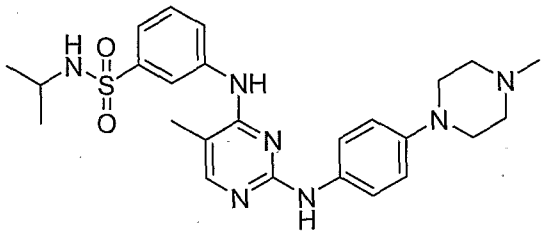
LX

[0209] A suspension of intermediate **32** (0.13 g, 0.43 mmol), 3-bromo-*N,N*-dimethyl-benzenesulfonamide (0.14 g, 0.53 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), Xantphos (30 mg, 0.052 mmol) and cesium carbonate (0.33 g, 1.0 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the

combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue triturated in a mixture of EtOAc/hexanes (1/5, 30 mL). After filtration, the title compound was obtained as an off white solid (60 mg, 29%).

[0210] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.17 (s, 3H), 2.23 (s, 3H), 2.44 (d, J = 5.0 Hz, 3H), 2.45–2.50 (m, 4H), 2.63 (s, 6H), 3.03 (t, J = 4.9 Hz, 4H), 6.81 (d, J = 9.1 Hz, 2H), 7.36 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 9.1 Hz, 2H), 7.54 (t, J = 8.0 Hz, 1H), 7.84 (t, J = 1.9 Hz, 1H), 7.90 (s, 1H), 8.46 (br d, J = 7.8 Hz, 1H), 8.57 (s, 1H), 8.74 (s, 1H). MS (ES+): *m/z* 482 $(M+H)^+$.

EXAMPLE 94. *N*-Isopropyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound LXI)

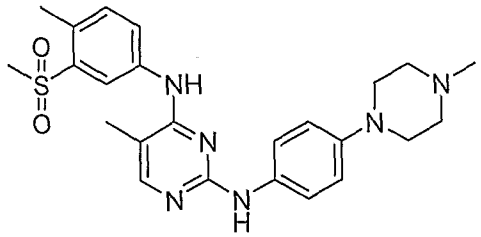


LXI

[0211] A suspension of intermediate **32** (0.10 g, 0.33 mmol), 3-bromo-*N*-isopropyl-benzenesulfonamide (0.11 g, 0.39 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.25 g, 0.77 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue triturated in a mixture of EtOAc/hexanes (1/10, 33 mL). After filtration, the title compound was obtained as an off white solid (47 mg, 29%).

[0212] ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.98 (d, J = 6.6 Hz, 6H), 2.11 (s, 3H), 2.24 (s, 3H), 2.45–2.50 (m, 4H), 3.03 (t, J = 4.8 Hz, 4H), 3.20–3.27 (m, 1H), 6.80 (d, J = 9.0 Hz, 2H), 7.40–7.52 (m, 4H), 7.59 (d, J = 7.1 Hz, 1H), 7.89 (s, 1H), 8.21 (br d, J = 7.9 Hz, 1H), 8.53 (s, 1H), 8.71 (s, 1H). MS (ES+): *m/z* 496 $(M+H)^+$.

EXAMPLE 95. N^4-(3-Methanesulfonyl-4-methyl-phenyl)-5-methyl-N^2-[4-(4-methyl-piperazin-1-yl)-phenyl]-pyrimidine-2,4-diamine (Compound LXII)

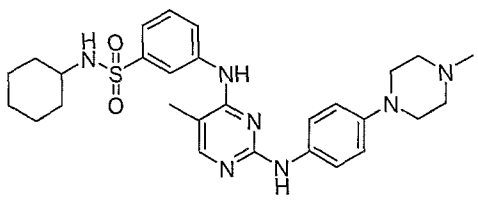


LXII

[0213] A suspension of intermediate **32** (0.10 g, 0.33 mmol), 4-bromo-2-methanesulfonyl-1-methyl-benzene (0.10 g, 0.40 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.25 g, 0.77 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue triturated in a mixture of EtOAc/hexanes (1/5, 30 mL). After filtration, the title compound was obtained as a light brown solid (41 mg, 27%).

[0214] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.09 (s, 3H), 2.22 (s, 3H), 2.45 (t, J = 4.7 Hz, 4H), 2.61 (s, 3H), 3.03 (t, J = 4.9 Hz, 4H), 3.20 (s, 3H), 6.80 (d, J = 9.1 Hz, 2H), 7.35 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 9.0 Hz, 2H), 7.87 (s, 1H), 8.05 (d, J = 2.4 Hz, 1H), 8.21 (br d, J = 7.0 Hz, 1H), 8.55 (s, 1H), 8.71 (s, 1H). MS (ES+): *m/z* 467 $(M+H)^+$.

EXAMPLE 96. *N*-Cyclohexyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound LXIII)

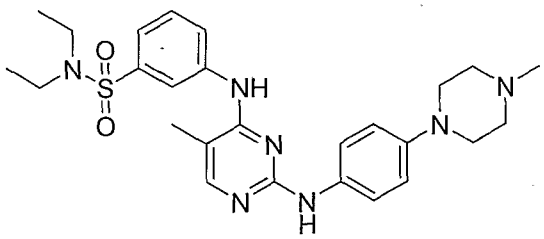


LXIII

[0215] A suspension of intermediate **32** (0.10 g, 0.33 mmol), 3-bromo-*N*-cyclohexyl-benzenesulfonamide (0.13 g, 0.41 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.25 g, 0.77 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue triturated in a mixture of EtOAc/hexanes (1/10, 33 mL). After filtration, the title compound was obtained as an off white solid (45 mg, 25%).

[0216] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.07–1.17 (m, 6H), 1.53–1.63 (m, 4H), 2.11 (s, 3H), 2.22 (s, 3H), 2.45 (t, J = 4.7 Hz, 4H), 2.90–3.00 (m, 1H), 3.02 (t, J = 4.8 Hz, 4H), 6.80 (d, J = 9.1 Hz, 2H), 7.43–7.53 (m, 4H), 7.65 (d, J = 7.3 Hz, 1H), 7.89 (s, 1H), 8.05 (s, 1H), 8.18 (br d, J = 7.7 Hz, 1H), 8.52 (s, 1H), 8.71 (s, 1H). MS (ES+): *m/z* 536 $(M+H)^+$.

EXAMPLE 97. *N,N*-Diethyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound LXIV)



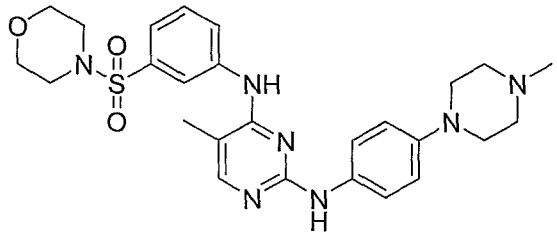
LXIV

[0217] A suspension of intermediate **32** (0.10 g, 0.33 mmol), 3-bromo-*N,N*-diethyl-benzenesulfonamide (0.12 g, 0.41 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.25 g, 0.77 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the

combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue triturated in a mixture of EtOAc/hexanes (1/10, 33 mL). After filtration, the title compound was obtained as an off white solid (45 mg, 27%).

[0218] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.06 (t, J = 7.1 Hz, 6H), 2.11 (s, 3H), 2.22 (s, 3H), 2.44 (t, J = 4.7 Hz, 4H), 3.03 (t, J = 4.8 Hz, 4H), 3.16 (q, J = 7.1 Hz, 4H), 6.80 (d, J = 9.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 9.0 Hz, 2H), 7.50 (t, J = 8.1 Hz, 1H), 7.89 (t, J = 1.9 Hz, 1H), 7.89 (s, 1H), 8.39 (br d, J = 7.9 Hz, 1H), 8.53 (s, 1H), 8.74 (s, 1H). MS (ES+): *m/z* 510 $(M+H)^+$.

EXAMPLE 98. 5-Methyl-N^2-[4-(4-methyl-piperazin-1-yl)-phenyl]-N^4-[3-(morpholine-4-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (Compound LXV)

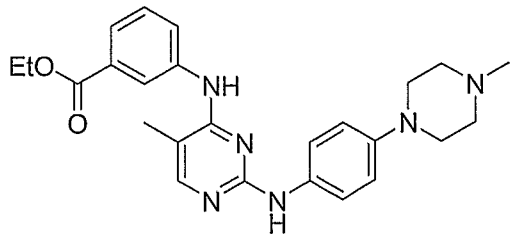


LXV

[0219] A suspension of intermediate **32** (0.10 g, 0.33 mmol), 4-(3-bromo-benzenesulfonyl)-morpholine (0.12 g, 0.39 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.25 g, 0.77 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue triturated in a mixture of EtOAc/hexanes (1/10, 33 mL). After filtration, the title compound was obtained as a light red solid (90 mg, 52%).

[0220] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.12 (s, 3H), 2.22 (s, 3H), 2.45 (t, J = 4.8 Hz, 4H), 2.89 (t, J = 4.6 Hz, 4H), 3.03 (t, J = 4.8 Hz, 4H), 3.64 (t, J = 4.7 Hz, 4H), 6.81 (d, J = 9.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 9.0 Hz, 2H), 7.56 (t, J = 8.1 Hz, 1H), 7.84 (t, J = 1.9 Hz, 1H), 7.91 (s, 1H), 8.47 (br d, J = 8.4 Hz, 1H), 8.59 (s, 1H), 8.75 (s, 1H). MS (ES+): *m/z* 524 $(M+H)^+$.

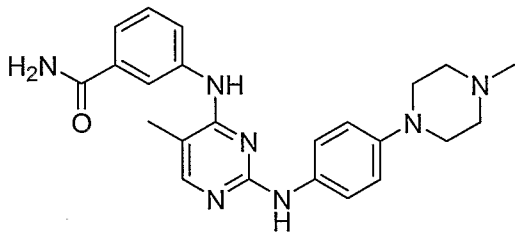
EXAMPLE 99. 3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzoic acid ethyl ester (Intermediate 36)



36

[0221] A suspension of intermediate **32** (0.10 g, 0.33 mmol), 3-bromo-benzoic acid ethyl ester (0.07 mL, 0.44 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.25 g, 0.77 mmol) in dioxane (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by flash chromatography on silica gel (DCM to 10% MeOH/DCM) to afford the title compound (0.10 g, 68%). MS (ES+): *m/z* 447 $(M+H)^+$.

EXAMPLE 100. 3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzamide (Compound LXVI)

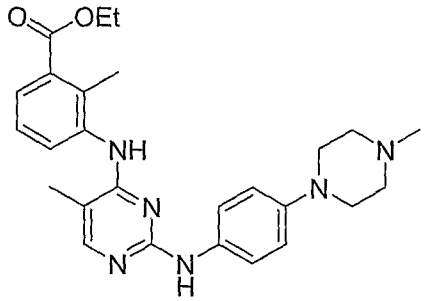


LXVI

[0222] A mixture of intermediate **36** (0.10 g, 0.22 mmol) in concentrated NH_4OH was sealed in a reaction tube and heated at 50 °C for 3 d. The mixture was poured into water (15 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue triturated in a mixture of EtOAc/hexanes (1/10, 33 mL). After filtration, the title compound was obtained as a white solid (10 mg, 11%).

[0223] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.10 (s, 3H), 2.22 (s, 3H), 2.40–2.50 (m, 4H), 2.95–3.05 (m, 4H), 6.75 (d, J = 9.1 Hz, 2H), 7.30–7.40 (m, 2H), 7.45 (d, J = 9.1 Hz, 2H), 7.53–7.58 (m, 1H), 7.85 (s, 1H), 7.90 (br s, 2H), 8.03 (s, 1H), 8.37 (s, 1H), 8.71 (s, 1H). MS (ES+): *m/z* 418 $(M+H)^+$.

EXAMPLE 101. 2-Methyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzoic acid ethyl ester (Compound LXVII)

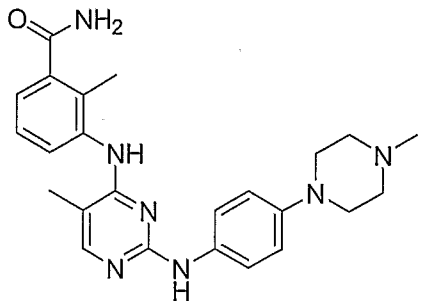


LXVII

[0224] A suspension of intermediate **32** (0.10 g, 0.33 mmol), 3-bromo-2-methyl-benzoic acid ethyl ester (0.10 mL, 0.41 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.25 g, 0.77 mmol) in dioxane (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by flash chromatography on silica gel (DCM to 30% MeOH and 1% TEA in DCM) to afford the title compound (0.14 g, 92%) as a light brown oil.

[0225] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.32 (t, J = 7.1 Hz, 3H), 2.10 (s, 3H), 2.21 (s, 3H), 2.32 (s, 3H), 2.40–2.45 (m, 4H), 2.94 (t, J = 4.8 Hz, 4H), 4.30 (q, J = 7.1 Hz, 2H), 6.57 (d, J = 9.1 Hz, 2H), 7.25 (d, J = 8.9 Hz, 2H), 7.35 (t, J = 7.8 Hz, 1H), 7.48 (dd, J = 7.9, 1.0 Hz, 1H), 7.70 (dd, J = 7.8, 1.1 Hz, 1H), 7.78 (s, 1H), 8.23 (s, 1H), 8.58 (s, 1H). MS (ES+): *m/z* 461 $(M+H)^+$.

EXAMPLE 102. 2-Methyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzamide (Compound LXVIII)

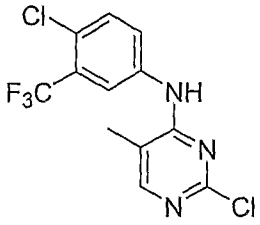


LXVIII

[0226] To a mixture of the above-described compound **LXVII** (0.10 g, 0.22 mmol) and formamide (0.05 mL, 1.3 mmol) in DMF (5 mL) at 100 °C was added NaOMe (0.10 g, 0.46 mmol) under the argon atmosphere. The mixture was stirred at the same temperature for 2 h and then at room temperature for additional 15 h. The mixture was poured into water (15 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue triturated in a mixture of EtOAc/hexanes (1/5, 30 mL). After filtration, the title compound was obtained as a white solid (20 mg, 21%).

[0227] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.09 (s, 3H), 2.21 (s, 3H), 2.23 (s, 3H), 2.40–2.45 (m, 4H), 2.97 (t, J = 4.8 Hz, 4H), 6.69 (d, J = 9.1 Hz, 2H), 7.24–7.28 (m, 2H), 7.35 (d, J = 9.0 Hz, 2H), 7.39–7.43 (m, 2H), 7.69 (s, 1H), 7.78 (s, 1H), 8.01 (s, 1H), 8.53 (s, 1H). MS (ES+): *m/z* 432 $(M+H)^+$.

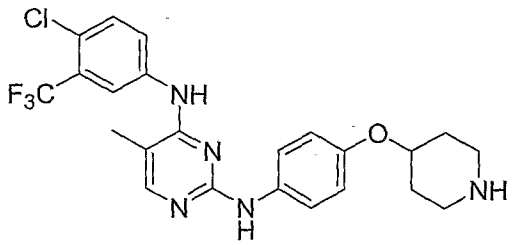
EXAMPLE 103. (2-Chloro-5-methyl-pyrimidin-4-yl)-(4-chloro-3-trifluoromethyl-phenyl)-amine (Intermediate 37)



37

[0228] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.30 g, 2.1 mmol), 4-bromo-1-chloro-2-trifluoromethyl-benzene (0.40 mL, 2.7 mmol), $Pd_2(dba)_3$ (0.10 g, 0.11 mmol), Xantphos (0.13 g, 0.22 mmol) and cesium carbonate (1.5 g, 4.6 mmol) in dioxane/DMF (6/1, 7 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by flash chromatography on silica gel (hexanes to 50% EtOAc/hexanes) to afford the title compound (0.65 g, 96%) as a white solid. MS (ES+): *m/z* 322 $(M+H)^+$.

EXAMPLE 104. N^4-(4-Chloro-3-trifluoromethyl-phenyl)-5-methyl-N^2-[4-(piperidin-4-yloxy)-phenyl]-pyrimidine-2,4-diamine (Compound LXIX)



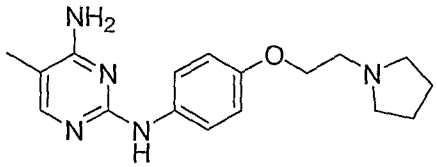
LXIX

[0229] A mixture of intermediate **37** (0.10 g, 0.31 mmol) and 4-(4-amino-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (0.12 g, 0.41 mmol) in acetic acid (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 150 °C for 15 min. After cooling to room temperature, the cap was removed and the mixture concentrated. The residue was taken in water (20 mL) and neutralized with 10% NaOH solution until solid precipitated. The resulting solid was filtered and purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried

over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to afford the title compound as a white solid (30 mg, 20%).

[0230] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.69–1.77 (m, 2H), 2.00–2.04 (m, 2H), 2.11 (s, 3H), 2.90–3.00 (m, 2H), 3.10–3.20 (m, 2H), 4.40–4.48 (m, 1H), 6.84 (d, J = 9.0 Hz, 2H), 7.49 (d, J = 9.0 Hz, 2H), 7.58 (d, J = 8.8 Hz, 1H), 7.94 (s, 1H), 8.12 (d, J = 2.6 Hz, 1H), 8.21 (br d, J = 8.2 Hz, 1H), 8.64 (s, 1H), 8.93 (s, 1H). MS (ES+): *m/z* 478 $(M+H)^+$.

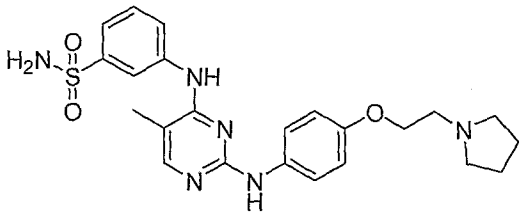
EXAMPLE 105. 5-Methyl-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine (Intermediate 38)



38

[0231] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.50 g, 3.5 mmol) and 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (1.1 g, 5.3 mmol) in acetic acid (8 mL) was sealed in a microwave reaction tube and irradiated with microwave at 150 °C for 15 min. After cooling to room temperature, the cap was removed and the mixture concentrated. The residue was taken in water (30 mL) and neutralized with 10% NaOH solution until pH ~10. The resulting aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to afford the title compound as a grey solid (0.80 g, 73%). It was used in the next step without purification. MS (ES+): *m/z* 314 $(M+H)^+$.

EXAMPLE 106. 3-{5-Methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound LXX)

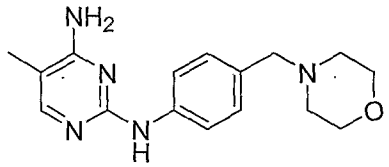


LXX

[0232] A mixture of intermediate **38** (0.10 g, 0.32 mmol), 3-bromo-benzenesulfonamide (0.10 g, 0.42 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 170 °C for 25 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and solid triturated in a mixture of EtOAc/hexanes (1/10, 33 mL). After filtration, the title compound was obtained as a white solid (11 mg, 7%).

[0233] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.65–1.72 (m, 4H), 2.11 (s, 3H), 2.49–2.52 (m, 4H), 2.75–2.80 (m, 2H), 4.00 (t, J = 5.9 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 7.34 (s, 2H), 7.45–7.50 (m, 2H), 7.52 (d, J = 9.0 Hz, 2H), 7.90 (s, 1H), 8.05 (s, 1H), 8.10–8.15 (m, 1H), 8.57 (s, 1H), 8.77 (s, 1H). MS (ES+): *m/z* 469 $(M+H)^+$.

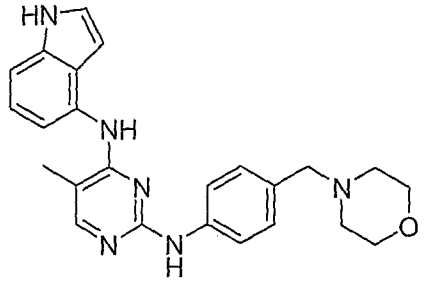
EXAMPLE 107. 5-Methyl-N^2-(4-morpholin-4-ylmethyl-phenyl)-pyrimidine-2,4-diamine (Intermediate 39)



39

[0234] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.40 g, 2.8 mmol) and 4-morpholin-4-ylmethyl-phenylamine (0.60 g, 3.1 mmol) in acetic acid (15 mL) was heated at 70 °C for 17 h. After cooling to room temperature, the mixture was concentrated. The residue was taken in water (30 mL) and neutralized with 10% NaOH solution until pH ~10. The resulting aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to afford the title compound as a brown syrup (0.70 g, 83%). It was used in the next step without purification. MS (ES+): *m/z* 300 $(M+H)^+$

EXAMPLE 108 N^4-(1*H*-Indol-4-yl)-5-methyl-N^2-(4-morpholin-4-ylmethyl-phenyl)-pyrimidine-2,4-diamine (Compound LXXI)



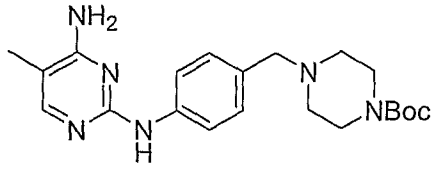
LXXI

[0235] A mixture of intermediate **39** (0.40 g, 1.3 mmol), 4-bromo-1-triisopropylsilanyl-1*H*-indole (0.50 g, 1.4 mmol), $Pd_2(dba)_3$ (0.10 g, 0.11 mmol), Xantphos (0.12 g, 0.21 mmol) and cesium carbonate (0.90 g, 2.8 mmol) was suspended in dioxane (20 mL) and heated at reflux under the argon atmosphere for 4 h. The reaction mixture was cooled to room temperature and diluted with DCM (30 mL). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexanes to EtOAc) to afford the TIPS protected precursor as a yellow oil.

[0236] To the above TIPS protected precursor (50 mg, 0.088 mmol) in THF (5 mL) was added TBAF (0.5 mL, 1M in THF). The mixture was stirred at room temperature for 1 h and then poured into water (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and solid dissolved in minimum amount of EtOAc and then hexanes added until solid precipitated. After filtration, the title compound was obtained as a light brown solid (6 mg, 1% overall yield).

[0237] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.17 (s, 3H), 2.25–2.30 (m, 4H), 3.29 (s, 2H), 3.54 (t, J = 4.5 Hz, 4H), 6.40 (t, J = 2.2 Hz, 1H), 6.89 (d, J = 8.5 Hz, 2H), 7.09 (t, J = 7.8 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 2.8 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 8.5 Hz, 2H), 7.85 (s, 1H), 8.14 (s, 1H), 8.77 (s, 1H), 11.10 (s, 1H). MS (ES+): *m/z* 415 $(M+H)^+$.

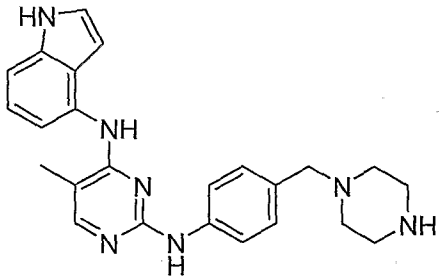
EXAMPLE 109. 4-[4-(4-Amino-5-methyl-pyrimidin-2-ylamino)-benzyl]-piperazine-1-carboxylic acid *tert*-butyl ester (Intermediate 40)



40

[0238] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.35 g, 2.4 mmol) and 4-(4-amino-benzyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.80 g, 2.8 mmol) in acetic acid (20 mL) was heated at 70 °C for 1 d. After cooling to room temperature, the mixture was concentrated. The residue was taken in water (30 mL) and neutralized with 10% NaOH solution until pH ~10. The resulting aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the title compound used in the next step without purification. MS (ES+): *m/z* 399 $(M+H)^+$.

EXAMPLE 110. N^4-(1*H*-Indol-4-yl)-5-methyl-N^2-(4-piperazin-1-ylmethyl-phenyl)-pyrimidine-2,4-diamine (Compound LXXII)



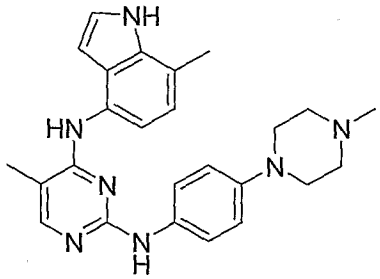
LXXII

[0239] A mixture of intermediate **40** (0.78 g, 2.0 mmol), 4-bromo-1-triisopropylsilanyl-1*H*-indole (0.70 g, 2.0 mmol), $Pd_2(dba)_3$ (0.15 g, 0.16 mmol), Xantphos (0.19 g, 0.32 mmol) and cesium carbonate (1.3 g, 4.0 mmol) was suspended in dioxane (20 mL) and heated at reflux under the argon atmosphere for 4.5 h. The reaction mixture was cooled to room temperature, filtered and the filtered solid was with DCM (30 mL). The filtrate was concentrated and the residue purified by flash chromatography on silica gel (hexanes to 30% EtOAc/hexanes) to afford the TIPS protected precursor.

[0240] To the above TIPS protected precursor (0.10 g, 0.15 mmol) in DCM (8 mL) was added TFA (2 mL). The mixture was stirred at room temperature for 2 h and then concentrated. The residue was purified by HPLC and the corrected fractions combined and poured into saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and solid triturated in a mixture of EtOAc/hexanes (1/5, 30 mL). After filtration,, the title compound was obtained as a white solid (25 mg, 3% overall yield).

[0241] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.17 (s, 3H), 2.20–2.30 (m, 4H), 2.73 (t, J = 4.6 Hz, 4H), 3.28 (s, 2H), 6.41 (t, J = 2.2 Hz, 1H), 6.89 (d, J = 8.5 Hz, 2H), 7.09 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H), 7.27 (t, J = 2.8 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.85 (s, 1H), 8.13 (s, 1H), 8.77 (s, 1H), 11.10 (s, 1H)
MS (ES+): *m/z* 414 $(M+H)^+$.

EXAMPLE 111. 5-Methyl-*N*^{4}-(7-methyl-1*H*-indol-4-yl)-*N*^{2}-(4-(4-methylpiperazin-1-yl)phenyl) pyrimidine-2,4-diamine (Compound LXXIII)

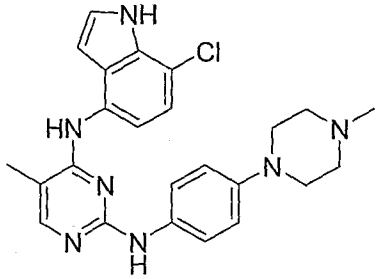


LXXIII

[0242] A mixture of intermediate **32** (674 mg, 2.25 mmol), 4-bromo-7-methyl-1*H*-indole (522 mg, 2.48 mmol), $Pd_2(dba)_3$ (182 mg, 0.2 mmol), Xantphos (360 mg, 0.6 mmol) and cesium carbonate (2.6 g, 8 mmol) was suspended in dioxane (50 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (136 mg of HCl salt, 13%) as a white solid.

[0243] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.21 (s, 3H), 2.55 (s, 3H), 2.80 (d, J = 4.6 Hz, 3H), 3.00-3.05 (m, 2H), 3.10-3.16 (m, 2H), 3.45–3.48 (m, 2H), 3.64-3.66 (m, 2H), 6.33-6.34 (m, 1H), 6.63 (br, 2H), 6.92-6.97 (m, 4H), 7.35 (t, J = 2.7 Hz, 1H), 7.83 (s, 1H), 10.04 (s, 1H), 10.24 (s, 1H), 11.08 (br s, 1H), 11.34 (s, 1H), 12.12 (br s, 1H). MS (ES+): *m/z* 428 $(M+H)^+$.

EXAMPLE 112. N^4-(7-Chloro-1*H*-indol-4-yl)-5-methyl-N^2-(4-(4-methylpiperazin-1-yl)phenyl) pyrimidine-2,4-diamine (Compound LXXIV)

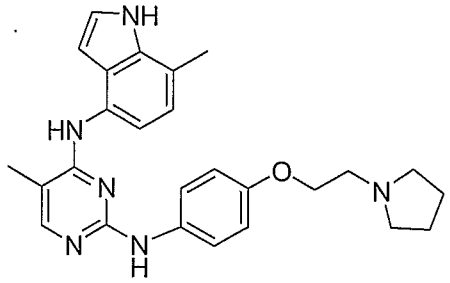


LXXIV

[0244] A mixture of intermediate **32** (298 mg, 1.0 mmol), 4-bromo-7-chloro-1*H*-indole (231 mg, 1.04 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), Xantphos (180 mg, 0.3 mmol) and cesium carbonate (1.3 g, 4 mmol) was suspended in dioxane (50 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (251 mg of HCl salt, 51%) as a white solid.

[0245] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.21 (s, 3H), 2.80 (d, J = 4.6 Hz, 3H), 3.01-3.05 (m, 2H), 3.08-3.13 (m, 2H), 3.46-3.48 (m, 2H), 3.65-3.67 (m, 2H), 6.46-6.47 (m, 1H), 6.64 (br s, 1H), 6.93 (d, J = 8.9 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.43-7.44 (m, 1H), 7.87 (s, 1H), 10.13 (s, 1H), 10.27 (s, 1H), 11.00 (br s, 1H), 11.70 (s, 1H), 12.23 (br s, H). MS (ES+): *m/z* 448 $(M+H)^+$.

EXAMPLE 113. N^2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenyl)-5-methyl-N^4-(7-methyl-1*H*-indol-4-yl) pyrimidine-2,4-diamine (Compound LXXV)

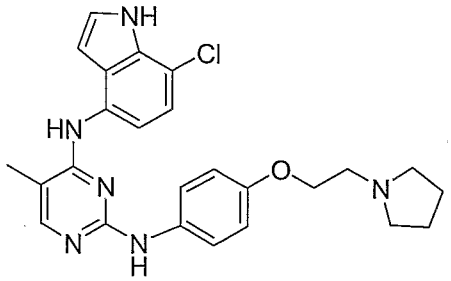


LXXV

[0246] A mixture of intermediate **38** (410 mg, 1.3 mmol), 4-bromo-7-methyl-1*H*-indole (275 mg, 1.3 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), Xantphos (180 mg, 0.3 mmol) and cesium carbonate (1.3 g, 4 mmol) was suspended in dioxane (50 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (92 mg of HCl salt, 15%) as a white solid.

[0247] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.88-1.90 (m, 2H), 1.93-2.02 (m, 2H), 2.21 (s, 3H), 2.55 (s, 3H), 3.06-3.10 (m, 2H), 3.51-3.54 (m, 4H), 4.26 (t, J = 4.9 Hz, 2H), 6.33-6.34 (m, 1H), 6.61 (br d, 2H), 6.93-6.95 (m, 2H), 7.03 (d, J = 8.9 Hz, 2H), 7.34 (t, J = 2.8 Hz, 1H), 7.85 (s, 1H), 10.07 (s, 1H), 10.33 (s, 1H), 10.91 (br s, 1H), 11.34 (s, 1H), 12.15 (br s, H). MS (ES+): *m/z* 443 $(M+H)^+$.

EXAMPLE 114. N^2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenyl)-5-methyl-N^4-(7-chloro-1*H*-indol-4-yl) pyrimidine-2,4-diamine (Compound LXXVI)



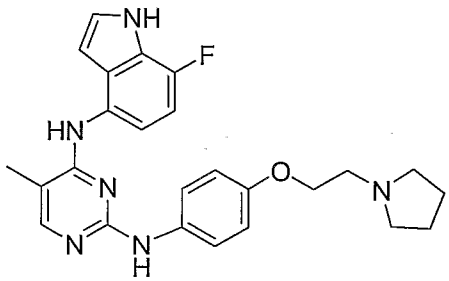
LLXVI

[0248] A mixture of intermediate **38** (270 mg, 0.86 mmol), 4-bromo-7-chloro-1*H*-indole (198 mg, 0.86 mmol), $Pd_2(dba)_3$ (72 mg, 0.08 mmol), Xantphos (140 mg, 0.24 mmol) and cesium carbonate (1.3 g, 4 mmol) was suspended in dioxane (50 mL) and heated at reflux

under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (33 mg of HCl salt, 8%) as a white solid.

[0249] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.88-1.90 (m, 2H), 1.93-2.02 (m, 2H), 2.22 (s, 3H), 3.06-3.10 (m, 2H), 3.51-3.54 (m, 4H), 4.27 (t, J = 4.9 Hz, 2H), 6.46-6.47 (m, 1H), 6.63 (br d, 2H), 6.95 (d, J = 8.2 Hz, 2H), 7.06 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 2.8 Hz, 1H), 7.90 (s, 1H), 10.13 (s, 1H), 10.40 (s, 1H), 10.94 (br s, 1H), 11.70 (s, 1H), 12.33 (br s, H). MS (ES+): *m/z* 463 $(M+H)^+$.

EXAMPLE 115. N^2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenyl)-5-methyl-N^4-(7-fluoro-1*H*-indol-4-yl) pyrimidine-2,4-diamine (Compound LXXVII)

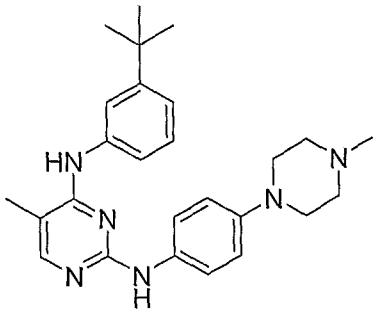


LXXVII

[0250] A mixture of intermediate **38** (413 mg, 1.3 mmol), 4-bromo-7-fluoro-1*H*-indole (310 mg, 1.45 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), Xantphos (180 mg, 0.3 mmol) and cesium carbonate (1.3 g, 4 mmol) was suspended in dioxane (50 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (10 mg of HCl salt, 1.5%) as a brown solid.

[0251] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.88-1.90 (m, 2H), 1.93-2.02 (m, 2H), 2.21 (s, 3H), 3.06-3.10 (m, 2H), 3.51-3.56 (m, 4H), 4.26 (t, J = 4.9 Hz, 2H), 6.42-6.43 (m, 1H), 6.63 (br d, 2H), 6.95-7.04 (m, 3H), 7.35 (d, J = 8.9 Hz, 1H), 7.42 (t, J = 2.8 Hz, 1H), 7.89 (s, 1H), 10.08 (s, 1H), 10.41 (s, 1H), 10.90 (br s, 1H), 11.85 (s, 1H), 12.33 (br s, H). MS (ES+): *m/z* 447 $(M+H)^+$.

EXAMPLE 116. N^4-(3-*tert*-Butylphenyl)-5-methyl-N^2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine (Compound LXXVIII)

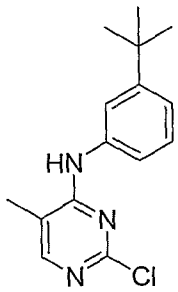


LXXVIII

[0252] A mixture of intermediate **32** (298 mg, 1.0 mmol), 1-*tert*-butyl-3-bromobenzene (256 mg, 1.2 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), Xantphos (180 mg, 0.3 mmol) and cesium carbonate (1.3 g, 4 mmol) was suspended in dioxane (50 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (27 mg of HCl salt, 6%) as a white solid.

[0253] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.25 (s, 9H), 2.16 (s, 3H), 2.80 (d, J = 4.6 Hz, 3H), 3.04-3.16 (m, 4H), 3.47-3.49 (m, 2H), 3.65-3.67 (m, 2H), 6.90 (d, J = 8.9 Hz, 2H), 7.26 (d, J = 9.0 Hz, 2H), 7.28-7.35 (m, 2H), 7.45 (t, J = 1.8 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.86 (s, 1H), 9.70 (s, 1H), 10.37 (s, 1H), 11.01 (br s, 1H), 12.34 (br s, H). MS (ES+): *m/z* 431 . $(M+H)^+$.

EXAMPLE 117. *N*-(3-*tert*-Butylphenyl)-2-chloro-5-methylpyrimidin-4-amine (Intermediate 41)

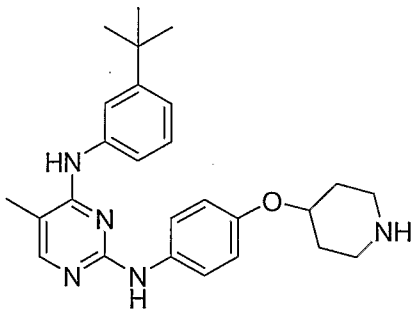


41

[0254] A mixture of 2-chloro-5-methylpyrimidin-4-amine (670 mg, 4.7 mmol), 1-*tert*-butyl-3-bromobenzene (1.5 g, 7 mmol), $Pd_2(dba)_3$ (366 mg, 0.4 mmol), Xantphos (695 mg, 1.2 mmol) and cesium carbonate (6.2 g, 19 mmol) was suspended in dioxane (150 mL) and

heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc (10 mL) and added hexanes (100 mL). The solid was collected by filtration and washed with hexanes to afford the crude title compound (1.2 g, 99%) as a yellow solid.

EXAMPLE 118. N^4-(3-*tert*-Butylphenyl)-5-methyl-N^2-(4-(piperidin-4-yloxy)phenyl)pyrimidine-2,4-diamine (Compound LXXIX)

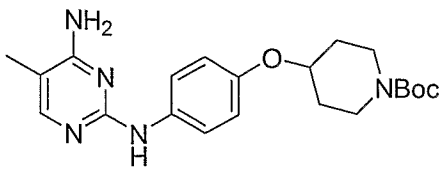


LXXIX

[0255] A mixture of intermediate **41** (740 mg, 2.68 mmol) and *tert*-butyl 4-(4-aminophenoxy)piperidine-1-carboxylate (500 mg, 1.71 mmol) was suspended in acetic acid (10 mL) and heated at 100 °C for 4 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (20 mL) and neutralized to pH~7. The resulting solution was extracted with EtOAc (30 mL) and the organic layer separated. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by HPLC to afford the title compound (276 mg of HCl salt, 35%) as a yellow solid.

[0256] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.22 (s, 9H), 1.77-1.81 (m, 2H), 2.03-2.07 (m, 2H), 2.14 (s, 3H), 3.00-3.04 (m, 2H), 3.18 (br s, 2H), 4.56-4.57 (m, 1H), 6.86 (d, J = 8.9 Hz, 2H), 7.26-7.31 (m, 4H), 7.40 (s, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.84 (s, 1H), 8.93 (br s, 1H), 8.99 (br s, 1H), 9.67 (s, 1H), 10.31 (s, 1H). MS (ES+): *m/z* 432 $(M+H)^+$.

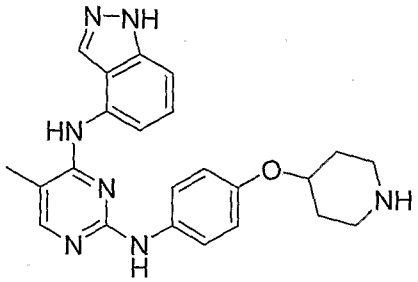
EXAMPLE 119. *tert*-Butyl 4-(4-(4-amino-5-methylpyrimidin-2-ylamino)phenoxy)piperidine-1-carboxylate (Intermediate 42)



42

[0257] A mixture of 2-chloro-5-methylpyrimidin-4-amine (540 mg, 3.7 mmol), *tert*-butyl 4-(4-aminophenoxy)piperidine-1-carboxylate (1.1 g, 3.7 mmol) was suspended in acetic acid (20 mL) and heated at 70 °C for 1 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (20 mL) and neutralized to pH~7. The resulting solution was extracted with EtOAc (30 mL) and the organic layer separated. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to afford the title compound (1.4 g, 95%) as a yellow solid.

EXAMPLE 120. N^4-(1*H*-Indazol-4-yl)-5-methyl-N^2-(4-(piperidin-4-yloxy)phenyl)pyrimidine-2,4-diamine (Compound LXXX)

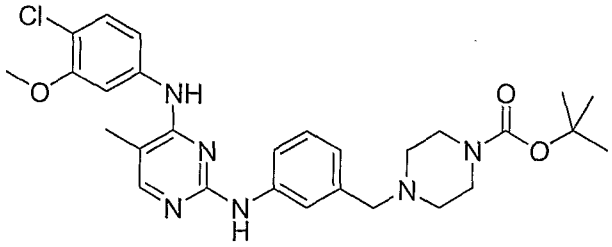


LXXX

[0258] A mixture of intermediate **42** (480 mg, 1.2 mmol), 4-bromo-1*H*-indazole (236 mg, 1.2 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), Xantphos (180 mg, 0.3 mmol) and cesium carbonate (1.3 g, 4 mmol) was suspended in dioxane (50 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (4 mg of HCl salt, 1.2%) as a yellow solid.

[0259] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.75-1.80 (m, 2H), 2.02-2.07 (m, 2H), 2.24 (s, 3H), 3.05-3.09 (m, 2H), 3.17-3.21 (m, 2H), 4.52 (br s, 1H), 6.63 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 7.3 Hz, 2H), 7.38-7.44 (m, 2H), 7.62 (d, J = 8.9 Hz, 2H), 7.92 (s, 1H), 8.02 (s, 1H), 9.00 (br s, 1H), 9.04 (br s, 1H), 10.20 (s, 1H), 10.33 (s, 1H). MS (*ES*+): *m/z* 416 $(M+H)^+$.

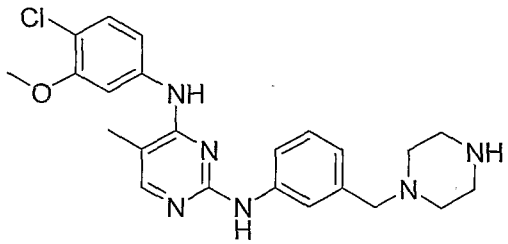
EXAMPLE 121. 4-{3-[4-(4-Chloro-3-methoxy-phenylamino)-5-methyl-pyrimidin-2-ylamino]-benzyl}-piperazine-1-carboxylic acid *tert*-butyl ester (Intermediate 43)



43

[0260] A mixture of intermediate **31** (0.092 g, 0.33 mmol), 4-(3-amino-benzyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.11 g, 0.39 mmol), $Pd_2(dba)_3$ (0.03 g, 0.033 mmol), Xantphos (0.038 g, 0.065 mmol) and cesium carbonate (0.32 g, 0.98 mmol) was suspended in dioxane (5 mL) and microwaved at 160 °C for 15 min. The reaction mixture was cooled to room temperature and centrifuged down. The reaction was decanted and the organic phase concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (0.075 g, 43%) as a brown solid.

EXAMPLE 122. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N^2-(3-piperazin-1-ylmethyl-phenyl)-pyrimidine-2,4-diamine (Compound LXXXI)

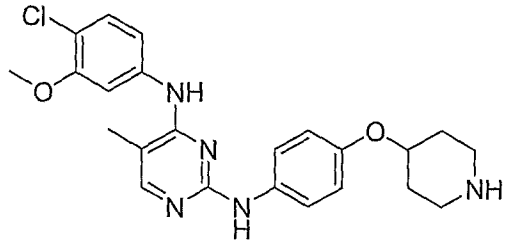


LXXXI

[0261] A solution of intermediate **43** (0.075 g, 0.14 mmol) in DCM (8 mL) was treated with TFA (2 mL). After 2 h of stirring, solvents were removed and resulting residue was triturated with diethyl ether resulting in white hygroscopic powder (0.05 g, 82%).

[0262] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.17 (s, 3H), 2.89 (br s, 4H), 3.2 (br s, 4H), 3.68 (s, 4H), 3.82 (br s, 3H), 7.16-7.19 (m, 2H), 7.28 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.39 (s, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.49 (d, 8.6 Hz, 1H), 7.98 (s, 1H), 8.8 (br s, 2H), 9.78 (br s, 1H), 10.57 (br s, 1H). MS (ES+): *m/z* 439 $(M+H)^+$.

EXAMPLE 123. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N^2-[4-(piperidin-4-yloxy)-phenyl]-pyrimidine-2,4-diamine (Compound LXXXII)

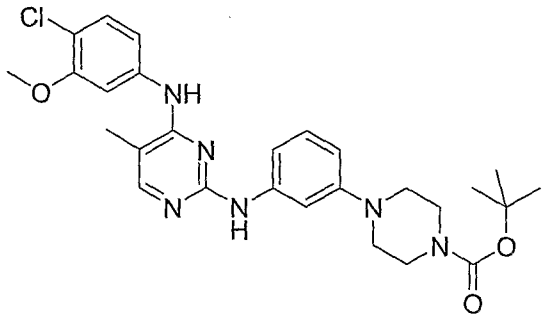


LXXXII

[0263] A mixture of intermediate **31** (0.66 g, 2.3 mmol) and 4-(4-amino-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (0.88 mg, 3.0 mmol) in acetic acid (15 mL) was microwaved at 160 °C for 15 min. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (20 mL) and the mixture was neutralized with 10% NaOH solution until solid precipitated. Filtration followed by column chromatography yielded the title compound as beige solids (0.51 g, 50%).

[0264] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.37-1.44 (m, 2H), 1.86-1.89 (m, 2H), 2.09 (s, 3H), 2.50-2.56 (m, 2H), 2.91-2.95 (m, 2H), 3.16 (s, 3H), 3.32 (br s, 3H), 3.72 (s, 3H), 4.09 (br s, 1H), 4.21-4.26 (m, 1H), 6.77 (d, J = 9 Hz, 2H), 7.27 (d, J = 8.5 Hz, 1H), 7.40-7.42 (m, 1H), 7.46-7.49 (m, 3H), 7.87 (s, 1H), 8.31 (s, 1H), 8.78 (s, 1H). MS (ES+): *m/z* 440 $(M+H)^+$.

EXAMPLE 124. 4-{3-[4-(4-Chloro-3-methoxy-phenylamino)-5-methyl-pyrimidin-2-ylamino]-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester (Intermediate 44)

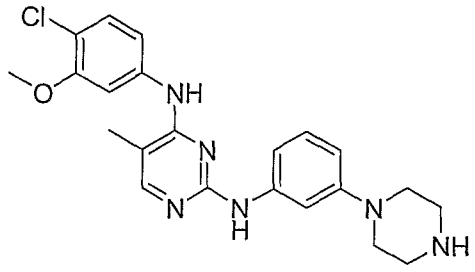


44

[0265] A mixture of intermediate **31** (0.13 g, 0.46 mmol) and 4-(3-amino-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.19 mg, 0.68 mmol) in acetic acid (8 mL) was heated at 80 °C for 15 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken up in water (20 mL) and the mixture was neutralized with 10% NaOH solution. This was then extracted with ethyl

acetate, washed with brine and evaporated to oily residue. Column chromatography yielded the title compound as white solids (0.12 g, 48%).

EXAMPLE 125. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N^2-(3-piperazin-1-yl-phenyl)-pyrimidine-2,4-diamine (Compound LXXXIII)

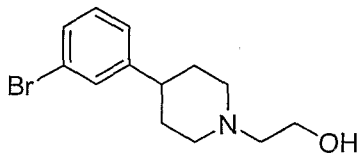


LXXXIII

[0266] A solution of intermediate **44** (0.11 g, 0.21 mmol) in DCM (8 mL) was treated with TFA (1 mL). After 3 h of stirring, solvents were removed and resulting residue was taken up in ethyl acetate and washed with 10% sodium bicarbonate solution. Organic phase then dried over sodium sulfate, filtered and evaporated to white powder. This was diluted with DCM (5 mL) and treated with 4M HCl in dioxane (0.5 mL). Solvents were imediately removed affording HCL salt of title compound as white solids (0.06 g, 67%).

[0267] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.18 (s, 3H), 3.12 (br s, 4H), 3.22 (br s, 4H), 3.65 (s, 3H), 6.80 (d, J = 8.1 Hz, 1H), 6.95 (s, 2H), 7.14 (t, J = 8.2 Hz, 1H), 7.23 (d, J = 7.0 Hz, 1H), 7.37-7.40 (m, 2H), 7.95 (s, 1H), 9.33 (br s, 2H), 9.88 (s, 1H), 10.62 (s, 1H). MS (ES+): *m/z* 425 $(M+H)^+$.

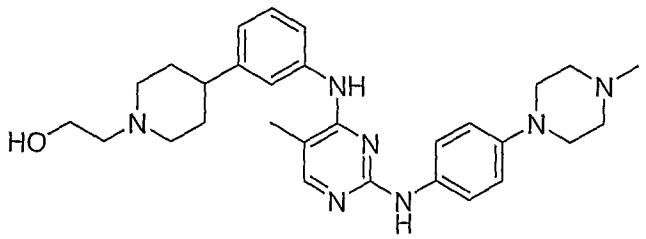
EXAMPLE 126. 2-[4-(3-Bromo-phenyl)-piperidin-1-yl]-ethanol (Intermediate 45)



45

[0268] 4-(3-Bromo-phenyl)-piperidine (1.2 g, 4.8 mmol) and 2-bromoethanol (0.72 mL, 10 mmol) were diluted with DMF (20 mL) and treated with potassium carbonate (2.7 g, 20 mmol). These were stirred at ambient temperature for 18 then poured onto water and extracted with ethyl acetate. Organic phase then washed with brine, dried over sodium sulfate, filtered and evaporated to clear oil (0.6 g, 44%).

EXAMPLE 127. 2-[4-(3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-phenyl)-piperidin-1-yl]-ethanol (Compound LXXXIV)

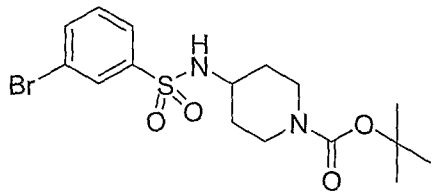


LXXXIV

[0269] A mixture of intermediate **32** (0.11 g, 0.38 mmol), intermediate **45** (0.21 g, 0.75 mmol), $Pd_2(dba)_3$ (0.034 g, 0.037 mmol), Xantphos (0.043 g, 0.075 mmol) and cesium carbonate (0.37 g, 1.1 mmol) was suspended in dioxane (10 mL) and microwaved at 160 °C for 15 min. The reaction mixture was cooled to room temperature and centrifuged down. The reaction was decanted and the organic phase concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (0.075 g, 43%) as a purple solid (0.02 g, 11%).

[0270] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.60-1.67 (m, 2H), 1.73 (d, J = 11.3 Hz, 2H), 2.02-2.07 (m, 2H), 2.08 (s, 3H), 2.21 (s, 3H), 2.39-2.45 (m, 7H), 2.95 (d, J = 11.4 Hz, 2H), 3.00 (t, J = 4.66 Hz, 4H), 3.50 (t, J = 6.44 Hz, 2H), 6.76 (d, J = 9 Hz, 2H), 6.92 (d, J = 8.5 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 7.45-7.49 (m, 3H), 7.66 (d, J = 7.7 Hz, 1H), 7.82 (s, 1H), 8.09 (s, 1H), 8.67 (s, 1H). MS (ES+): *m/z* 502 $(M+H)^+$.

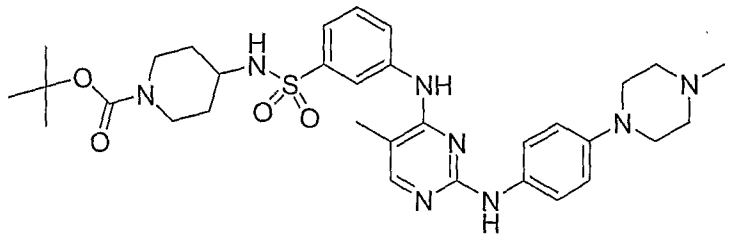
EXAMPLE 128. 4-(3-Bromo-benzenesulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (Intermediate 46)



46

[0271] 3-Bromo-benzenesulfonyl chloride (2.2 g, 8.7 mmol) and 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester (2 g, 10 mmol) were combined and diluted with DCM (50 mL) and TEA (3.6 mL, 26 mmol). After 16 h, reaction was poured into separatory funnel and washed with water. Organic phase was then washed with brine, dried over sodium sulfate, filtered and evaporated to clear oil which solidified upon standing (3.6 g, 98%).

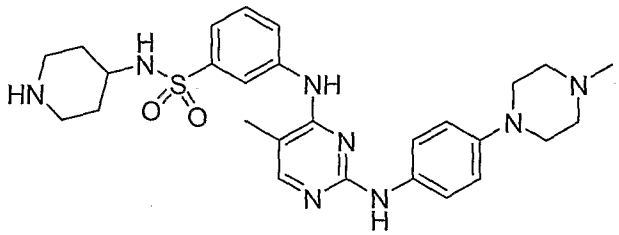
EXAMPLE 129. 4-(3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (Intermediate 47)



47

[0272] A mixture of intermediate **32** (0.15 g, 0.518 mmol), intermediate **46** (0.28 g, 0.67 mmol), $Pd_2(dba)_3$ (0.024 g, 0.026 mmol), Xantphos (0.03 g, 0.052 mmol) and cesium carbonate (0.34 g, 1 mmol) was suspended in dioxane (10 mL) and microwaved at 160 °C for 15 min. The reaction mixture was cooled to room temperature and centrifuged down. The reaction was decanted onto ice. Resulting precipitate dried and carried on directly for deprotection step (0.2 g).

EXAMPLE 130. 3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-*N*-piperidin-4-yl-benzenesulfonamide (Compound LXXXV)

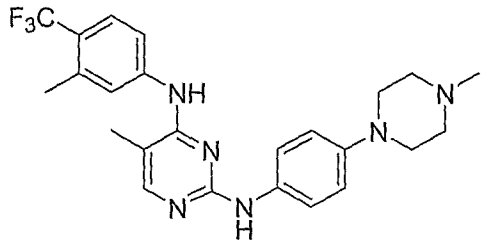


LXXXV

[0273] Intermediate **47** (0.2 g, 0.32 mmol) was diluted with DCM (10 mL) and treated with TFA (0.3 mL). After 3 h, reaction solvents removed and resulting residue was purified by HPLC (0.01g, 6%).

[0274] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.30-1.35 (m, 2H), 1.56-1.58 (m, 2H), 1.98 (s, 2H), 2.11 (s, 3H), 2.21 (s, 3H), 2.43-2.45 (m, 4H), 2.84-2.87 (m, 2H), 3.02 (t, J = 4.6 Hz, 2H), 6.80 (d, J = 9 Hz, 2H), 7.45-7.51 (m, 4H), 7.78 (br s, 1H), 7.88 (s, 1H), 8.05 (s, 1H), 8.20 (d, J = 7.6 Hz, 1H), 8.53 (s, 1H), 8.71 (s, 1H). MS (ES+): *m/z* 537 $(M+H)^+$.

EXAMPLE 131. N^4-(4-(Trifluoromethyl)-3-methylphenyl)-5-methyl-N^2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine hydrochloride (Compound LXXXVI)

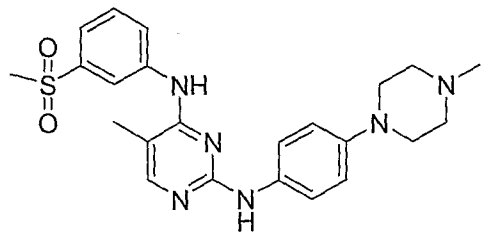


LXXXVI

[0275] A suspension of intermediate **32** (0.12 g, 0.40 mmol), 1-bromo-3-(trifluoromethyl)-2-methylbenzene (0.14 g, 0.59 mmol), $Pd_2(dba)_3$ (37 mg, 0.04 mmol), Xantphos (47 mg, 0.08 mmol) and cesium carbonate (0.39 g, 1.20 mmol) in dioxane (20 mL) was degassed with argon for 2 min then refluxed in a sealed tube for overnight. After cooling to room temperature, the solvent was removed by rotovap and the resulting mixture was purified by silica gel with 10% $CH_3OH/CHCl_3$ as an eluent to afford the title compound as a white solid. The white was dissolved in $CHCl_3$ (30 mL) and titrated with 2 M HCl in dioxane to pH 1. The solvent was removed by rotovap and the solid was recrystalized from acetone (25 mg, 13%).

[0276] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.20 (s, 3H), 2.26 (s, 3H), 2.77 (d, J = 4.5 Hz, 3H), 3.00-3.20 (m, 4H), 3.45 (d, J = 11.6 Hz, 2H), 3.63 (d, J = 12.2 Hz, 2H), 6.71 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 7.55 (t, J = 7.9 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 7.77 Hz, 1H), 7.94 (s, 1H), 10.13 (s, 1H), 10.60 (s, 1H), 11.28 (s, 1H). MS (ES+): *m/z* 457 $(M+H)^+$.

EXAMPLE 132. 5-Methyl-N^2-(4-(4-methylpiperazin-1-yl)phenyl)-N^4-(3-(methylsulfonyl)phenyl)-pyrimidine-2,4-diamine (Compound LXXXVII)

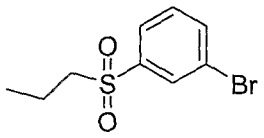


LXXXVII

[0277] A suspension of intermediate **32** (0.13 g, 0.44 mmol), 1-bromo-3-(methylsulfonyl)benzene (0.24 g, 1.0 mmol), $Pd_2(dba)_3$ (40 mg, 0.04 mmol), Xantphos (50 mg, 0.08 mmol) and cesium carbonate (0.43 g, 1.32 mmol) in dioxane (50 mL) was degassed with argon for 2 min then refluxed for overnight. After cooling to room temperature, the solvent was removed by rotovap and the resulting mixture was purified by silica gel with 30% $CH_3OH/CHCl_3$ as an eluent to afford the title compound as pale yellow solid (35 mg, 15%).

[0278] ^1H NMR (500 MHz, DMSO-d_6): δ 2.11 (s, 3H), 2.23 (s, 3H), 2.46 (br s, 4H), 3.03 (t, J = 4.4 Hz, 4H), 3.19 (s, 3H), 6.81 (d, J = 9.0 Hz, 2H), 7.45 (d, J = 8.9 Hz, 2H), 7.5-7.6 (m, 2H), 7.91 (s, 1H), 8.05 (s, 1H), 8.36 (d, J = 6.7 Hz, 1H), 8.60 (s, 1H), 8.77 (s, 1H). MS (ES+): *m/z* 453 $(M+H)^+$.

EXAMPLE 133. 1-Bromo-3-(propylsulfonyl)benzene (Intermediate 48)

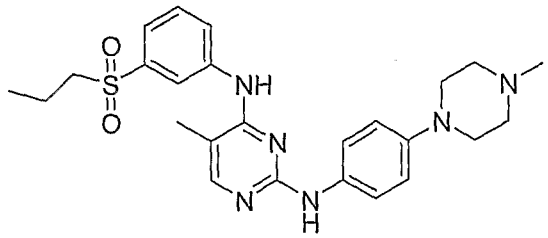


48

[0279] To a solution of 3-bromobenzenethiol (0.50 g, 2.6 mmol) in dioxane (50 mL) was added 1-iodopropane (1.1 g, 6.5 mmol) and cesium carbonate (2.2 g, 6.8 mmol) was stirred at reflux until all 3-bromobenzenethiol reacted. The reaction was quenched with saturated $NaHCO_3$ solution (25 mL) and the mixture extracted with $CHCl_3$ (60 mL). The product in the $CHCl_3$ was refluxed with mCPBA (2.9 g, 13 mmol) until all starting reacted. The organic layer was washed with 2M NaOH to remove the excess of mCPBA, dried over Na_2SO_4 and filtered. The filtrate was concentrated and the crude product was purified with silica gel column with 1:1 hexanes/$CHCl_3$ as an eluent to yield colorless oil (0.30 g, 43% in 2-steps).

[0280] ^1H NMR (500 MHz, DMSO-d_6): 0.92 (t, J = 7.4 Hz, 3H), 1.52-1.60 (m, 2H), 3.35-3.38 (m, 2H), 7.63 (t, J = 8.0 Hz, 1H), 7.88-7.91 (m, 1H), 7.95-7.98 (m, 1H), 8.04 (t, J = 1.8 Hz, 1H).

EXAMPLE 134. 5-Methyl-N^2-(4-(4-methylpiperazin-1-yl)phenyl)-N^4-(3-(propylsulfonyl)phenyl)-pyrimidine-2,4-diamine hydrochloride (Compound LXXXVIII)

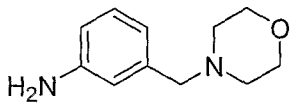


LXXXVIII

[0281] A suspension of intermediate **32** (0.25 g, 0.84 mmol), intermediate **48** (0.26 g, 1 mmol), $Pd_2(dba)_3$ (8 mg, 0.01 mmol), Xantphos (16 mg, 0.03 mmol) and cesium carbonate (0.82 g, 2.52 mmol) in dioxane (50 mL) was degassed with argon for 2 min then refluxed for overnight. After cooling to room temperature, the solvent was removed by rotovap and the resulting mixture was purified by silica gel with 10% $CH_3OH/CHCl_3$ as an eluent to afford the title compound as a white solid. The white was dissolved in $CHCl_3$ (30 mL) and titrated with 2 M HCl in dioxane to pH 1. The solvent was removed by rotovap and the solid was recrystalized from methanol (65 mg, 15%).

[0282] ^1H NMR (500 MHz, DMSO-d_6): 0.90 (t, J = 7.4 Hz, 3H), 1.50-1.60 (m, 2H), 2.18 (s, 3H), 2.81 (s, 3H), 3.00-3.13 (m, 4H), 3.27 (t, J = 7.7 Hz, 2H), 3.48 (d, J = 10.9 Hz, 2H), 3.75 (d, J = 11.4 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.9 Hz, 2H), 7.64 (t, J = 8.0 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.93 (s, 1H), 8.00 (s, 1H), 8.07 (s, 1H), 9.92 (s, 1H), 10.36 (s, 1H), 10.99 (s, 1H). MS (ES+): m/z 481 $(M+H)^+$.

EXAMPLE 135. 3-(Morpholinomethyl)benzenamine (Intermediate 49)



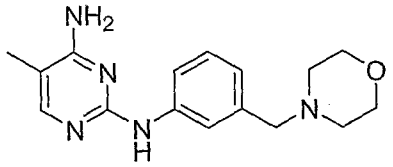
49

[0283] Zinc chloride (0.1 g, 0.73 mmol) was added to the solution of 3-nitrobenzaldehyde (5.9 g, 39.02 mmol), morpholine (3.4 g, 39.02 mmol), sodium cyanoborohydride (2.7 g, 43 mmol) in methanol (50 mL) at room temperature. The solution was heated to reflux for 1 hour. After cooling down , the reaction was quenched by water (2 mL) and the methanol was removed by rotovap. The crude product was dissolved in 2M NaOH (50 mL) and extracted by $CHCl_3$, dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum.

[0284] The above crude product in methanol (200mL) was reduced by Raney Ni and hydrazine at room temperature. The reaction was monitored by TLC in ethyl acetate. After all starting material reacted, the methanol was removed by rotovap. The crude was purified by silica gel with ethyl acetate as an eluent to yield a white solid (1.5 g, 50% in 2-steps).

[0285] ^{1}H NMR (500 MHz, DMSO-d_6): 2.31 (s, 4H), 3.28 (s, 2H), 3.56 (t, J = 4.6 Hz, 4H), 4.97 (s, 2H), 6.40-6.45 (m, 2H), 6.53 (t, J = 1.8 Hz, 1H), 6.93 (t, J = 7.7 Hz, 1H).

EXAMPLE 136 5-Methyl-N^2-(3-(morpholinomethyl)phenyl)pyrimidine-2,4-diamine (Intermediate 50)

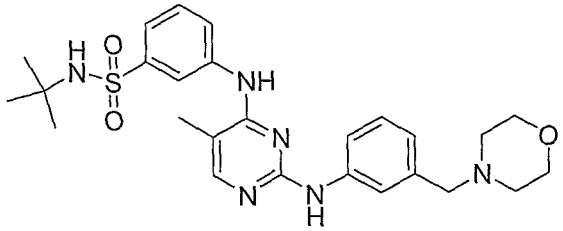


50

[0286] A mixture of 2-chloro-5-methylpyrimidin-4-amine (0.17 g, 1.17 mmol) and intermediate **49** (0.25 g, 1.30 mmol) was suspended in acetic acid (10 mL) and heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (20 mL) and neutralized to pH~8. The resulting solution was extracted with $CHCl_3$ (100 mL) and the organic layer separated. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by silica gel column with 10 % CH_3OH/EtOAc as an eluent to afford the title compound as oil (0.15g, 43%).

[0287] ^{1}H NMR (500 MHz, DMSO-d_6): 1.91 (s, 3H), 2.35 (s, 4H), 3.17 (s, 2H), 3.57(t, J = 4.4 Hz, 4H), 6.37 (s, 2H), 6.78 (d, J = 7.5 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 7.59 (s, 1H), 7.69 (s, 1H), 7.74 (d, J = 9.3 Hz, 1H), 8.68 (s, 1H).

EXAMPLE 137. *N-tert*-Butyl-3-[5-methyl-2-(3-morpholin-4-ylmethyl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide hydrochloride (Compound LXXXIX)

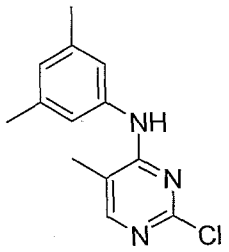


LXXXIX

[0288] A suspension of intermediate **50** (1.0 g, 3.42 mmol), 3-bromo-*N*-*tert*-butyl-benzenesulfonamide (1.28 g, 4.28 mmol), $Pd_2(dba)_3$ (30 mg, 0.03 mmol), Xantphos (40 mg, 0.07 mmol) and cesium carbonate (3.34 g, 10.24 mmol) in dioxane (50 mL) was degassed with argon for 2 min then refluxed for overnight. After cooling to room temperature, the solvent was removed by rotovap and the resulting mixture was purified by silica gel with 10% $CH_3OH/CHCl_3$ as an eluent to afford the title compound as a white solid. The white was dissolved in hot dioxane (150 mL) and titrated with 2 M HCl in dioxane to pH 1. The solvent was removed by rotovap and the solid was recrystalized from methanol (0.15 g, 8%).

[0289] ^{1}H NMR (500 MHz, DMSO-d_6): 1.08 (s, 9H), 2.20 (s, 3H), 3.0-3.2 (m, 4H), 3.7-4.0 (m, 4H), 4.23 (s, 2H), 7.33 (t, J = 7.9 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.48 (s, 1H), 7.55-7.65 (m, 3H), 7.71 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 7.4 Hz, 1H), 8.01 (s, 1H), 9.96 (br s, 1H), 10.61 (br s, 1H), 11.31 (br s, 1H). MS (ES+): *m/z* 511 $(M+H)^+$.

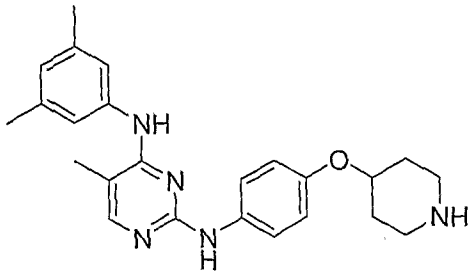
EXAMPLE 138. 2-Chloro-5-methyl-*N*-(3,5-dimethylphenyl)pyrimidin-4-amine (Intermediate 51)



51

[0290] A mixture of 1-bromo-3,5-dimethylbenzene (104 μL, 0.77 mmol), 2-chloro-5-methyl-pyrimidin-4-ylamine (104 mg, 0.72 mmol), $Pd(OAC)_2$ (15 mg, 0.07 mmol), Xantphos (83 mg, 0.14 mmol) and potassium *tert*-butoxide (159 mg, 1.42 mmol) in dioxane (8 mL) was microwaved at 160 °C for 20 min. The reaction mixture was cooled to room temperature and filtered rinsing with DCM and methanol. The filtrate was concentrated and purified using gradient flash chromatography (0-100% ethyl acetate in hexanes) to afford the title compound as a yellow oil (89 mg, 50%). MS (ES+): *m/z* 248 $(M+H)^+$.

EXAMPLE 139. 5-Methyl-N^4-(3,5-dimethylphenyl)-N^2-(4-(piperidin-4-yloxy)phenyl)pyrimidine-2,4-diamine (Compound XC)

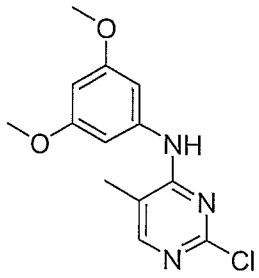


XC

[0291] A mixture of intermediate **51** (89 mg, 0.36 mmol), and 4-(4-amino-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (139 mg, 0.47 mmol) in acetic acid was stirred at room temperature for 16h, then heated to 95 °C for 2 h. The reaction mixture was concentrated *in vacuo*, and purified by preparative HPLC. The product was basified with $NaHCO_3$ (aq)(10 mL) and extracted with ethyl acetate (3x30 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The freebase was taken up in MeOH (5 mL) and conc HCl (5 drops) and after 2 min was concentrated *in vacuo* in the presence of DCM and hexanes to afford the HCl salt of the title compound as an off-white solid (63 mg, 40%).

[0292] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.72-1.83 (m, 2H), 2.02-2.08 (m, 2H), 2.14 (d, J = 0.6 Hz, 3H), 2.24 (s, 6H), 3.04-3.15 (m, 2H), 3.21-3.31 (m, 2H), 4.57-4.60 (m, 1H), 6.85 (s, 1H), 6.91 (d, J = 8.9 Hz, 2H), 7.20 (s, 2H), 7.37 (d, J = 8.9 Hz, 2H), 7.85 (s, 1H), 8.50 (br s, 1H), 8.56 (br s, 1H), 9.36 (br s, 1H), 10.10 (br s, 1H). MS (ES+): *m/z* 404 $(M+H)^+$.

EXAMPLE 140. 2-Chloro-*N*-(3,5-dimethoxyphenyl)-5-methylpyrimidin-4-amine (Intermediate 52)

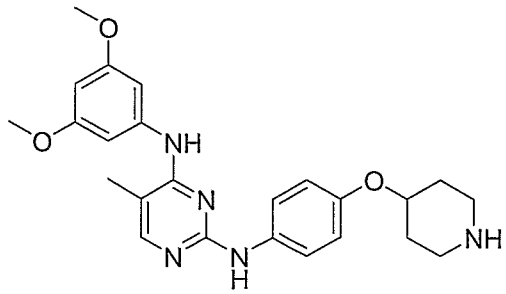


52

[0293] A mixture of 1-bromo-3,5-dimethoxybenzene (436 mg, 2.01 mmol), 2-chloro-5-methyl-pyrimidin-4-ylamine (287 mg, 2.00 mmol), $Pd(OAc)_2$ (44 mg, 0.20 mmol), Xantphos (237 mg, 0.41 mmol) and potassium *tert*-butoxide (448 mg, 3.99 mmol) in dioxane (15 mL) and DMF (5 mL) was microwaved at 160 °C for 20 min. The reaction mixture was cooled to room temperature and filtered rinsing with DCM and methanol. The filtrate was concentrated and purified using gradient flash chromatography (0-100% ethyl acetate in hexanes) to afford the title compound as a yellow solid (182 mg, 33%).

[0294] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.17 (s, 3H), 3.74 (s, 6H), 6.27 (t, J = 2.2 Hz, 1H), 6.99 (d, J =2.2 Hz, 2H), 8.06 (s, 1H), 8.71 (s, 1H). MS (ES+): *m/z* 280 $(M+H)^+$.

EXAMPLE 141. N^4-(3,5-Dimethoxyphenyl)-5-methyl-N^2-(4-(piperidin-4-yloxy)phenyl)pyrimidine-2,4-diamine (Compound XCI)

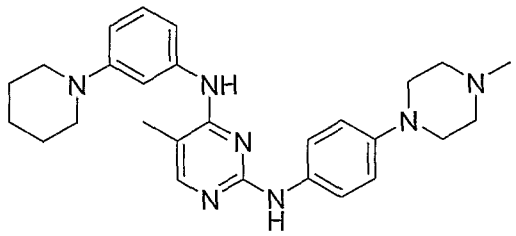


XCI

[0295] A mixture of intermediate **52** (100 mg, 0.36 mmol), and 4-(4-amino-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (106 mg, 0.36 mmol) in acetic acid was heated to 95 °C for 2 h. The reaction mixture was concentrated *in vacuo*, and purified by preparative HPLC to afford the TFA salt of the title compound as a tan solid (75 mg, 39%).

[0296] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.74-1.83 (m, 2H), 2.03-2.11 (m, 2H), 2.15 (s, 3H), 3.06-3.15 (m, 2H), 3.21-3.30 (m, 2H), 3.69 (s, 6H), 4.57-4.60 (m, 1H), 6.39 (t, J = 2.2 Hz, 1H), 6.80 (d, J =2.2 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 7.37 (d, J =9.0 Hz, 2H), 7.86 (s, 1H), 8.53 (br s, 1H), 8.58 (br s, 1H), 9.49 (br s, 1H), 10.24 (br s, 1H). MS (ES+): *m/z* 436 $(M+H)^+$.

EXAMPLE 142. 5-Methyl-N^2-(4-(4-methylpiperazin-1-yl)phenyl)-N^4-(3-(piperidin-1-yl)phenyl)pyrimidine-2,4-diamine (Compound XCII)

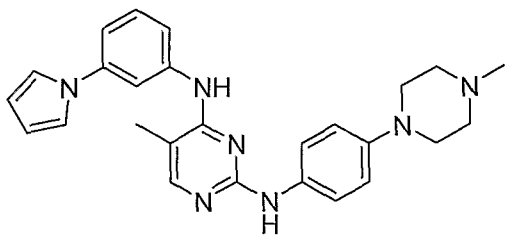


XCII

[0297] A mixture of 1-(3-bromophenyl)piperidine (91 mg, 0.38 mmol), intermediate **32** (99 mg, 0.33 mmol), $Pd_2(dba)_3$ (15 mg, 0.02 mmol), Xantphos (24 mg, 0.04 mmol) and cesium carbonate (219 mg, 0.67 mmol) in dioxane (4 mL) was microwaved at 160 °C for 15 min. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, taken up in methanol, and filtered rinsing with DCM and methanol. The filtrate was concentrated and purified by preparative HPLC to afford the TFA salt of the title compound as an off-white solid (14 mg, 8%).

[0298] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.47-1.53 (m, 2H), 1.56-1.61 (m, 4H), 2.07 (s, 3H), 2.21 (s, 3H), 2.44 (t, J =4.9 Hz, 4H), 3.01 (t, J =4.9 Hz, 4H), 3.08 (t, J =5.4 Hz, 4H), 6.63 (dd, J = 8.2, 2.3 Hz, 1H), 6.76 (d, J =9.0 Hz, 2H), 7.12 (t, J = 8.3 Hz, 1H), 7.14 (s, 1H), 7.27 (d, J =7.6 Hz, 1H), 7.50 (d, J =9.0 Hz, 2H), 7.81 (s, 1H), 8.00 (s, 1H), 8.67 (s, 1H). MS (ES+): *m/z* 458 $(M+H)^+$.

EXAMPLE 143. N^4-(3-(1*H*-Pyrrol-1-yl)phenyl)-5-methyl-N^2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine (Compound XCIII)

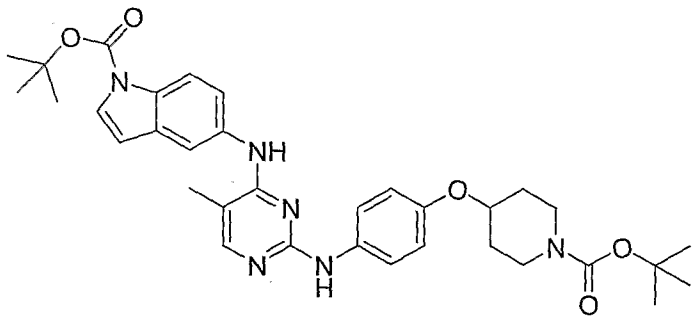


XCIII

[0299] A mixture of 1-(3-bromophenyl)-1*H*-pyrrole (86 mg, 0.39 mmol), intermediate **32** (99 mg, 0.33 mmol), $Pd_2(dba)_3$ (16 mg, 0.02 mmol), Xantphos (26 mg, 0.05 mmol) and cesium carbonate (215 mg, 0.66 mmol) in dioxane (4 mL) was microwaved at 160 °C for 15 min. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, taken up in methanol, and filtered rinsing with DCM and methanol. The filtrate was concentrated and purified by preparative HPLC to afford the TFA salt of the title compound as an off-white solid (32 mg, 18%).

[0300] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.11 (s, 3H), 2.21 (s, 3H), 2.42 (t, J=4.9 Hz, 4H), 2.95 (t, J=4.9 Hz, 4H), 6.24 (t, J=2.2 Hz, 2H), 6.58 (d, J=8.9 Hz, 2H), 7.23 (dd, J= 7.8, 1.8 Hz, 1H), 7.31 (t, J= 2.2 Hz, 2H), 7.37 (t, J=8.1 Hz, 1H), 7.43 (d, J=9.0 Hz, 2H), 7.60 (d, J=8.8 Hz, 1H), 7.86 (t, J=2.2 Hz, 1H), 7.87 (s, 1H), 8.30 (s, 1H), 8.74 (s, 1H). MS (ES+): *m/z* 440 $(M+H)^+$.

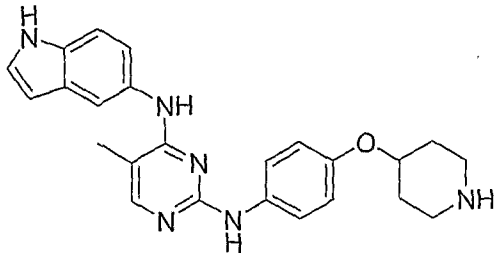
EXAMPLE 144. 5-{2-[4-(1-*tert*-Butoxycarbonyl-piperidin-4-yloxy)-phenylamino]-5-methyl-pyrimidin-4-ylamino}-indole-1-carboxylic acid *tert*-butyl ester (Intermediate 53)



53

[0301] A mixture of *tert*-butyl 5-bromo-1*H*-indole-1-carboxylate (161 mg, 0.54 mmol), intermediate **42** (202 mg, 0.50 mmol), $Pd_2(dba)_3$ (29 mg, 0.03 mmol), Xantphos (36 mg, 0.07 mmol) and cesium carbonate (321 mg, 0.98 mmol) in dioxane (5 mL) was microwaved at 160 °C for 20 min. The reaction mixture was cooled to room temperature and filtered rinsing with DCM. The filtrate was concentrated and purified by gradient flash chromatography (0-20% MeOH in DCM) to afford the title compound as a light-brown solid (290 mg, 94%). MS (ES+): *m/z* 615 $(M+H)^+$.

EXAMPLE 145. N^4-(1*H*-Indol-5-yl)-5-methyl-N^2-(4-(piperidin-4-yloxy)phenyl)pyrimidine-2,4-diamine (Compound XCIV)

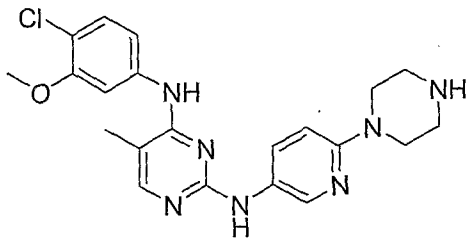


XCIV

[0302] To a solution of acetyl chloride (670 μL, 9.42 mmol) in methanol (22 mL) was added intermediate **53** (290 mg, 0.47 mmol), and the reaction mixture was heated to 60 °C for 4 h. The mixture was concentrated *in vacuo* and purified by preparative HPLC to afford the TFA salt of the title compound as a brown solid (6 mg, 2%).

[0303] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.70-1.78 (m, 2H), 1.98-2.07 (m, 2H), 2.16 (s, 3H), 3.02-3.11 (m, 2H), 3.21-3.30 (m, 2H), 4.44-4.53 (m, 1H), 6.43 (s, 1H), 6.75 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.7 Hz, 2H), 7.40-7.42 (m, 2H), 7.71 (s, 1H), 7.78 (s, 1H), 8.48 (br s, 1H), 8.54 (br s, 1H), 9.65 (br s, 1H), 9.99 (br s, 1H), 11.18 (s, 1H). MS (ES+): *m/z* 415 $(M+H)^+$.

EXAMPLE 146. *N*4-(4-Chloro-3-methoxy-phenyl)-5-methyl-*N*2-(6-piperazin-1-yl-pyridin-3-yl)-pyrimidine-2,4-diamine (Compound XCV)



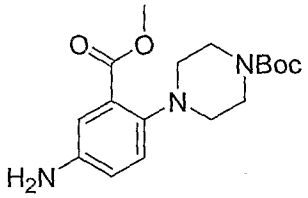
XCV

[0304] A mixture of intermediate **31** (0.10 g, 0.35 mmol), 4-(5-amino-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester (0.10 g, 0.36 mmol), $Pd_2(dba)_3$ (30 mg, 0.033 mmol), Xantphos (35 mg, 0.06 mmol) and cesium carbonate (0.23 g, 0.71 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 170 °C for 30 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM and the filtrate

concentrated. The residue was purified by flash chromatography on silica gel (hexanes to EtOAc) to afford the Boc-protected precursor. To a solution of the precursor in DCM (5 mL) was added TFA (3 mL). The mixture was stirred at room temperature for 30 min, concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the resulting solid triturated in a mixture of hexanes/EtOAc (10/1, 55 mL). After filtration, the title compound was obtained as a white solid (20 mg, 13%).

[0305] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.09 (s, 3H), 2.81 (t, J = 5.0 Hz, 4H), 3.29–3.31 (m, 4H), 3.73 (s, 3H), 6.70 (d, J = 9.1 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 7.42 (d, J = 9.1 Hz, 1H), 7.49 (d, J = 2.2 Hz, 1H), 7.76 (dd, J = 9.1, 2.6 Hz, 1H), 7.86 (s, 1H), 8.29 (s, 1H), 8.31 (d, J = 2.6 Hz, 1H), 8.71 (s, 1H). MS (ES+): *m/z* 426 $(M+H)^+$.

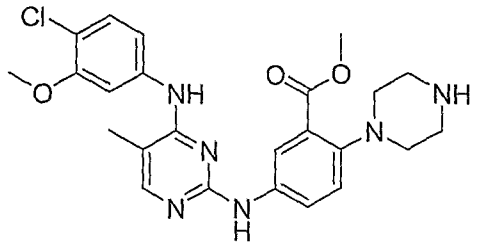
EXAMPLE 147. 4-(4-Amino-2-methoxycarbonyl-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (Intermediate 54)



54

[0306] To a solution of 4-(2-methoxycarbonyl-4-nitro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (1.0 g, 2.7 mmol) in MeOH (30 mL) was added 10 wt% Pd/C (0.1 equiv by wt) under argon atmosphere. The mixture was evacuated and then refilled with hydrogen (3 cycles) and stirred at room temperature for 2 h. The heterogeneous reaction mixture was filtered through a pad of Celite, washed with MeOH and concentrated *in vacuo*. The crude amino-compound was used in the next step without purification. MS (ES+): *m/z* 336 $(M+H)^+$.

EXAMPLE 148. 5-[4-(4-Chloro-3-methoxy-phenylamino)-5-methyl-pyrimidin-2-ylamino]-2-piperazin-1-yl-benzoic acid methyl ester (Compound XCVI)

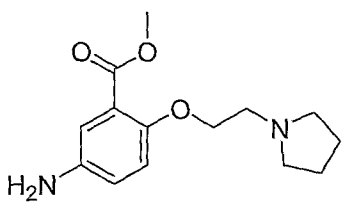


XCVI

[0307] A mixture of intermediate **31** (0.10 g, 0.35 mmol), intermediate **54** (0.14 g, 0.42 mmol), $Pd_2(dba)_3$ (30 mg, 0.033 mmol), Xantphos (35 mg, 0.06 mmol) and cesium carbonate (0.23 g, 0.71 mmol) was suspended in dioxane (15 mL) and heated at reflux under the argon atmosphere for 2.5 h. The reaction mixture was cooled to room temperature and diluted with DCM (30 mL). The mixture was filtered and the filtrate concentrated. The residue was purified by flash chromatography on silica gel (hexanes to 60% EtOAc/hexanes) to afford the Boc-protected precursor. To a solution of the precursor in DCM (5 mL) was added TFA (2 mL). The mixture was stirred at room temperature for 1 h, concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a white solid (40 mg, 24%).

[0308] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.11 (s, 3H), 2.80–2.90 (m, 8H), 3.73 (s, 3H), 3.74 (s, 3H), 6.98 (d, J = 8.9 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.40–7.48 (m, 2H), 7.69 (dd, J = 8.9, 2.6 Hz, 1H), 7.90 (d, J = 2.6 Hz, 1H), 7.91 (s, 1H), 8.36 (s, 1H), 9.04 (s, 1H). MS (ES+): *m/z* 483 $(M+H)^+$.

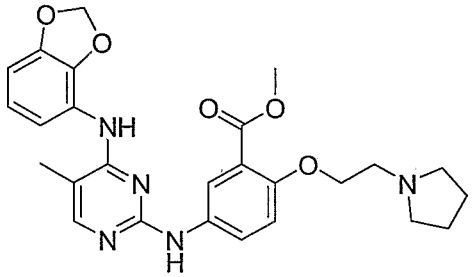
EXAMPLE 149. 5-Amino-2-(2-pyrrolidin-1-yl-ethoxy)-benzoic acid methyl ester (Intermediate 55)



55

[0309] A suspension of 5-amino-2-hydroxy-benzoic acid methyl ester (1.0 g, 6.0 mmol), 1-(2-chloro-ethyl)-pyrrolidine hydrochloride (1.2 g, 7.1 mmol) and cesium carbonate (5.0 g, 15 mmol) in DMF (40 mL) was heated at 60 °C for 17 h. The mixture was allowed to cool to room temperature, poured into water (60 mL) and extracted with EtOAc (2 x 50 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue purified by flash chromatography on silica gel (DCM to 30% MeOH/DCM) to afford the title compound (0.2 g, 13%) as a light brown solid. MS (ES+): *m/z* 265 $(M+H)^+$.

EXAMPLE 150. 5-[4-(Benzo[1,3]dioxol-4-ylamino)-5-methyl-pyrimidin-2-ylamino]-2-(2-pyrrolidin-1-yl-ethoxy)-benzoic acid methyl ester (Compound XCVII)

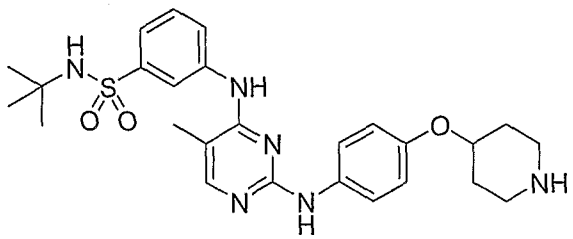


XCVII

[0310] A mixture of intermediate **30** (0.15 g, 0.57 mmol), intermediate **55** (0.20 g, 0.75 mmol), $Pd_2(dba)_3$ (50 mg, 0.055 mmol), Xantphos (60 mg, 0.10 mmol) and cesium carbonate (0.30 g, 0.92 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as an off white solid (30 mg, 11%).

[0311] ^1H NMR (500 MHz, DMSO-d_6): δ 1.65–1.72 (m, 4H), 2.07 (s, 3H), 2.50–2.62 (m, 4H), 2.75–2.85 (m, 2H), 3.73 (s, 3H), 4.02 (t, J = 5.8 Hz, 2H), 5.88 (s, 2H), 6.78–6.88 (m, 3H), 6.92 (dd, J = 8.0, 2.1 Hz, 1H), 7.75–7.80 (m, 2H), 7.83 (s, 1H), 8.22 (s, 1H), 8.89 (s, 1H). MS (ES+): *m/z* 492 $(M+H)^+$.

EXAMPLE 151. *N-tert*-Butyl-3-{5-methyl-2-[4-(piperidin-4-yloxy)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound XCVIII)

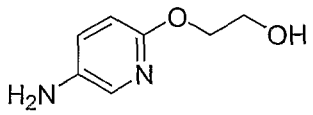


XCVIII

[0312] A mixture of intermediate **33** (0.15 g, 0.42 mmol) and 4-(4-amino-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (0.15 g, 0.51 mmol) in acetic acid (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 150 °C for 20 min. After cooling to room temperature, the cap was removed and the mixture concentrated. The residue was taken in water (20 mL) and the pH adjusted with 10% NaOH solution until solid precipitated. The solid was filtered and then purified by HPLC. The corrected fractions were combined, poured into saturated $NaHCO_3$ solution (30 mL) and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a white solid (20 mg, 9%).

[0313] ^1H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 1.65–1.73 (m, 2H), 1.95–2.05 (m, 2H), 2.12 (s, 3H), 2.89–2.95 (m, 2H), 3.10–3.20 (m, 2H), 4.40–4.45 (m, 1H), 6.84 (d, J = 9.1 Hz, 2H), 7.45–7.60 (m, 6H), 7.90 (s, 1H), 8.10–8.15 (m, 2H), 8.55 (s, 1H), 8.81 (s, 1H). MS (ES+): *m/z* 511 $(M+H)^+$.

EXAMPLE 152. 2-(5-Amino-pyridin-2-yloxy)-ethanol (Intermediate 56)

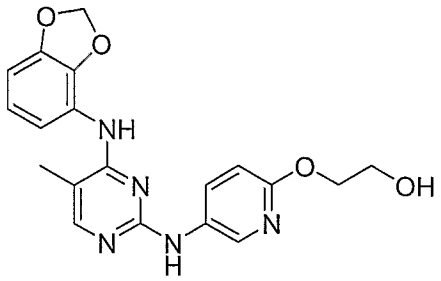


56

[0314] To a solution of 2-(5-nitro-pyridin-2-yloxy)-ethanol (1.0 g, 5.4 mmol) in MeOH (30 mL) was added 10 wt% Pd/C (0.1 equiv by wt) under argon atmosphere. The mixture was evacuated and then refilled with hydrogen (3 cycles) and stirred at room temperature for 1 h. The heterogeneous reaction mixture was filtered through a pad of Celite, washed with

MeOH and concentrated *in vacuo*. The crude amino-compound was used in the next step without purification. MS (ES+): *m/z* 155 $(M+H)^+$.

EXAMPLE 153. 2-{5-[4-(Benzo[1,3]dioxol-4-ylamino)-5-methyl-pyrimidin-2-ylamino]-pyridin-2-yloxy}-ethanol (Compound XCIX)

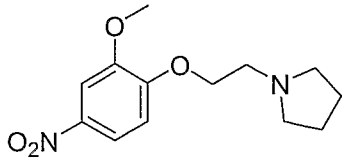


XCIX

[0315] A mixture of intermediate **30** (0.10 g, 0.38 mmol), intermediate **56** (0.10 g, 0.65 mmol), $Pd_2(dba)_3$ (30 mg, 0.033 mmol), Xantphos (35 mg, 0.06 mmol) and cesium carbonate (0.26 g, 0.80 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as an off white solid (50 mg, 35%).

[0316] ^1H NMR (500 MHz, DMSO-d_6): δ 2.06 (s, 3H), 3.66 (q, J = 5.4 Hz, 2H), 4.15 (t, J = 5.2 Hz, 2H), 4.77 (t, J = 5.5 Hz, 2H), 5.91 (s, 2H), 6.52 (d, J = 9.0 Hz, 1H), 6.78–6.90 (m, 3H), 7.82 (s, 1H), 7.96 (dd, J = 8.9, 2.7 Hz, 1H), 8.22 (d, J = 2.6 Hz, 1H), 8.27 (s, 1H), 8.84 (s, 1H). MS (ES+): *m/z* 382 $(M+H)^+$.

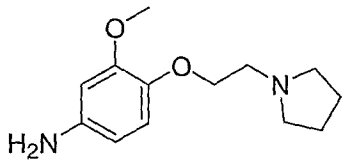
EXAMPLE 154. 1-[2-(2-Methoxy-4-nitro-phenoxy)-ethyl]-pyrrolidine (Intermediate 57)



57

[0317] A suspension of potassium 2-methoxy-4-nitro-phenolate (2.0 g, 9.7 mmol), 1-(2-chloro-ethyl)-pyrrolidine hydrochloride (2.0 g, 12 mmol) and cesium carbonate (7.0, 22 mmol) in DMF (35 mL) was heated at 80 °C for 16 h. The mixture was allowed to cool to room temperature, poured into water (60 mL) and extracted with EtOAc (2 x 50 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and used in the next step without purification.
MS (ES+): *m/z* 267 $(M+H)^+$.

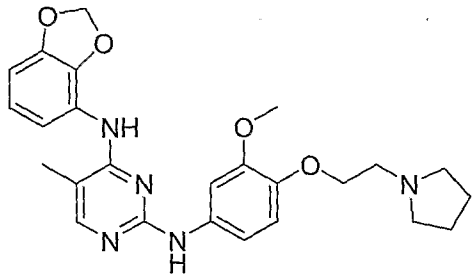
EXAMPLE 155. 3-Methoxy-4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (Intermediate 58)



58

[0318] To a solution of intermediate **57** (1.7 g, 6.4 mmol) in MeOH (30 mL) was added 10 wt% Pd/C (0.1 equiv by wt) under argon atmosphere. The mixture was evacuated and then refilled with hydrogen (3 cycles) and stirred at room temperature for 1 h. The heterogeneous reaction mixture was filtered through a pad of Celite, washed with MeOH and concentrated *in vacuo*. The crude amino-compound was used in the next step without purification. MS (ES+): *m/z* 237 $(M+H)^+$.

EXAMPLE 156. N^4-Benzo[1,3]dioxol-4-yl-N^2-[3-methoxy-4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5-methyl-pyrimidine-2,4-diamine (Compound C)



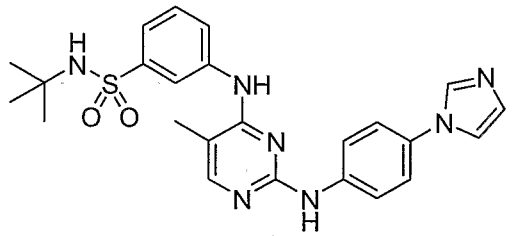
C

[0319] A mixture of intermediate **30** (0.10 g, 0.38 mmol), intermediate **58** (0.11 g, 0.46 mmol), $Pd_2(dba)_3$ (30 mg, 0.033 mmol), Xantphos (35 mg, 0.06 mmol) and cesium carbonate (0.25 g, 0.77 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with

DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a white solid (50 mg, 28%).

[0320] ^1H NMR (500 MHz, DMSO-d_6): δ 1.65–1.72 (m, 4H), 2.06 (s, 3H), 2.50–2.62 (m, 4H), 2.75–2.85 (m, 2H), 3.50 (s, 3H), 3.94 (t, J = 6.1 Hz, 2H), 5.84 (s, 2H), 6.67 (d, J = 8.8 Hz, 1H), 6.78 (dd, J = 7.8, 1.1 Hz, 1H), 6.83 (t, J = 7.9 Hz, 1H), 6.92 (dd, J = 8.1, 1.1 Hz, 1H), 7.14 (dd, J = 8.7, 2.4 Hz, 1H), 7.23(d, J = 2.4 Hz, 1H), 7.83 (s, 1H), 8.21 (s, 1H), 8.69 (s, 1H). MS (ES+): *m/z* 464 $(M+H)^+$.

EXAMPLE 157. *N-tert*-Butyl-3-[2-(4-imidazol-1-yl-phenylamino)-5-methyl-pyrimidin-4-ylamino]-benzenesulfonamide (Compound CI)

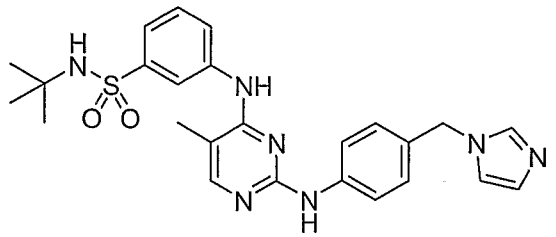


CI

[0321] A mixture of intermediate **33** (0.40 g, 1.1 mmol), 4-imidazol-1-yl-phenylamine (0.20 g, 1.3 mmol), $Pd_2(dba)_3$ (0.10 g, 0.11 mmol), Xantphos (0.12 g, 0.21 mmol) and cesium carbonate (0.80 g, 2.5 mmol) in dioxane/DMF (3/1, 8 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 30 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (40 mL). The combined aqueous layers were extracted with EtOAc (2 x 40 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as an off white solid (0.15 g, 28%).

[0322] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.15 (s, 3H), 7.07 (s, 1H), 7.43 (d, J = 9.0 Hz, 2H), 7.50–7.60 (m, 3H), 7.61 (s, 1H), 7.79 (d, J = 9.0 Hz, 2H), 7.98 (s, 1H), 8.08–8.13 (m, 3H), 8.64 (s, 1H), 9.19 (s, 1H). MS (ES+): *m/z* 478 $(M+H)^+$.

EXAMPLE 158. *N-tert*-Butyl-3-[2-(4-imidazol-1-ylmethyl-phenylamino)-5-methyl-pyrimidin-4-ylamino]-benzenesulfonamide (Compound CII)

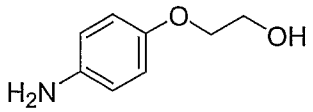


CII

[0323] A mixture of intermediate **33** (0.10 g, 0.28 mmol), 4-imidazol-1-ylmethyl-phenylamine (60 mg, 0.35 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), Xantphos (30 mg, 0.052 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, *dried* over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a white solid (40 mg, 29%).

[0324] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.13 (s, 3H), 5.07 (s, 2H), 6.89 (s, 1H), 7.12 (d, J = 8.6 Hz, 2H), 7.15 (s, 1H), 7.46 (t, J = 7.9 Hz, 1H), 7.49–7.52 (m, 1H), 7.56 (s, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.72 (s, 1H), 7.94 (s, 1H), 8.09 (s, 1H), 8.14 (d, J = 8.1 Hz, 1H), 8.60 (s, 1H), 9.02 (s, 1H). MS (ES+): *m/z* 492 $(M+H)^+$.

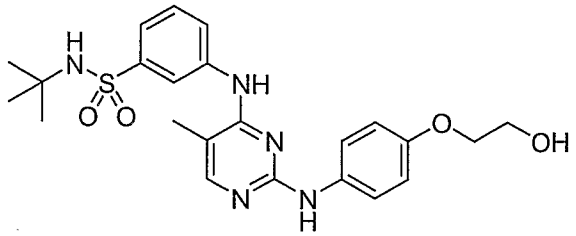
EXAMPLE 159. 2-(4-Amino-phenoxy)-ethanol (Intermediate 59)



59

[0325] A solution of 2-(4-nitro-phenoxy)-ethanol (2.1 g, 12 mmol) in MeOH (30 mL) was flushed with argon and then *charged* with 10 wt% Pd/C (0.1 equiv by wt). The mixture was evacuated under house vacuum and then refilled with hydrogen from hydrogen balloon. The cycle was repeated again and the mixture stirred at room temperature for 2 h. The heterogeneous reaction mixture was filtered through a pad of Celite, washed with MeOH and concentrated *in vacuo* to furnish the title compound (1.8 g, 99%) as a brown solid. MS (ES+): *m/z* 154 $(M+H)^+$.

EXAMPLE 160. *N-tert*-Butyl-3-{2-[4-(2-hydroxy-ethoxy)-phenylamino]-5-methyl-pyrimidin-4-ylamino}-benzenesulfonamide (Compound CIII)

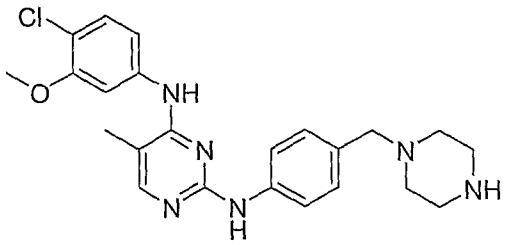


CIII

[0326] A mixture of intermediate **33** (0.10 g, 0.28 mmol), intermediate **59** (55 mg, 0.36 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), Xantphos (30 mg, 0.052 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a white solid (15 mg, 11%).

[0327] ^1H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.12 (s, 3H), 3.69 (q, J = 5.2 Hz, 2H), 3.91 (t, J = 5.1 Hz, 2H), 4.82 (t, J = 5.5 Hz, 2H), 6.80 (d, J = 9.1 Hz, 2H), 7.45–7.50 (m, 2H), 7.52 (d, J = 9.0 Hz, 2H), 7.55 (s, 1H), 7.90 (s, 1H), 8.08–8.15 (m, 2H), 8.53 (s, 1H), 8.77 (s, 1H). MS (ES+): *m/z* 472 $(M+H)^+$.

EXAMPLE 161. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N^2-(4-piperazin-1-ylmethyl-phenyl)-pyrimidine-2,4-diamine (Compound CIV)

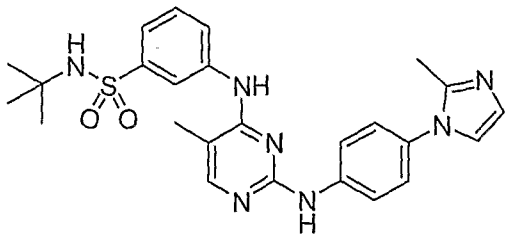


CIV

[0328] A mixture of intermediate **31** (0.10 g, 0.35 mmol), 4-(4-amino-benzyl)-piperazine-1-carboxylic acid tert-butyl ester (0.12 g, 0.41 mmol), $Pd_2(dba)_3$ (30 mg, 0.033 mmol), Xantphos (35 mg, 0.06 mmol) and cesium carbonate (0.23 g, 0.71 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM and the filtrate concentrated. The residue was purified by flash chromatography on silica gel (hexanes to 60% EtOAc/hexanes) to afford the Boc-protected precursor. To a solution of the precursor in DCM (5 mL) was added TFA (3 mL). The mixture was stirred at room temperature for 1 h, concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a white solid (13 mg, 9%).

[0329] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.11 (s, 3H), 2.30–2.40 (m, 4H), 2.83 (t, J = 4.8 Hz, 4H), 3.37 (s, 2H), 3.75 (s, 3H), 7.08 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.6 Hz, 1H), 7.43 (dd, J = 8.6, 2.2 Hz, 1H), 7.47 (d, J = 2.2 Hz, 1H), 7.59 (d, J = 8.6 Hz, 2H), 7.91 (s, 1H), 8.37 (s, 1H), 8.99 (s, 1H). MS (ES+): *m/z* 439 $(M+H)^+$.

EXAMPLE 162. *N-tert*-Butyl-3-{5-methyl-2-[4-(2-methyl-imidazol-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound CV)

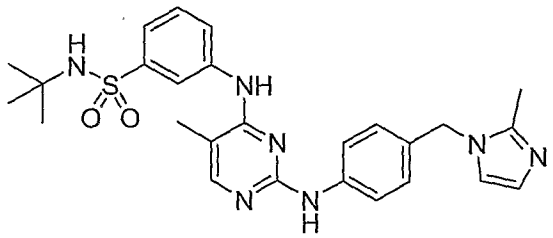


CV

[0330] A mixture of intermediate **33** (0.10 g, 0.28 mmol), 4-(2-methyl-imidazol-1-yl)-phenylamine (60 mg, 0.35 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), Xantphos (30 mg, 0.052 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a white solid (30 mg, 22%).

[0331] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.11 (s, 9H), 2.15 (s, 3H), 2.24 (s, 3H), 6.87 (d, J = 1.2 Hz, 1H), 7.18 (d, J = 1.3 Hz, 1H), 7.22 (d, J = 8.9 Hz, 2H), 7.50–7.55 (m, 2H), 7.56 (s, 1H), 7.79 (d, J = 8.9 Hz, 2H), 7.98 (s, 1H), 8.07–8.10 (m, 2H), 8.65 (s, 1H), 9.26 (s, 1H). MS (ES+): *m/z* 492 $(M+H)^+$.

EXAMPLE 163. *N-tert*-Butyl-3-{5-methyl-2-[4-(2-methyl-imidazol-1-ylmethyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound CVI)

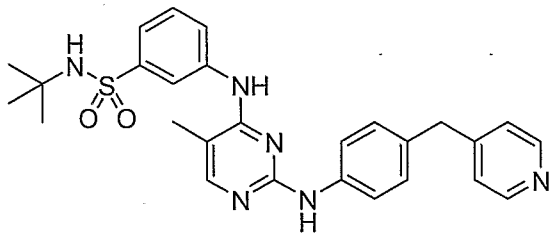


CVI

[0332] A mixture of intermediate **33** (0.10 g, 0.28 mmol), 4-(2-methyl-imidazol-1-ylmethyl)-phenylamine (65 mg, 0.35 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), Xantphos (30 mg, 0.052 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a white solid (30 mg, 21%).

[0333] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.13 (s, 3H), 2.24 (s, 3H), 5.01 (s, 2H), 6.73 (d, J = 1.2 Hz, 1H), 7.01 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 1.1 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.48–7.51 (m, 1H), 7.56 (s, 1H), 7.62 (d, J = 8.6 Hz, 2H), 7.94 (s, 1H), 8.08 (s, 1H), 8.12 (d, J = 8.1 Hz, 1H), 8.60 (s, 1H), 9.02 (s, 1H). MS (ES+): *m/z* 506 $(M+H)^+$.

EXAMPLE 164. *N-tert*-Butyl-3-[5-methyl-2-(4-pyridin-4-ylmethyl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide (Compound CVII)



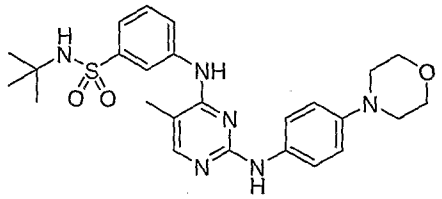
CVII

[0334] A mixture of intermediate **33** (0.10 g, 0.28 mmol), 4-Pyridin-4-ylmethyl-phenylamine (65 mg, 0.35 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), Xantphos (30 mg, 0.052 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The

filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a white solid (45 mg, 32%).

[0335] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.11 (s, 9H), 2.13 (s, 3H), 3.87 (s, 2H), 7.07 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 6.0 Hz, 2H), 7.43 (t, J = 7.9 Hz, 1H), 7.47–7.50 (m, 1H), 7.56 (d, J = 6.3 Hz, 2H), 7.58 (s, 1H), 7.93 (s, 1H), 8.09 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.44 (d, J = 5.8 Hz, 2H), 8.58 (s, 1H), 8.94 (s, 1H). MS (ES+): m/z 503 $(M+H)^+$.

EXAMPLE 165. *N-tert*-Butyl-3-[5-methyl-2-(4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide (Compound CVIII)

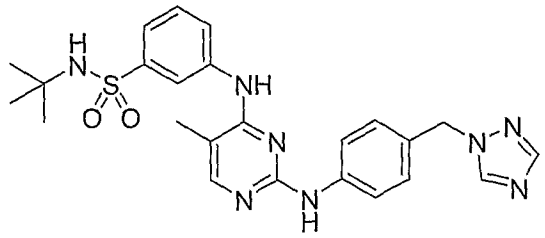


CVIII

[0336] A mixture of intermediate **33** (0.10 g, 0.28 mmol), 4-morpholin-4-yl-phenylamine (60 mg, 0.34 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), Xantphos (30 mg, 0.052 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane/DMF (3/1, 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a grey solid (45 mg, 32%).

[0337] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.12 (s, 3H), 3.00 (t, J = 4.8 Hz, 4H), 3.73 (t, J = 4.8 Hz, 4H), 6.82 (d, J = 9.1 Hz, 2H), 7.45–7.52 (m, 4H), 7.56 (s, 1H), 7.89 (s, 1H), 8.10–8.17 (m, 2H), 8.52 (s, 1H), 8.73 (s, 1H). MS (ES+): m/z 497 $(M+H)^+$.

EXAMPLE 166. *N-tert*-Butyl-3-[5-methyl-2-(4-[1,2,4]triazol-1-ylmethyl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide (Compound CIX)

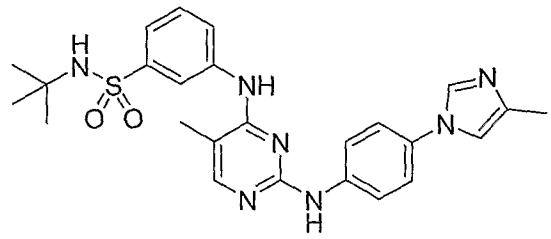


CIX

[0338] A mixture of intermediate **33** (0.10 g, 0.28 mmol), 4-[1,2,4]triazol-1-ylmethyl-phenylamine (60 mg, 0.34 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), Xantphos (30 mg, 0.052 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane (4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a white solid (37 mg, 27%).

[0339] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.17 (s, 9H), 2.13 (s, 3H), 5.29 (s, 2H), 7.14 (d, J = 8.6 Hz, 2H), 7.46 (t, J = 7.8 Hz, 1H), 7.48–7.51 (m, 1H), 7.56 (s, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.94 (s, 1H), 7.95 (s, 1H), 8.08 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.59 (s, 1H), 8.60 (s, 1H), 9.04 (s, 1H). MS (ES+): *m/z* 493 $(M+H)^+$.

EXAMPLE 167. *N-tert*-Butyl-3-{5-methyl-2-[4-(4-methyl-imidazol-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound CX)

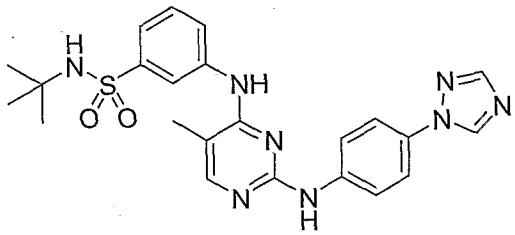


CX

[0340] A mixture of intermediate **33** (0.10 g, 0.28 mmol), 4-(4-methyl-imidazol-1-yl)-phenylamine (60 mg, 0.35 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), Xantphos (30 mg, 0.052 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as an off white solid (20 mg, 15%).

[0341] ^1H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.15 (s, 3H), 2.16 (s, 3H), 7.30 (s, 1H), 7.38 (d, J = 9.0 Hz, 2H), 7.50–7.56 (m, 2H), 7.57 (s, 1H), 7.76 (d, J = 9.0 Hz, 2H), 7.96 (s, 1H), 7.97 (s, 1H), 8.09–8.13 (m, 2H), 8.63 (s, 1H), 9.16 (s, 1H). MS (ES+): *m/z* 492 $(M+H)^+$.

EXAMPLE 168. *N-tert*-Butyl-3-[5-methyl-2-(4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide (Compound CXI)



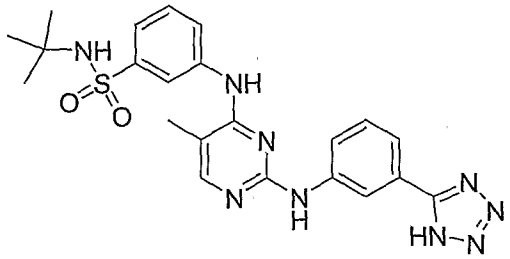
CXI

[0342] A mixture of intermediate **33** (0.10 g, 0.28 mmol), 4-[1,2,4]triazol-1-yl-phenylamine (55 mg, 0.34 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), Xantphos (30 mg, 0.052 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was

concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a white solid (40 mg, 29%).

[0343] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.15 (s, 3H), 7.50–7.58 (m, 3H), 7.63 (d, J = 9.1 Hz, 2H), 7.83 (d, J = 9.0 Hz, 2H), 7.99 (s, 1H), 8.09 (s, 1H), 8.10–8.15 (m, 1H), 8.17 (s, 1H), 8.66 (s, 1H), 9.12 (s, 1H), 9.27 (s, 1H). MS (ES+): *m/z* 479 $(M+H)^+$.

EXAMPLE 169. *N-tert*-Butyl-3-{5-methyl-2-[3-(1*H*-tetrazol-5-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound CXII)

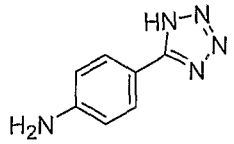


CXII

[0344] A mixture of intermediate **33** (0.10 g, 0.28 mmol), 3-(1*H*-tetrazol-5-yl)-phenylamine (55 mg, 0.34 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), Xantphos (30 mg, 0.052 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a white solid (15 mg, 11%).

[0345] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.13 (s, 9H), 2.15 (s, 3H), 7.26 (t, J = 7.9 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.44 (dd, J = 7.9, 1.1 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.58 (s, 1H), 7.79 (dd, J = 8.1, 1.4 Hz, 1H), 7.98 (s, 1H), 8.16 (s, 1H), 8.22 (s, 1H), 8.27 (d, J = 7.8 Hz, 1H), 8.57 (s, 1H), 9.08 (s, 1H). MS (ES+): *m/z* 480 $(M+H)^+$.

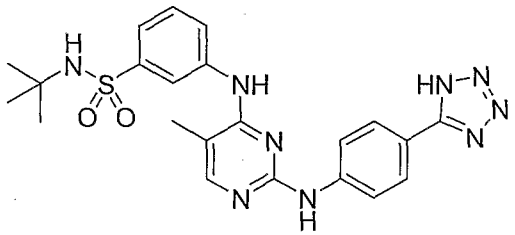
EXAMPLE 170. 4-(1*H*-Tetrazol-5-yl)-phenylamine (Intermediate 60)



60

[0346] To a solution of 5-(4-nitro-phenyl)-1*H*-tetrazole (1.0 g, 5.2 mmol) in MeOH (30 mL) was added 10 wt% Pd/C (0.1 equiv by wt) under argon atmosphere. The mixture was evacuated, refilled with hydrogen (3 cycles) and stirred at room temperature for 1.5 h. The heterogeneous reaction mixture was filtered through a pad of Celite, washed with MeOH and concentrated *in vacuo*. The crude amino-compound was used in the next step without purification. MS (ES+): *m/z* 162 $(M+H)^+$.

EXAMPLE 171. *N-tert*-Butyl-3-{5-methyl-2-[4-(1*H*-tetrazol-5-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound CXIII)

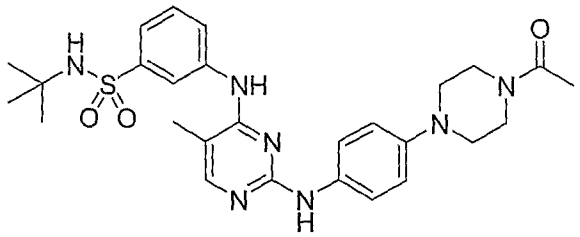


CXIII

[0347] A mixture of intermediate **33** (0.10 g, 0.28 mmol), intermediate **60** (60 mg, 0.37 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), Xantphos (30 mg, 0.052 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane/DMF (3/1; 4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a white solid (15 mg, 11%).

[0348] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.13 (s, 9H), 2.16 (s, 3H), 7.52–7.56 (m, 2H), 7.57 (s, 1H), 7.83 (s, 4H), 8.01 (s, 1H), 8.08 (s, 1H), 8.13–8.19 (m, 1H), 8.69 (s, 1H), 9.34 (s, 1H). MS (ES+): *m/z* 480 $(M+H)^+$.

EXAMPLE 172. 3-{2-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-5-methyl-pyrimidin-4-ylamino}-*N-tert*-butyl-benzenesulfonamide (Compound CXIV)

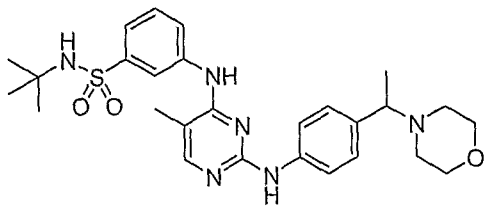


CXIV

[0349] A mixture of intermediate **33** (0.10 g, 0.28 mmol), 1-[4-(4-amino-phenyl)-piperazin-1-yl]-ethanone (80 mg, 0.36 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), Xantphos (30 mg, 0.052 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as an off white solid (55 mg, 37%).

[0350] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 2.04 (s, 3H), 2.12 (s, 3H), 2.97 (t, J = 5.2 Hz, 2H), 3.03 (t, J = 5.1 Hz, 2H), 3.57 (q, J = 5.4 Hz, 4H), 6.85 (d, J = 9.0 Hz, 2H), 7.46–7.52 (m, 4H), 7.56 (s, 1H), 7.90 (s, 1H), 8.10–8.17 (m, 2H), 8.52 (s, 1H), 8.75 (s, 1H). MS (ES+): *m/z* 538 $(M+H)^+$.

EXAMPLE 173. *N-tert*-Butyl-3-{5-methyl-2-[4-(1-morpholin-4-yl-ethyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound CXV)

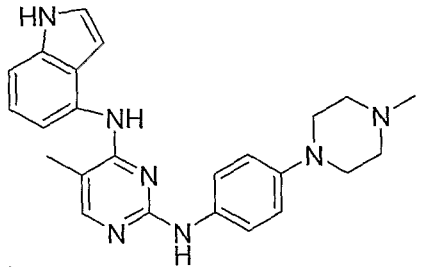


CXV

[0351] A mixture of intermediate **33** (0.10 g, 0.28 mmol), 4-(1-morpholin-4-yl-ethyl)-phenylamine (80 mg, 0.39 mmol), $Pd_2(dba)_3$ (30 mg, 0.033 mmol), Xantphos (35 mg, 0.061 mmol) and cesium carbonate (0.26 g, 0.80 mmol) in dioxane (4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the cap was removed and the resulting mixture filtered. The filtered solid was washed with DCM, the filtrate concentrated and the residue purified by HPLC. The corrected fractions were combined and poured into saturated $NaHCO_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and then taken up in minimum amount of EtOAc. Hexanes were added until solid precipitated. After filtration, the title compound was obtained as a white solid (40 mg, 27%).

[0352] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 9H), 1.25 (d, J = 6.6 Hz, 3H), 2.13 (s, 3H), 2.20–2.30 (m, 2H), 2.30–2.40 (m, 2H), 3.24 (q, J = 6.6 Hz, 1H), 3.54 (t, J = 4.4 Hz, 4H), 7.10 (d, J = 8.5 Hz, 2H), 7.45–7.52 (m, 2H), 7.55 (s, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.93 (s, 1H), 8.09 (s, 1H), 8.15 (d, J = 7.7 Hz, 1H), 8.57 (s, 1H), 8.92 (s, 1H). MS (ES+): *m/z* 525 $(M+H)^+$.

EXAMPLE 174. N^4-(1*H*-Indol-4-yl)-5-methyl-N^2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine (Compound CXVI)

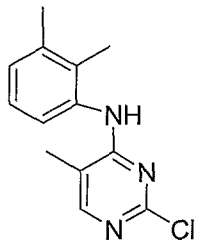


CXVI

[0353] A mixture of intermediate **32** (270 mg, 0.9 mmol), 4-bromo-1*H*-indole (196 mg, 0.9 mmol), $Pd_2(dba)_3$ (91 mg, 0.09 mmol), Xantphos (157 mg, 0.27 mmol) and cesium carbonate (1.2 g, 3.6 mmol) were suspended in dioxane (100 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (55 mg of HCl salt, 14%) as a white solid.

[0354] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.22 (s, 3H), 2.79 (d, J = 4.3 Hz, 3H), 2.98-3.03 (m, 2H), 3.08-3.14 (m, 2H), 3.46–3.48 (m, 2H), 3.64–3.66 (m, 2H), 6.35-6.36 (m, 1H), 6.63 (br d, J = 8.0 Hz, 1H), 6.98 (d, J = 9.1 Hz, 2H), 7.05 (d, J = 7.4 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.36 (t, J = 2.8 Hz, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.86 (s, 1H), 10.07 (s, 1H), 10.27 (s, 1H), 11.00 (br s, 1H), 11.38 (s, 1H), 12.16 (br s, H). MS (ES+): *m/z* 414 $(M+H)^+$.

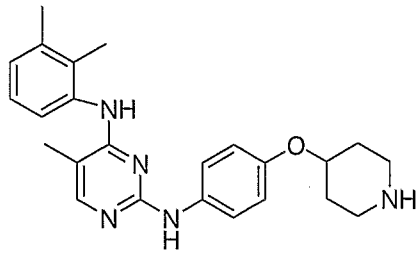
EXAMPLE 175. 2-Chloro-5-methyl-*N*-(2,3-dimethylphenyl)pyrimidin-4-amine (Intermediate 61)



61

[0355] A mixture of 2-chloro-5-methylpyrimidin-4-amine (143.6 mg, 1 mmol), 1-bromo-2,3-dimethylbenzene (222 mg, 1.2 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), Xantphos (174 mg, 0.3 mmol) and cesium carbonate (1.3 g, 4 mmol) were suspended in dioxane (150 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc (10 mL) and added hexanes (100 mL). The solid was collected by filtration and washed with hexanes to afford the crude title compound as a yellow solid.

EXAMPLE 176. 5-Methyl-N^4-(2,3-dimethylphenyl)-N^2-(4-(piperidin-4-yloxy)phenyl)pyrimidine-2,4-diamine (Compound CXVII)

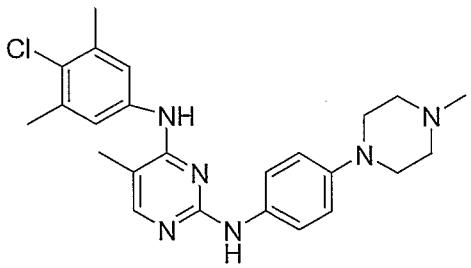


CXVII

[0356] A mixture of intermediate **61** (1.0 mmol) and *tert*-butyl 4-(4-aminophenoxy)piperidine-1-carboxylate (292.4 mg, 1.0 mmol) were suspended in acetic acid (10 mL) and heated at 100°C for 4 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (20 mL) and neutralized to pH~7. The resulting solution was extracted with EtOAc (30 mL) and the organic layer separated. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by HPLC to afford the title compound (105 mg of HCl salt, 24%) as a yellow solid.

[0357] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.76-1.83 (m, 2H), 2.03 (s, 3H), 2.05-2.09 (m, 2H), 2.17 (s, 3H), 2.30 (s, 3H), 3.02-3.05 (m, 2H), 3.18 (br s, 2H), 4.53-4.56 (m, 1H), 6.72 (d, J = 8.5 Hz, 2H), 7.11-7.14 (m, 3H), 7.19-7.24 (m, 2H), 7.87 (s, 1H), 9.06 (br s, 1H), 9.13 (br s, 1H), 9.92 (s, 1H), 10.43 (s, 1H). MS (ES+): *m/z* 404 $(M+H)^+$.

EXAMPLE 177. N^4-(4-Chloro-3,5-dimethylphenyl)-5-methyl-N^2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine (Compound CXVIII)



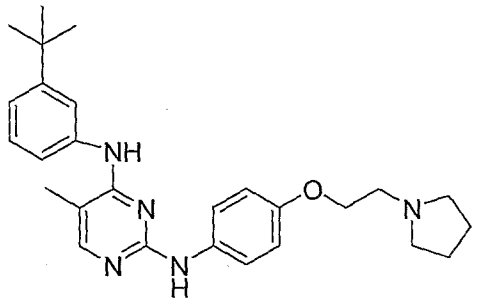
CXVIII

[0358] A mixture of intermediate **32** (240 mg, 0.8 mmol), 5-bromo-2-chloro-1,3-dimethylbenzene (212 mg, 0.96 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), Xantphos (170 mg, 0.3 mmol) and cesium carbonate (1.3 g, 4 mmol) were suspended in dioxane (100 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the

filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (63 mg of HCl salt, 17%) as a white solid.

[0359] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.15 (s, 3H), 2.17 (s, 3H), 2.80 (d, J = 4.5 Hz, 3H), 3.06-3.14 (m, 4H), 3.48-3.52 (m, 2H), 3.75–3.77 (m, 2H), 6.93 (d, J = 8.9 Hz, 2H), 7.29 (d, J = 8.9 Hz, 2H), 7.46 (s, 2H), 7.90 (s, 1H), 9.65 (s, 1H), 10.49 (s, 1H), 11.13 (br s, 2H). MS (ES+): *m/z* 437 $(M+H)^+$.

EXAMPLE 178. N^2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenyl)-N^4-(3-tert-butylphenyl)-5-methyl-pyrimidine-2,4-diamine (Compound CXIX)

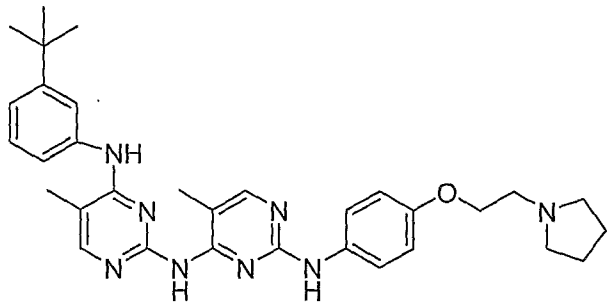


CXIX

[0360] A mixture of intermediate **41** (365 mg, 1.32 mmol) and 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (410 mg, 1.98 mmol) were suspended in acetic acid (20 mL) and heated at 100°C for 4 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (20 mL) and neutralized to pH~7. The resulting solution was extracted with EtOAc (30 mL) and the organic layer separated. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by HPLC to afford the title compound (127 mg of HCl salt, 20%) as a white solid.

[0361] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.89-1.91 (m, 2H), 1.98-2.02 (m, 2H), 2.17 (s, 3H), 3.07-3.12 (m, 2H), 3.52-3.57 (m, 4H), 4.32 (t, J = 4.8 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 7.29-7.38 (m, 4H), 7.43-7.44 (m, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.89 (s, 1H), 9.75 (s, 1H), 10.51 (s, 1H), 11.07 (br, 1H). MS (ESI+): *m/z* 446 $(M+H)^+$.

EXAMPLE 179. N^2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenyl)-N^4-(4-(3-tert-butylphenylamino)-5-methylpyrimidin-2-yl)-5-methylpyrimidine-2,4-diamine (Compound CXX)

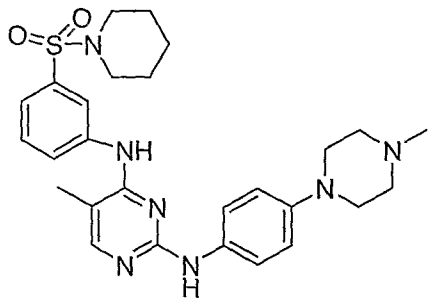


CXX

[0362] A mixture of intermediate **41** (210 mg, 0.67 mmol), intermediate **38** (185 mg, 0.67 mmol), $Pd_2(dba)_3$ (55 mg, 0.06 mmol), Xantphos (104 mg, 0.18 mmol) and cesium carbonate (782 g, 2.4 mmol) were suspended in dioxane (50 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (94 mg of HCl salt, 24%) as a yellow solid.

[0363] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.29 (s, 9H), 1.84-1.88 (m, 2H), 1.94-2.01 (m, 2H), 2.14 (s, 3H), 2.27 (s, 3H), 3.06-3.10 (m, 2H), 3.51-3.56 (m, 4H), 4.29 (t, J = 4.9 Hz, 2H), 6.97 (d, J = 9.1 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 7.34 (t, J = 7.9 Hz, 2H), 7.57 (t, J = 1.9 Hz, 2H), 7.65 (d, J = 9.1 Hz, 1H), 7.72 (d, J = 8.6 Hz, 2H), 8.15 (s, 1H), 8.39 (s, 1H), 9.82 (s, 1H), 10.21 (br s, 1H), 10.68 (br s, 1H), 10.93 (br s, 1H). MS (ES+): *m/z* 553 $(M+H)^+$.

EXAMPLE 180. 5-Methyl-N^2-[4-(4-methyl-piperazin-1-yl)-phenyl]-N^4-[3-(piperidine-1-sulfony)-phenyl]-pyrimidine-2,4-diamine (Compound CXXI)



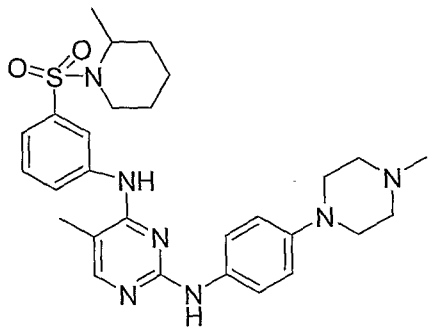
CXXI

[0364] A mixture of intermediate **32** (150 mg, 0.5 mmol), 1-(3-bromo-benzenesulfonyl)-piperidine (152 mg, 0.5 mmol), $Pd_2(dba)_3$ (46 mg, 0.05 mmol), Xantphos (87 mg, 0.15 mmol)

and cesium carbonate (652 mg, 2 mmol) were suspended in dioxane (20 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (84 mg of HCl salt, 37%) as a white solid.

[0365] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.30-1.34 (m, 2H), 1.50-1.55 (m, 4H), 2.17 (s, 3H), 2.81 (d, J = 4.5 Hz, 3H), 2.88 (t, J = 5.3 Hz, 4H), 3.04-3.16 (m, 4H), 3.47-3.51 (m, 2H), 3.75–3.77 (m, 2H), 6.33-6.34 (m, 1H), 6.95 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 9.0 Hz, 2H), 7.56-7.63 (m, 2H), 7.83 (t, J = 1.7 Hz, 1H), 7.92 (s, 1H), 8.05 (d, J = 9.3 Hz, 1H), 9.94 (s, 1H), 10.38 (s, 1H), 10.88 (br s, 1H). MS (ES+): *m/z* 522 $(M+H)^+$.

EXAMPLE 181. 5-Methyl-N^2-[4-(4-methyl-piperazin-1-yl)-phenyl]-N^4-[3-(2-methyl-piperidine-1-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (Compound CXXII)

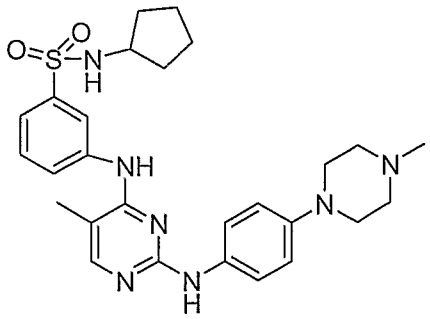


CXXII

[0366] A mixture of intermediate **32** (161 mg, 0.54 mmol), 1-(3-bromo-benzenesulfonyl)-2-methyl-piperidine (172 mg, 0.54 mmol), $Pd_2(dba)_3$ (46 mg, 0.05 mmol), Xantphos (87 mg, 0.15 mmol) and cesium carbonate (652 mg, 2 mmol) were suspended in dioxane (20 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (10 mg of HCl salt, 3%) as a white solid.

[0367] ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.98 (d, J = 6.9 Hz, 3H), 1.15-1.21 (m, 1H), 1.36-1.40 (m, 3H), 1.47-1.53 (m, 2H), 2.18 (s, 3H), 2.80 (d, J = 4.5 Hz, 3H), 2.94-2.99 (m, 1H), 3.05-3.16 (m, 4H), 3.47-3.49 (m, 2H), 3.59–3.61 (m, 2H), 3.73–3.76 (m, 2H), 4.08–4.10 (m, 1H), 6.93 (d, J = 8.9 Hz, 2H), 7.25 (d, J = 8.9 Hz, 2H), 7.58 (t, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 7.1 Hz, 2H), 7.96 (br, 1H), 9.95 (s, 1H), 10.45 (s, 1H), 11.00 (br s, 1H). MS (ES+): *m/z* 536 $(M+H)^+$.

EXAMPLE 182. *N*-Cyclopentyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidine-4-ylamino}-benzenesulfonamide (Compound CXXIII)

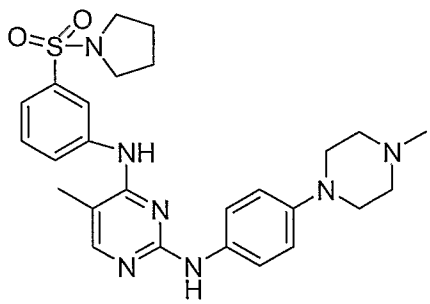


CXXIII

[0368] A mixture of intermediate **32** (229 mg, 0.78 mmol), 3-bromo-N-cyclopentyl-benzenesulfonamide (280 mg, 0.92 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), Xantphos (180 mg, 0.3 mmol) and cesium carbonate (1.3 g, 4 mmol) were suspended in dioxane (100 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (130 mg of HCl salt, 25%) as a white solid.

[0369] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.27-1.36 (m, 4H), 1.36-1.58 (m, 4H), 2.18 (s, 3H), 2.80 (d, J = 4.6 Hz, 3H), 3.05-3.15 (m, 4H), 3.36-3.42 (m, 1H), 3.47-3.49 (m, 2H), 3.74–3.76 (m, 2H), 6.94 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.9 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 7.1 Hz, 2H), 7.92 (br, 2H), 7.93 (br, 1H), 9.96 (s, 1H), 10.45 (s, 1H), 11.98 (br s, 1H). MS (ES+): *m/z* 522 $(M+H)^+$.

EXAMPLE 183. 5-Methyl-N^2-[4-(4-methyl-piperazin-1-yl)-phenyl]-N^4-[3-(pyrrolidine-1-sulfony) phenyl]-pyrimidine-2,4-diamine (Compound CXXIV)



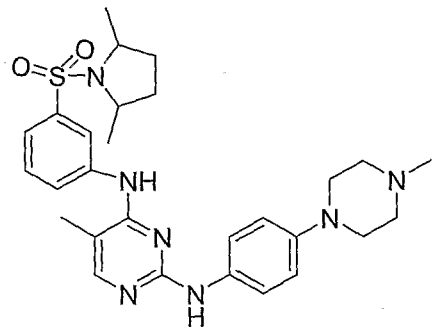
CXXIV

[0370] A mixture of intermediate **32** (298 mg, 1.0 mmol), 1-(3-bromo-benzenesulfonyl)-pyrrolidine (360 mg, 1.24 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), Xantphos (180 mg, 0.3 mmol) and cesium carbonate (1.3 g, 4 mmol) were suspended in dioxane (100 mL) and

heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (200 mg of HCl salt, 37%) as a white solid.

[0371] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.61-1.65 (m, 4H), 2.19 (s, 3H), 2.80 (br, 3H), 3.06-3.16 (m, 10H), 3.74–3.77 (br, 2H), 6.94 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 9.0 Hz, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.91 (t, J = 1.7 Hz, 1H), 7.93 (s, 1H), 8.05 (d, J = 7.5 Hz, 1H), 9.95 (s, 1H), 10.43 (s, 1H), 11.07 (br s, 1H). MS (ES+): *m/z* 508 $(M+H)^+$.

EXAMPLE 184. N^4-[3-(2,5-Dimethyl-pyrrolidine-1-sulfonyl)-phenyl]-5-methyl-N^2-[4-(4-methyl-piperazin-1-yl)-phenyl]-pyrimidine-2,4-diamine (Compound CXXV)

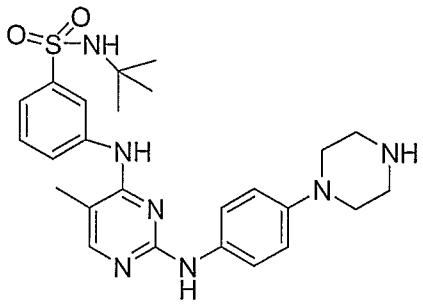


CXXV

[0372] A mixture of intermediate **32** (298 mg, 1.0 mmol), 1-(3-bromo-benzenesulfonyl)-2,5-dimethyl-pyrrolidine (318 mg, 1.0 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), Xantphos (180 mg, 0.3 mmol) and cesium carbonate (1.3 g, 4 mmol) were suspended in dioxane (100 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (100 mg of HCl salt, 17%) as a white solid.

[0373] ^{1}H NMR (500 MHz, *DMSO*-d_6): δ 1.26 (s, 3H), 1.27 (s, 3H), 1.45-1.48 (m, 4H), 2.19 (s, 3H), 2.80 (d, J = 4.6 Hz, 3H), 3.06-3.15 (m, 4H), 3.47-3.50 (m, 2H), 3.60-3.64 (m, 2H), 3.74–3.76 (m, 2H), 6.94 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 9.0 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.93 (br, 2H), 8.02 (br, 1H), 9.97 (s, 1H), 10.47 (s, 1H), 11.07 (br s, 1H). MS (ES+): *m/z* 536 $(M+H)^+$.

EXAMPLE 185. *N-tert*-Butyl-3-[5-methyl-2-(4-piperazin-1-yl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide (Compound CXXVI)

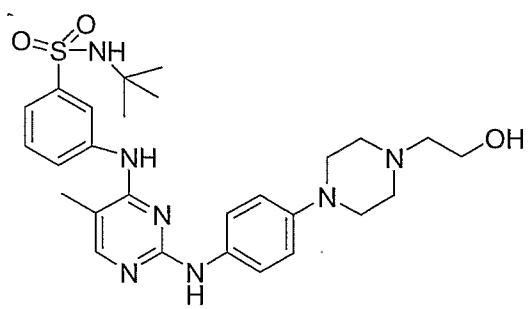


CXXVI

[0374] A mixture of intermediate **33** (355 mg, 1.0 mmol), *tert*-butyl 4-(4-aminophenyl)piperazine-1-carboxylate (278 mg, 1.0 *mmol*), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), Xantphos (180 mg, 0.3 mmol) and cesium carbonate (1.3 g, 4 mmol) were suspended in dioxane (100 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and trifuloroacetic acid (2 mL) was added. The mixture was stirred for 4 h at room temperature before 10% NaOH was added. The organic layer was separated and aqueous was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layers were dried (Na_2SO_4). The solvent was removed *in vacuo*. The residue was purified by HPLC to afford the title compound (62 mg, 12%) as a white solid.

[0375] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.10 (s, 9H), 2.18 (s, 3H), 3.20 (br, 4H), 3.33 (br, 4H), 6.94 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 9.0 Hz, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.63 (s, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.87 (br, 1H), 7.92 (br, 1H), 7.96 (br, 1H), 9.30 (br, 1H), 9.96 (s, 1H), 10.46 (s, 1H). MS (ES+): *m/z* 496 $(M+H)^+$.

EXAMPLE 186. *N-tert*-Butyl-3-(2-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-phenylamino}-[5-methyl-pyrimidin-4-ylamino]-benzenesulfonamide (Compound CXXVII)

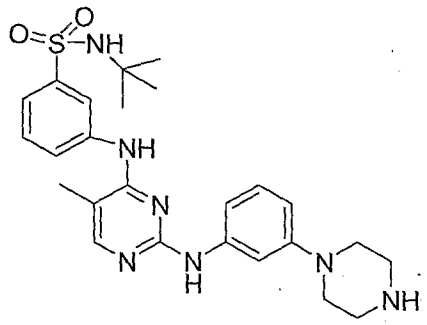


CXXVII

[0376] The above-described compound **CXXVI** (31mg, 0.06 mmol) was dissolved in DMF (10 mL) followed by adding 2-bromoethanol (16 mg, 0.13 mmol) and diisopropylethylamine (33 mg, 0.25 mmol). The mixture was stirred for 48 h at room temperature. Solvent was removed in vacuo and residue was dissolved in EtOAc (20 mL). The solution was washed with saturated $NaHCO_3$ and brine. The combined organic layers were dried and concentrated until 2 mL solution followed by adding Et_2O (20 mL). The solid was collected by centrifugation and transferred to its HCl salt (10.7 mg, 30%).

[0377] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.09 (s, 9H), 2.17 (s, 3H), 3.12-3.23 (m, 4H), 3.56-3.60 (m, 2H), 3.69-3.74 (m, 2H), 3.83 (br, 2H), 4.13 (br, 2H), 6.94 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 9.0 Hz, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.63 (s, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.87 (br, 1H), 7.93 (br, 1H), 7.95 (br, 1H), 9.98 (s, 1H), 10.53 (s, 1H), 10.75 (br, 1H). MS (ES+): *m/z* 540 $(M+H)^+$.

EXAMPLE 187. *N-tert*-Butyl-3-[5-methyl-2-(3-piperazin-1-yl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide (Compound CXXVIII)

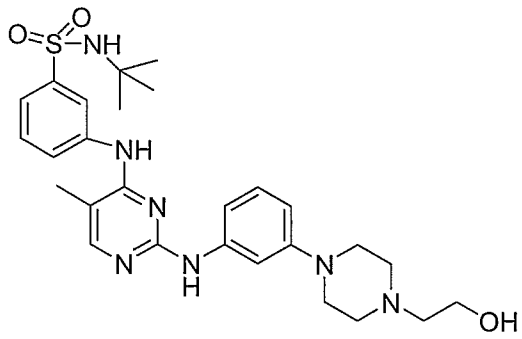


CXXVIII

[0378] A mixture of intermediate **33** (240 mg, 0.67 mmol), *tert*-butyl 4-(3-aminophenyl)piperazine-1-carboxylate (166 mg, 0.6 mmol), $Pd_2(dba)_3$ (55 mg, 0.06 mmol), Xantphos (104 mg, 0.18 mmol) and cesium carbonate (782 mg, 2.4 mmol) were suspended in dioxane (100 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and trifuloroacetic acid (2 mL) was added. The mixture was stirred for 4 h at room temperature before 10% NaOH was added. The organic layer was separated and aqueous was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layers were dried (Na_2SO_4). The solvent was removed *in vacuo*. The residue was purified by HPLC to afford the title compound (18 mg, 6%) as a white solid.

[0379] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.10 (s, 9H), 2.19 (s, 3H), 3.17 (br, 4H), 3.27-3.29 (m, 4H), 6.80 (d, J = 8.1 Hz, 1H), 6.87 (br, 1H), 6.96 (d, J = 8.1 Hz, 1H), 7.16 (t, J = 8.1 Hz, 1H), 7.53 (t, J = 8.3 Hz, 1H), 7.61 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.94 (br, 3H), 9.19 (br, 2H), 9.93 (s, 1H), 10.48 (s, 1H). MS (ES+): *m/z* 496 $(M+H)^+$.

EXAMPLE 188. *N-tert*-Butyl-3-(2-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-phenylamino}-[5-methyl-pyrimidin-4-ylamino]-benzenesulfonamide (Compound CXXIX)

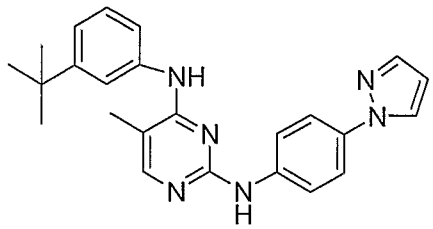


CXXIX

[0380] The above-describeed compound **CXXVI** (12mg, 0.024 mmol) was dissolved in DMF (10 mL) followed by adding 2-bromoethanol (6.1 mg, 0.048 mmol) and diisopropylethylamine (12 mg, 0.092 mmol). The mixture was stirred for 48 h at room temperature. Solvent was removed in vacuo and residue was dissolved in EtOAc (20 mL). The solution was washed with saturated $NaHCO_3$ and brine. The combined organic layers were dried and concentrated until 2 mL solution followed by adding Et_2O (20 mL). The solid was collected by centrifugation and transferred to its HCl salt (7 mg, 51%).

[0381] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.09 (s, 9H), 2.19 (s, 3H), 3.12-3.22 (m, 4H), 3.56-3.60 (m, 2H), 3.69-3.74 (m, 2H), 3.81 (br, 2H), 4.12 (br, 2H), 6.80 (br, 1H), 6.88 (br, 1H), 6.96 (br, 1H), 7.16 (br, 1H), 7.57 (br, 1H), 7.60 (s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.94 (br, 3H), 9.94 (s, 1H), 10.49 (s, 1H). MS (ES+): *m/z* 540 $(M+H)^+$.

EXAMPLE 189. N^2-(4-(1*H*-Pyrazol-1-yl)phenyl)-N^4-(3-*tert*-butylphenyl)-5-methylpyrimidine-2,4-diamine (Compound CXXX)

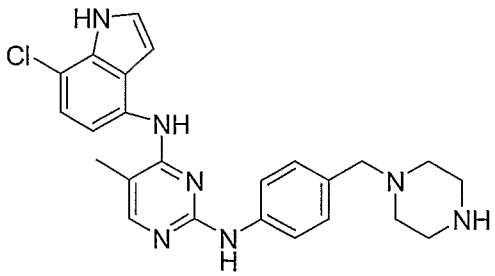


CXXX

[0382] A mixture of intermediate **41** (580 mg, 2.1 mmol) and 4-(1*H*-pyrazol-1-yl)benzenamine (335 mg, 2.1 mmol) were suspended in acetic acid (10 mL) and heated at 100°C for 4 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (20 mL) and neutralized to pH~7. The resulting solution was extracted with EtOAc (30 mL) and the organic layer separated. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by HPLC to afford the title compound (31 mg, 4%) as a yellow solid.

[0383] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.24 (s, 9H), 2.18 (s, 3H), 6.53 (t, J = 2.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.44 (s, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 8.9 Hz, 2H), 7.67 (d, J = 8.9 Hz, 2H), 7.73 (s, 1H), 7.95 (s, 1H), 8.43 (d, J = 2.4 Hz, 1H), 9.81 (br s, 1H), 10.67 (s, 1H). MS (ES+): *m/z* 399 $(M+H)^+$.

EXAMPLE 190. N^4-(7-Chloro-1*H*-indol-4-yl)-5-methyl-N^2-(4-((piperazin-1-yl)methyl)phenyl)-pyrimidine-2,4-diamine (Compound CXXXI)



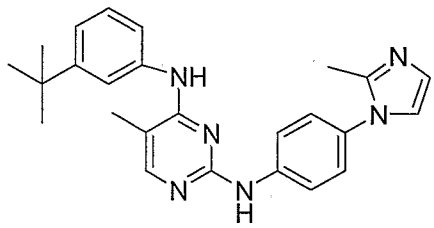
CXXXI

[0384] A mixture of intermediate **40** (150 mg, 0.37 mmol), 4-bromo-7-chloro-1*H*-indole (87 mg, 0.37 mmol), $Pd_2(dba)_3$ (38 mg, 0.04 mmol), Xantphos (76 mg, 0.12 mmol) and cesium carbonate (521 mg, 1.6 mmol) were suspended in dioxane (50 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate

concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and trifuloroacetic acid (2 mL) was added. The mixture was stirred for 4 h at room temperature before 10% NaOH was added. The organic layer was separated and aqueous was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layers were dried (Na_2SO_4). The solvent was removed *in vacuo*. The residue was purified by HPLC to afford the title compound (26 mg, 15%) as a white solid.

[0385] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.21 (s, 3H), 3.30 (br, 4H), 3.50 (br, 4H), 4.42 (br, 2H), 6.91 (s, 1H), 7.11 (d, J = 8.3 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.42 (t, J = 2.7 Hz, 1H), 7.70 (br, 4H), 8.03 (s, 1H), 9.87 (br, 1H), 9.95 (s, 1H), 10.64 (s, 1H), 11.64 (s, 1H). MS (ES+): *m/z* 448 $(M+H)^+$.

EXAMPLE 191. N^4-(3-*tert*-Butylphenyl)-5-methyl-N^2-(4-(2-methyl-1*H*-imidazol-1-yl)phenyl)-pyrimidine-2,4-diamine (Compound CXXXII)

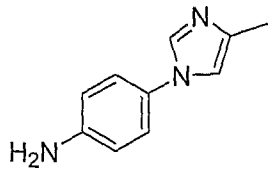


CXXXII

[0386] A mixture of intermediate **41** (180 mg, 0.65 mmol) and 4-(2-methyl-1*H*-imidazol-1-yl)benzenamine (113 mg, 0.65 mmol), $Pd_2(dba)_3$ (55 mg, 0.06 mmol), Xantphos (104 mg, 0.18 mmol) and cesium carbonate (782 mg, 2.4 mmol) were suspended in dioxane (100 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (78 mg of HCl salt, 27%) as a white solid.

[0387] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.26 (s, 9H), 2.21 (s, 3H), 2.50 (s, 3H), 7.31-7.36 (m, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 8.9 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.9 Hz, 2H), 7.75 (d, J = 2.1 Hz, 1H), 7.79 (d, J = 2.1 Hz, 2H), 8.03 (s, 1H), 10.02 (s, 1H), 11.26 (s, 1H). MS (ES+): *m/z* 413 $(M+H)^+$.

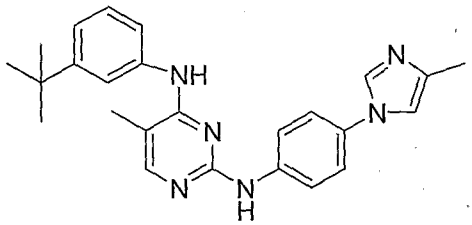
EXAMPLE 192. 4-(4-Methyl-1*H*-imidazol-1-yl)benzenamine (Intermediate 62)



62

[0388] To a solution of 1-fluoro-4-nitrobenzene (1.7 g, 12 mmol) in DMF (100 mL) was added 4-methyl-1H-imidazole (0.82 g, 10 mmol) and K_2CO_3 (11g, 80 mmol). The mixture was heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc (100 mL) and washed with brine (100 mL x 2). The organic layer was dried and concentrated. The solid was dissolved in MeOH and bubbled with Ar for 2 min. before adding 10% Pd-C. The hydrogenation was finished in 4 h. The catalyst was removed by filtration and solvent was removed *in vacuo* to afford title compound (1.5 g, 87%) as brown solid.

EXAMPLE 193. N^4-(3-*tert*-Butylphenyl)-5-methyl-N^2-(4-(4-methyl-1*H*-imidazol-1-yl)phenyl) pyrimidine-2,4-diamine (Compound CXXXIII)

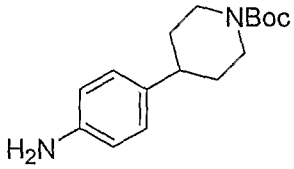


CXXXIII

[0389] A mixture of intermediate **41** (318 mg, 1.15 mmol) and intermediate **62** (200 mg, 1.15 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), Xantphos (180 mg, 0.3 mmol) and cesium carbonate (1.3 g, 4 mmol) were suspended in dioxane (100 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (66 mg of HCl salt, 20%) as a white solid.

[0390] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.26 (s, 9H), 2.19 (s, 3H), 2.36 (s, 3H), 7.30 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.44 (t, J = 1.8 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 9.0 Hz, 2H), 7.68 (d, J = 9.0 Hz, 2H), 7.94 (s, 1H), 7.99 (s, 1H), 9.53 (d, J = 1.3 Hz, 1H), 9.72 (br s, 1H), 10.81(br s, 1H). MS (ES+): *m/z* 413 $(M+H)^+$.

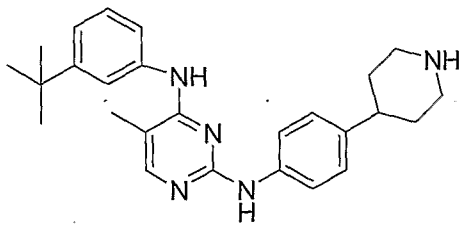
EXAMPLE 194. *tert*-Butyl 4-(4-aminophenyl)piperidine-1-carboxylate (Intermediate 63)



63

[0391] To a solution of 4-(4-nitrophenyl)piperidine (412 mg, 2 mmol) in CH2Cl2 (100 mL) was added di-tert-butyl carbonate (480 mg, 2.2 mmol) and N,N-dimethylpyridin-4-amine (50 mg, 0.4 mmol). The mixture was stirred for 20 h at room temperature. The mixture was added saturated NaHCO3 (100 mL). The organic layer was separated and aqueous was extracted with CH2Cl2 (50 mL x 2). The combined organic solution was dried and concentrated *in vacuo*. The residue was dissolved in MeOH and bubbled with Ar for 2 min. before adding 10% Pd-C. The hydrogenation was finished in 4 h. The catalyst was removed by filtration and solvent was removed *in vacuo* to afford title compound (460 mg, 83%) as white solid.

EXAMPLE 195. N^4-(3-*tert*-Butylphenyl)-5-methyl-N^2-(4-(piperidin-4-yl)phenyl)pyrimidine-2,4-diamine (Compound CXXXIV)

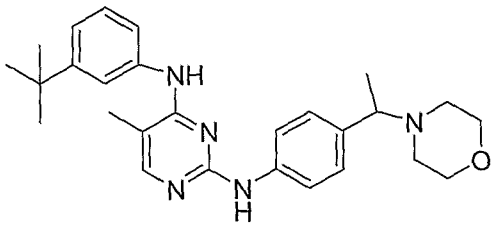


CXXXIV

[0392] A mixture of intermediate **41** (170 mg, 0.6 mmol) and intermediate **63** (170 mg, 0.6 mmol) were suspended in acetic acid (10 mL) and heated at 100°C for 4 h. The mixture was allowed to cool to room temperature and acetic acid removed under reduced pressure. The residue was taken in water (20 mL) and neutralized to pH~7. The resulting solution was extracted with EtOAc (30 mL) and the organic layer separated. The organic layer was washed with brine, dried over MgSO4 and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by HPLC to afford the title compound (8 mg, 3%) as a white solid.

[0393] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.26 (s, 9H), 1.76-1.88 (m, 4H), 2.17 (s, 3H), 2.76-2.81 (m, 1H), 2.93-3.00 (m, 2H), 3.36-3.40 (m, 2H), 7.07 (d, J = 8.5 Hz, 1H), 7.30-7.36 (m, 4H), 7.44 (s, 1H), 7.46 (d, J = 8.7 Hz, 1H), 7.91 (s, 1H), 8.84 (br s, 1H), 8.92 (br s, 1H), 9.73 (s, 1H), 10.45 (s, 1H). MS (ES+): *m/z* 416 $(M+H)^+$.

EXAMPLE 196. N^4-(3-*tert*-Butylphenyl)-5-methyl-N^2-(4-(1-morpholinoethyl)phenyl)pyrimidine-2,4-diamine (Compound CXXXV)

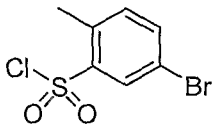


CXXXV

[0394] A mixture of intermediate **41** (276 mg, 1.0 mmol) and 4-(1-morpholinoethyl)benzenamine (210 mg, 1.0 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), Xantphos (180 mg, 0.3 mmol) and cesium carbonate (1.3 g, 4 mmol) were suspended in dioxane (100 mL) and heated at reflux under the argon atmosphere for 20 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (17 mg of HCl salt, 4%) as a yellow solid.

[0395] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.26 (s, 9H), 1.66 (d, J = 6.8 Hz, 3H), 2.19 (s, 3H), 2.79 (br, 2H), 2.92 (br, 1H), 3.61-3.64 (m, 2H), 3.77-3.82 (m, 2H), 3.94-3.99 (m, 2H), 7.32 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 1.9 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.46-7.52 (m, 5H), 7.97 (s, 1H), 9.86 (s, 1H), 10.78 (s, 1H), 11.72(br s, 1H). MS (ES+): *m/z* 446 $(M+H)^+$.

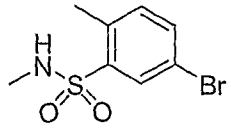
EXAMPLE 197. 5-Bromo-2-methyl-benzenesulfonyl chloride (Intermediate 64)



64

[0396] Bromide (1.99 g, 11.61 mmol) was stirred vigorously and treated with chlorosulfonic acid (1.55 mL, 23.22 mmol). Once addition was complete, resulting red syrup was heated to 60°C. Reaction TLC after 10 min showed no starting material and reaction was quenched by pouring onto ice. Product was extracted by washing with EtOAc (2 x 150 mL). Organic phase dried over Na_2SO_4, filtered and evaporated to yellow oil (2.2g, 70%).

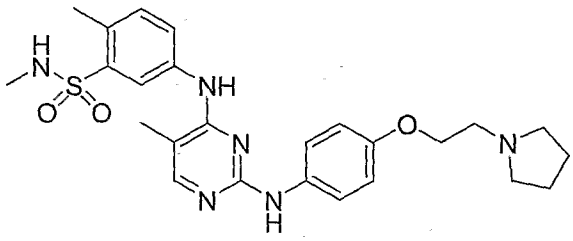
EXAMPLE 198. 5-Bromo-2,*N*-dimethyl-benzenesulfonamide (Intermediate 65)



65

[0397] A stirring suspension of intermediate **64** (0.43 g, 1.58 mmol) in DCM (5 mL) was treated with 2.0M methylamine solition in THF (2.4 mL, 4.8 mmol). After 16 h reaction solvents were removed and resulting residue diluted with EtOAc (150 mL) and washed with water. Organic phase dried over Na_2SO_4, filtered and evaporated to white solids (0.37 g, 89%).

EXAMPLE 199. 2,*N*-Dimethyl-5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound CXXXVI)

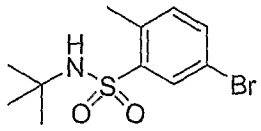


CXXXVI

[0398] A mixture of intermediate **65** (0.14 g, 0.52 mmol), intermediate **38** (0.14 g, 0.43 mmol), $Pd_2(dba)_3$ (0.040 g, 0.043 mmol), Xantphos (0.050 g, 0.087 mmol) and cesium carbonate (0.43 g, 1.3 mmol) were suspended in dioxane (10 mL), sealed in a microwave reaction tube and irradiated with microwaves at 160 °C for 15 min. The reaction mixture was cooled to room temperature and centrifuged down. The reaction was decanted and the organic phase concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound as a white solid (0.052 g, 24%).

[0399] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.66-1.70 (m, 4H), 2.08 (s, 3H), 2.43 (d, J = 4.9 Hz, 3H), 2.5 (br s, 4H), 2.78, (t, *J* = 5.7 Hz), 4.00 (t, *J* = 5.9 Hz), 6.79 (d, *J* = 9.0 Hz, 2H), 7.31 (d, *J* = 9.7 Hz, 1H), 7.42 (q, *J* = 9.8 Hz, 1H), 7.49 (d, *J* = 9.0 Hz, 1H), 7.87 (s, 1H), 7.97 (d, *J* = 2.3 Hz, 1H), 8.07-8.09 (m, 1H), 8.49 (s, 1H), 8.75 (s, 1H). MS (ES+): *m/z* 497 $(M+H)^+$.

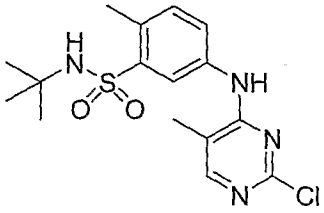
EXAMPLE 200. 5-Bromo-*N*-*tert*-butyl-2-methyl-benzenesulfonamide (Intermediate 66)



66

[0400] A stirring suspension of intermediate **64** (1.22 g, 4.5 mmol) in DCM (25 mL) was treated with *tert*-butylamine (1.4 mL, 13.6 mmol). After 16 h, reaction solvents were removed and resulting solids triturated with water. Solids were dried uner vacuum overnight (1.3 g, 94%).

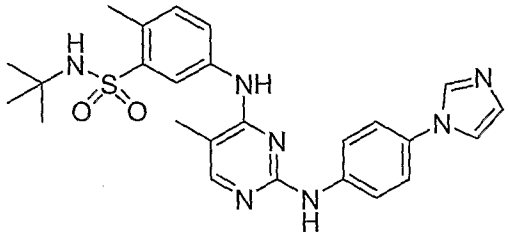
EXAMPLE 201. *N*-*tert*-Butyl-5-(2-chloro-5-methyl-pyrimidin-4-ylamino)-2-methyl-benzenesulfonamide (Intermediate 67)



67

[0401] A mixture of intermediate **66** (0.90 g, 2.96 mmol), 2-chloro-5-methyl-pyrimidin-4-ylamine (0.33 g, 2.28 mmol), $Pd_2(dba)_3$ (0.21 g, 0.23 mmol), Xantphos (0.264 g, 0.46 mmol) and cesium carbonate (2.2 g, 6.8 mmol) were suspended in dioxane (15 mL), sealed in a microwave reaction tube and irradiated with microwaves at 160 °C for 15 min. The reaction mixture was cooled to room temperature and centrifuged down. The reaction was decanted and the organic phase concentrated *in vacuo*. The residue was purified on silica gel column to afford the title compound as a white solid (0.12 g, 14%).

EXAMPLE 202 *N*-*tert*-Butyl-5-[2-(4-imidazol-1-yl-phenylamino)-5-methyl-pyrimidin-4-ylamino]-2-methyl-benzenesulfonamide (Compound CXXXVII)

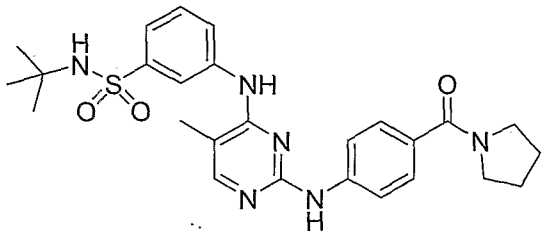


CXXXVII

[0402] A mixture of intermediate **67** (0.113 g, 0.31 mmol), 4-imidazol-1-yl-phenylamine (0.059 g, 0.37 mmol), $Pd_2(dba)_3$ (0.028 g, 0.03 mmol), Xantphos (0.036 g, 0.06 mmol) and cesium carbonate (0.3 g, 0.92 mmol) were suspended in dioxane (6 mL), sealed in a microwave reaction tube and irradiated with microwaves at 160 °C for 15 min. The reaction was decanted and the organic phase concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound as a white solid (0.052 g, 24%).

[0403] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.11 (s, 9H), 2.13 (s, 3H), 2.58 (s, 3H), 7.07 (s, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 8.9 Hz, 2H), 7.48 (s, 1H), 7.60 (s, 1H), 7.78 (d, J = 8.9 Hz, 2H), 7.94 (s, 1H), 7.98-8.00 (m, 1H), 8.09 (s, 1H), 8.12 (d, J = 2.3 Hz, 1H), 8.56 (s, 1H), 9.16 (s, 1H). MS (ES+): *m/z* 492 $(M+H)^+$.

EXAMPLE 203. *N-tert*-Butyl-3-{5-methyl-2-[4-(pyrrolidine-1-carbonyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound CXXXVIII)

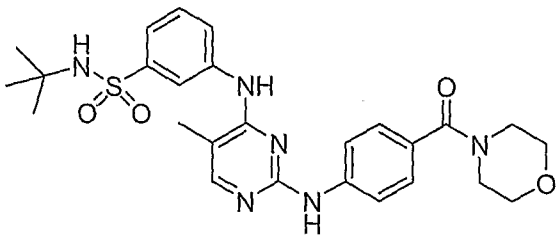


CXXXVIII

[0404] A mixture of intermediate **33** (0.11 g, 0.32 mmol), (4-amino-phenyl)-pyrrolidin-1-yl-methanone (0.072 g, 0.38 mmol), $Pd_2(dba)_3$ (0.029 g, 0.032 mmol), Xantphos (0.037 g, 0.063 mmol) and cesium carbonate (0.3 g, 0.95 mmol) were suspended in dioxane (6 mL), sealed in a microwave reaction tube and irradiated with microwaves at 160 °C for 15 min. The reaction was decanted and the organic phase concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound as a white solid (0.040 g, 25%).

[0405] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.11 (s, 9H), 1.8 (br s, 4H), 2.14 (s, 3H), 3.44 (t, J = 6.6 Hz, 4H), 7.38 (d, J = 9.0 Hz, 2H), 7.52-7.54 (m, 2H), 7.56 (s, 1H), 7.70 (d, J = 9.8 Hz, 2H), 7.98 (s, 1H), 8.08-8.10 (m, 2H), 8.60 (br s, 1H), 9.24 (s, 1H). MS (ES+): *m/z* 509 $(M+H)^+$.

EXAMPLE 204. *N-tert*-Butyl-3-{5-methyl-2-[4-(morpholine-4-carbonyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound CXXXIX)

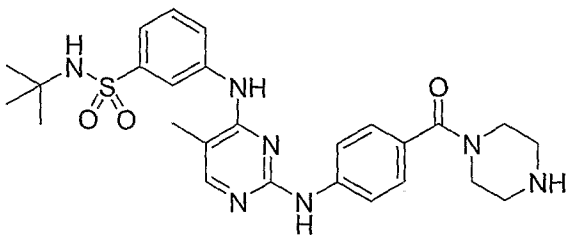


CXXXIX

[0406] A mixture of intermediate **33** (0.13 g, 0.37 mmol), (4-amino-phenyl)-morpholin-4-yl-methanone (0.092 g, 0.45 mmol), $Pd_2(dba)_3$ (0.034 g, 0.037 mmol), Xantphos (0.043 g, 0.075 mmol) and cesium carbonate (0.37 g, 1.1 mmol) were suspended in dioxane (6 mL), sealed in a microwave reaction tube and irradiated with microwaves at 160 °C for 15 min. The reaction was decanted and the organic phase concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound as a white solid (0.065 g, 33%).

[0407] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.11 (s, 9H), 2.14 (s, 3H), 3.49 (br s, 4H), 3.59 (br s, 4H), 5.75 (s, 1H), 7.25 (d, J = 9.0 Hz, 2H), 7.52-7.54 (m, 2H), 7.56 (s, 1H), 7.71 (d, J = 9.0 Hz, 2H), 7.98 (s, 1H), 8.06-8.08 (m, 2H), 8.65 (br s, 1H), 9.26 (s, 1H). MS (ES+): *m/z* 525 $(M+H)^+$.

EXAMPLE 205. *N-tert*-Butyl-3-{5-methyl-2-[4-(piperazine-1-carbonyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide (Compound CXL)



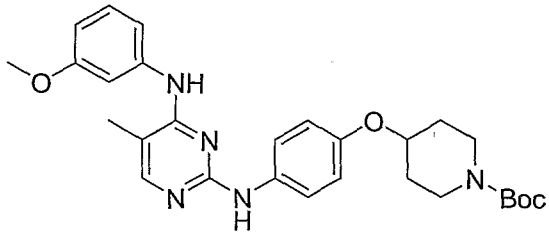
CXL

[0408] A mixture of intermediate **33** (0.12 g, 0.33 mmol), 4-(4-amino-benzoyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.12 g, 0.45 mmol), $Pd_2(dba)_3$ (0.030 g, 0.037 mmol), Xantphos (0.038 g, 0.075 mmol) and cesium carbonate (0.33 g, 1.1 mmol) were suspended in dioxane (6 mL), sealed in a microwave reaction tube and irradiated with microwaves at 160 °C for 15 min. The reaction was decanted and the organic phase concentrated *in vacuo*. The residue was purified by silica gel chromatography (25%-100% EtOAc in Hexanes). Product was then treated with 20 mL of 20% TFA solution in DCM.

Solvents then removed by rotary evaporation. Resulting material purified by HPLC to afford the title compound as a white solid (0.045 g, 26%).

[0409] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.11 (s, 9H), 2.14 (s, 3H), 2.82 (br s, 4H), 3.48 (br s, 4H), 7.24 (d, J = 9.0 Hz, 2H), 7.51-7.53 (m, 2H), 7.55 (s, 1H), 7.71 (d, J = 9.0 Hz, 2H), 7.94 (s, 1H), 8.06-8.08 (m, 2H), 8.65 (br s, 1H), 9.25 (s, 1H). MS (ES+): *m/z* 524 $(M+H)^+$.

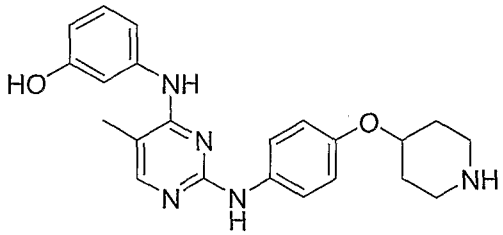
EXAMPLE 206. *tert*-Butyl 4-(4-(4-(3-methoxyphenylamino)-5-methylpyrimidin-2-ylamino)phenoxy)piperidine-1-carboxylate (Intermediate 68)



68

[0410] A mixture of 1-bromo-3-methoxybenzene (69.5 μL, 0.56 mmol), intermediate **42** (205 mg, 0.51 mmol), $Pd_2(dba)_3$ (23 mg, 0.03 mmol), Xantphos (33 mg, 0.06 mmol) and cesium carbonate (359 mg, 1.10 mmol) in dioxane (3 mL) was irradiated in the microwave at 160 °C for 20 min. The reaction mixture was cooled to room temperature, filtered and the filtrate rinsed with DCM and MeOH. The combined liquids were concentrated *in vacuo*, and purified using gradient flash chromatography (0-100% ethyl acetate in hexanes) to afford the title compound as a beige solid (215 mg, 83%).

EXAMPLE 207. 3-(2-(4-(Piperidin-4-yloxy)phenylamino)-5-methylpyrimidin-4-ylamino)phenol (Compound CXLI)



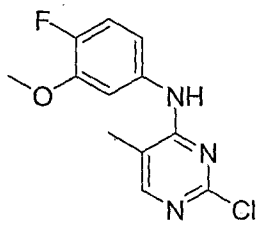
CXLI

[0411] To a mixture of intermediate **68** (215 mg, 0.42 mmol) in DCM (4 mL) was added BBr_3 (120 μL, 1.27 mmol) and stirred at room temperature for 64h. The reaction was quenched with MeOH and concentrated *in vacuo*. The residue was purified by preparative HPLC and the fractions concentrated *in vacuo* to afford the TFA salt of the title compound

(116 mg, 56%). The TFA salt was taken up in MeOH and passed through SPE PL-HCO_3 MP-Resin cartridges, concentrated *in vacuo*, triturated with ether, and filtered to provide the title compound as a white solid (31 mg, 69% recovery).

[0412] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.51-1.60 (m, 2H), 1.90-1.98 (m, 2H), 2.07 (s, 3H), 2.70-2.78 (m, 2H), 3.02-3.09 (m, 2H), 4.28-4.36 (m, 1H), 6.48 (dd, J = 8.1, 2.2 Hz ,1H), 6.79 (d, J = 9.1 Hz, 2H), 7.06-7.11 (m, 2H), 7.16 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 9.1 Hz, 2H), 7.82 (s, 1H), 8.08 (s, 1H), 8.73 (s, 1H), 9.27 (br s, 1H). MS (ES+): m/z 392 $(M+H)^+$.

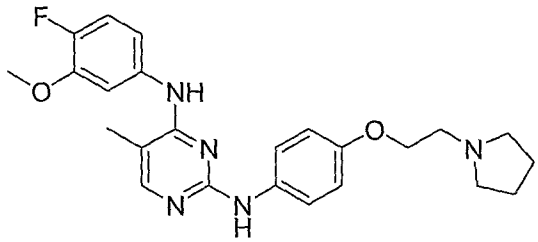
EXAMPLE 208. (2-Chloro-5-methyl-pyrimidin-4-yl)-(4-fluoro-3-methoxy-phenyl)-amine (Intermediate 69)



69

[0413] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (1.2 g, 8.1 mmol), 4-bromo-1-fluoro-2-methoxy-benzene (1.8 g, 8.9 mmol), $Pd_2(dba)_3$ (0.74 g, 0.81 mmol), Xantphos (0.93 g, 1.6 mmol) and cesium carbonate (7.88 g, 24.2 mmol) were suspended in dioxane (60 mL) and heated at reflux under the argon atmosphere for 5 h. The reaction mixture was cooled to room temperature and diluted with DCM (30 mL). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to afford the title compound (0.3 g, 14%) as a beige solid.

EXAMPLE 209. N^4-(4-Fluoro-3-methoxy-phenyl)-5-methyl-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine (Compound CXLII)

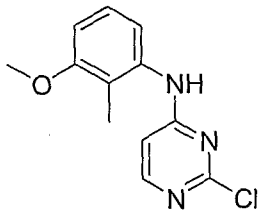


CXLII

[0414] A mixture of intermediate **69** (0.1 g, 0.37 mmol) and 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (0.16 g, 0.75 mmol) were suspended in acetic acid (10 mL) and heated to 110 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated *in*

vacuo. The residue was purified by HPLC to afford the title compound (0.03 g, 17%) as green solids. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.88 (br s, 2H), 2.0 (br s, 2H), 2.15 (s, 3H), 3.08 (br s, 2H), 3.55 (br s, 4H), 3.7 (s, 3H), 4.32 (br s, 2H), 6.9 (d, J = 7.9 Hz, 2H), 7.13 (br s, 1H), 7.21-7.25 (m, 1H), 7.32-7.34 (m, 3H), 7.89 (s, 1H), 9.78 (br s, 1H), 10.48 (br s, 1H), 10.92 (br s, 1H). MS (ES+): *m/z* 438 $(M+H)^+$.

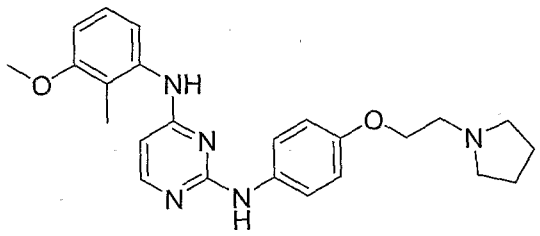
EXAMPLE 210. (2-Chloro-pyrimidin-4-yl)-(3-methoxy-2-methyl-phenyl)-amine (Intermediate 70)



70

[0415] A mixture of 3-methoxy-2-methyl-phenylamine (0.68 g, 5 mmol) and 2,4-dichloro-pyrimidine (0.74 g, 5 mmol) were suspended in ethyl alcohol (10 mL) and stirred at room temperature for 20 h. The reaction mixture was diluted with DCM (50 mL), filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to afford the title compound (0.085 g, 7%) as yellow solids.

EXAMPLE 211. N^4-(3-Methoxy-2-methyl-phenyl)-N^2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine (Compound CXLIII)



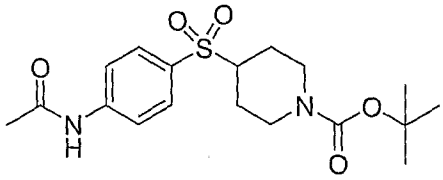
CXLIII

[0416] A mixture of intermediate **70** (0.08 g, 0.32 mmol) and 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (0.13 g, 0.64 mmol) were suspended in acetic acid (10 mL) and heated to 80 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by HPLC to afford the title compound (0.03 g, 17%) as grey solids.

[0417] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.89 (br s, 2H), 2.0 (br s, 4H), 3.08 (br s, 2H), 3.4 (br s, 4H), 3.54 (br s, 4H), 3.83 (s, 3H), 4.31 (br s, 2H), 6.86 (br s, 2H), 6.97 (d, J = 8.1

Hz, 2H), 7.26 (t, J = 8.1 Hz 1H), 7.34 (br s, 2H), 7.89 (s, 1H), 9.73 (br s, 1H), 10.62 (br s, 2H), 11.01 (br s, 1H). MS (ES+): *m/z* 420 $(M+H)^+$.

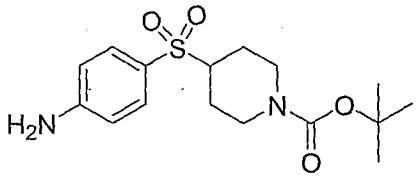
EXAMPLE 212. 4-(4-Acetylamino-benzenesulfonyl)-piperidine-1-carboxylic acid *tert*-butyl ester (Intermediate 71)



71

[0418] A mixture of 4-(4-bromo-benzenesulfonyl)-piperidine-1-carboxylic acid *tert*-butyl ester (4 g, 9.92 mmol), acetamide (0.88 g, 14.9 mmol), $Pd_2(dba)_3$ (0.46 g, 0.49 mmol), Xantphos (0.56 g, 0.99 mmol) and cesium carbonate (9.7 g, 29.8 mmol) were suspended in dioxane (60 mL) and heated at reflux under the argon atmosphere for 4 h. The reaction mixture was cooled to room temperature and poured onto ice. Resulting yellow solids collected by filtration and dried. Crude product was purified by flash chromatography on silica gel to afford the title compound as a beige solid (3.12 g, 82%).

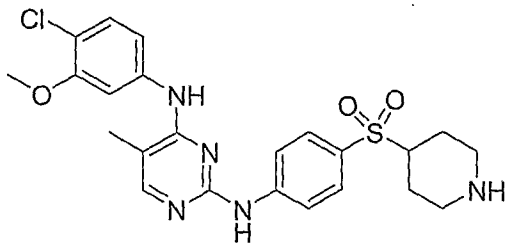
EXAMPLE 213. 4-(4-Amino-benzenesulfonyl)-piperidine-1-carboxylic acid *tert*-butyl ester (Intermediate 72)



72

[0419] A suspension of intermediate **71** (2.6 g, 6.7 mmol) was diluted with 60 mL of Claisen's alkali (88 g KOH dissolved in 63 mL H_2O diluted up to 250 mL with MeOH) and heated to 90 °C. After 2 h, reaction was removed from heating, cooled to room temperature and diluted with water (50 mL). Grey solids collected by suction filtration, washed with water and dried overnight (2.2 g, 97%).

EXAMPLE 214. N^4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N^2-[4-(piperidine-4-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (Compound CXLIV)

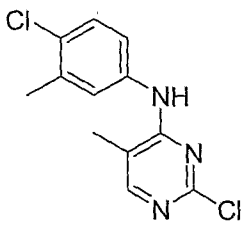


CXLIV

[0420] A mixture of intermediate **31** (0.14 g, 0.51 mmol), intermediate **72** (0.19 g, 0.56 mmol), $Pd_2(dba)_3$ (0.046 g, 0.051 mmol), Xantphos (0.59 g, 0.1 mmol) and cesium carbonate (0.5 g, 1.52 mmol) were suspended in dioxane (8 mL) and microwaved at 160 °C for 15 min. The reaction mixture was cooled to room temperature and centrifuged down. Solvents were then decanted and evaporated. Resulting residue was purified by flash chromatography on silica gel to afford the *N*-protected precursor of title compound. These solids were treated with 20% TFA in DCM solution and immediately evaporated. Residue was dissolved in minimum amount to EtOAc and added dropwise to large excess of diethyl ether. Resulting light yellow powder was collected by filtration and dried (0.16 g, 55%).

[0421] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.61-1.69 (m, 2H), 1.98-2.01 (m, 2H), 2.16 (s, 3H), 2.86 (q, J = 12 Hz, 2H), 3.35 (d, J = 12.6 Hz, 2H), 3.64 (tt, J = 11.7 Hz, J = 3.8 Hz, 1H), 3.79 (s, 3H), 7.34 (dd, J = 8.7 Hz, J = 2.0 Hz, 1H), 7.39-7.41 (m, 2H), 7.6 (d, J = 8.9 Hz, 2H), 7.91 (d, J = 8.9 Hz, 2H), 8.02 (s, 1H), 8.19-8.21 (m, 1H), 8.6-8.63 (m, 1H), 8.89 (br s, 1H). MS (ES+): *m/z* 488 $(M+H)^+$.

EXAMPLE 215. (4-Chloro-3-methyl-phenyl)-(2-chloro-5-methyl-pyrimidin-4-yl)-amine (Intermediate 73)

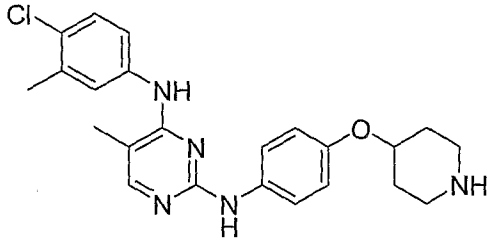


73

[0422] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.34 g, 2.34 mmol), 4-bromo-1-chloro-2-methyl-benzene (0.58 g, 2.8 mmol), $Pd_2(dba)_3$ (0.21 g, 0.23 mmol), Xantphos (0.47 g, 0.47 mmol) and cesium carbonate (2.3 g, 7 mmol) were suspended in

dioxane (9 mL) microwaved at 160 °C for 20 min. The reaction mixture was cooled to room temperature and centrifuged down. Solvents were then decanted and evaporated. Resulting residue was purified by flash chromatography on silica gel to afford title compound as yellow solids (0.24 g, 38%).

EXAMPLE 216. N^4-(4-Chloro-3-methyl-phenyl)-5-methyl-N^2-[4-(piperidin-4-yloxy)-phenyl]-pyrimidine-2,4-diamine (Compound CXLV)

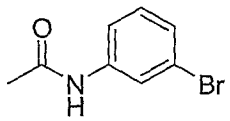


CXLV

[0423] A mixture of intermediate **73** (0.071 g, 0.27 mmol) and 4-(4-amino-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (0.1 g, 0.35 mmol) were diluted with HOAc (5 mL) and microwaved at 150 °C for 15 min. Solvents then removed and resulting residue purified on HPLC. Title compound isolated as white solids (0.025 g, 22%).

[0424] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.76-1.83 (m, 2H), 2.05-2.09 (m, 2H), 2.13 (s, 3H), 2.27 (s, 3H), 3.10 (br s, 2H), 3.16 (br s, 2H), 4.58-4.61 (m, 1H), 6.93 (d, J = 9 Hz, 2H), 7.34-7.39 (m, 3H), 7.43-7.45 (m, 1H), 7.59 (s, 1H), 7.87 (s, 1H), 8.51 (br s, 1H), 8.55 (br s, 1H), 9.38 (br s, 1H), 10.0 (br s, 1H). MS (ES+): *m/z* 424 $(M+H)^+$.

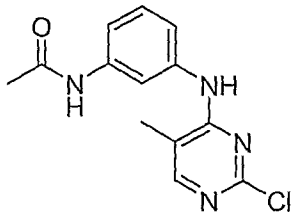
EXAMPLE 217. *N*-(3-Bromo-phenyl)-acetamide (Intermediate 74)



74

[0425] A solution of 3-bromo-phenylamine (1.04 g, 6 mmol) was treated with DIEA (2.3 mL, 13.3 mmol) and chilled to zero degrees. Acetyl chloride (0.47 mL, 6.7 mmol) was added dropwise via syringe. Reaction was allowed to return to room temperature and stir for 1 hour. Reaction was then poured onto water and washed once. Organic phase was evaporated to beige solids (1.25 g, 98%).

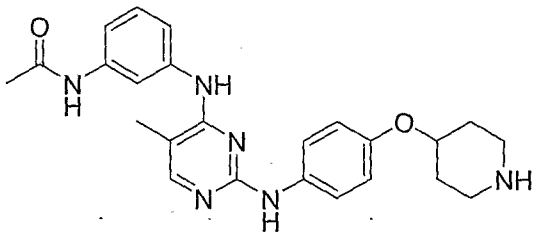
EXAMPLE 218. *N*-[3-(2-Chloro-5-methyl-pyrimidin-4-ylamino)-phenyl]-acetamide (Intermediate 75)



75

[0426] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.71 g, 4.9 mmol), intermediate **74** (1.25 g, 5.9 mmol), $Pd_2(dba)_3$ (0.45 g, 0.49 mmol), Xantphos (0.57 g, 0.98 mmol) and cesium carbonate (4.8 g, 14.7 mmol) were suspended in dioxane (40 mL) refluxed for 18 h. The reaction mixture was then cooled to room temperature, filtered and solvents evaporated. Resulting residue was purified by flash chromatography on silica gel to afford title compound as white solids (0.44, 32%).

EXAMPLE 219. *N*-(3-{5-Methyl-2-[4-(piperidin-4-yloxy)-phenylamino]-pyrimidin-4-ylamino}-phenyl)-acetamide (Compound CXLVI)

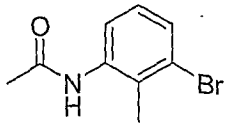


CXLVI

[0427] A mixture of intermediate **75** (0.074 g, 0.27 mmol) and 4-(4-amino-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (0.1 g, 0.35 mmol) were diluted with HOAc (5 mL) and microwaved at 150 °C for 15 min. Solvents then removed and resulting residue purified on HPLC. Title compound isolated as white solids (0.072 g, 62%).

[0428] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.74-1.81 (m, 2H), 2.03-2.07 (m, 5H), 2.15 (s, 3H), 3.09 (br s, 2H), 3.24 (br s, 2H), 4.54-4.57 (m, 1H), 6.85 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 7.7 Hz, 2H), 7.29-7.39 (m, 4H), 7.77 (s, 1H), 7.87 (s, 1H), 8.55 (br s, 1H), 8.60 (br s, 1H), 9.67 (s, 1H), 10.0 (br s, 1H), 10.2 (br s, 1H). MS (ES+): *m/z* 433 $(M+H)^+$.

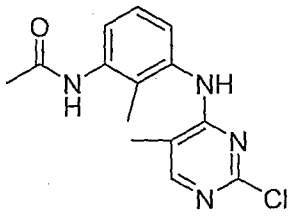
EXAMPLE 220. *N*-(3-Bromo-2-methyl-phenyl)-acetamide (Intermediate 76)



76

[0429] A solution of 3-bromo-2-methyl-phenylamine (4.1 g, 21.9 mmol) was treated with DIEA (8.4 mL, 48 mmol) and chilled to zero degrees. Acetyl chloride (1.7 mL, 24.1 mmol) was added dropwise via syringe. Reaction was allowed to return to room temperature and stir for 1 hour. Reaction was then poured onto water and washed once. Organic phase was evaporated to off-white solids. Trituration with hexanes afforded title compound as white solids (4.4 g, 89%).

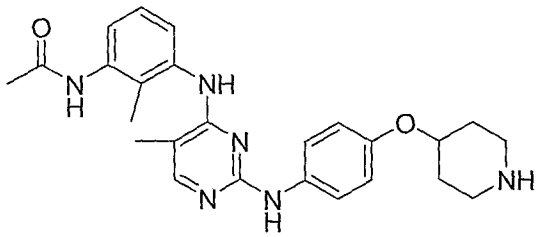
EXAMPLE 221. *N*-[3-(2-Chloro-5-methyl-pyrimidin-4-ylamino)-2-methyl-phenyl]-acetamide (Intermediate 77)



77

[0430] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.86 g, 5.9 mmol), intermediate **76** (1.6 g, 7.1 mmol), $Pd_2(dba)_3$ (0.55 g, 0.59 mmol), Xantphos (0.69 g, 1.2 mmol) and cesium carbonate (5.8 g, 17.8 mmol) were suspended in dioxane (40 mL) refluxed for 16 h. The reaction mixture was then cooled to room temperature, filtered and solvents evaporated. Resulting residue was purified by flash chromatography on silica gel to afford title compound as white solids (0.56 g, 32%).

EXAMPLE 222. *N*-(2-Methyl-3-{5-methyl-2-[4-(piperidin-4-yloxy)-phenylamino]-pyrimidin-4-ylamino}-phenyl)-acetamide (Compound CXLVII)

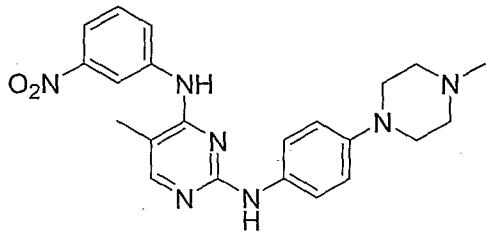


CXLVII

[0431] A mixture of intermediate **77** (0.15 g, 0.5 mmol) and 4-(4-Amino-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (0.19 g, 0.65 mmol) were diluted with HOAc (5 mL) and microwaved at 150 °C for 15 min. Solvents then removed and resulting residue purified on HPLC. Title compound isolated as white solids (0.091 g, 41%).

[0432] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.71-1.78 (m, 2H), 2.02-2.08 (m, 8H), 2.16 (s, 3H), 3.09 (br s, 2H), 3.24 (br s, 2H), 4.50-4.52 (m, 1H), 6.77 (d, J = 8.4 Hz, 2H), 7.09-7.15 (m, 3H), 7.27 (t, J = 7.9 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.86 (s, 1H), 8.54 (br s, 1H), 8.59 (br s, 1H), 9.45 (s, 1H), 9.84 (br s, 1H), 10.34 (br s, 1H). MS (ES+): *m/z* 447 $(M+H)^+$.

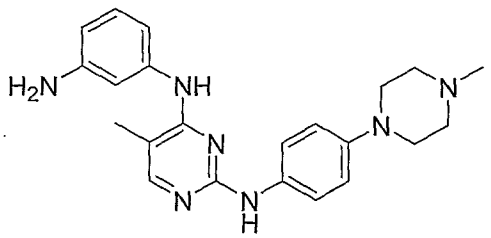
EXAMPLE 223. 5-Methyl-N^2-[4-(4-methyl-piperazin-1-yl)-phenyl]-N^4-(3-nitro-phenyl)-pyrimidine-2,4-diamine (Intermediate 78)



78

[0433] A mixture of 1-bromo-3-nitro-benzene (0.77 g, 3.8 mmol), intermediate **32** (0.95 g, 3.2 mmol), $Pd_2(dba)_3$ (0.29 g, 0.32 mmol), Xantphos (0.37 g, 0.64 mmol) and cesium carbonate (3.1 g, 9.6 mmol) were suspended in dioxane (40 mL) refluxed for 16 h. The reaction mixture was then cooled to room temperature, filtered and solvents evaporated. Resulting residue was purified by flash chromatography on silica gel to afford title compound as white solids (0.53 g, 40%).

EXAMPLE 224. N^4-(3-Amino-phenyl)-5-methyl-N^2-[4-(4-methyl-piperazin-1-yl)-phenyl]-pyrimidine-2,4-diamine (Intermediate 79)

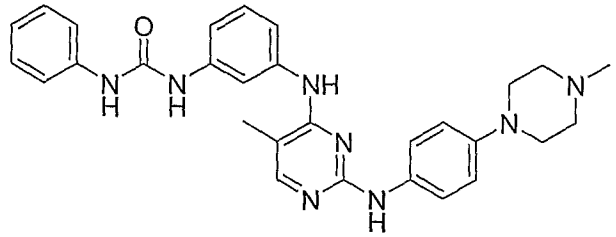


79

[0434] Slurry of intermediate **78** (0.23 g, 0.54 mmol) in MeOH (25 mL) was purged with argon and treated with Pd/C 10% wt. (0.18 g). Reaction atmosphere was replaced with hydrogen and stirred for 4 h. Hydrogen balloon was then removed and argon was flushed

through reaction before filtration through Celite. Solvents were then evaporated to pale brown solids (0.17 g, 83%).

EXAMPLE 225. 1-(3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-phenyl)-3-phenyl-urea (Compound CXLVIII)

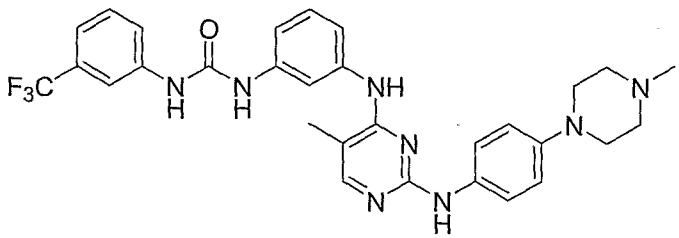


CXLVIII

[0435] A suspension of intermediate **79** (0.17 g, 0.45 mmol) in DCM (10 mL) was treated with phenyl isocyanate (0.058 mL, 0.54 mmol) and stirred for 1 hour. Reaction solvents then removed and resulting residue purified by HPLC to provide title compound as white solids (0.075 g, 33%).

[0436] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.09 (s, 3H), 2.15 (s, 3H), 2.30-2.32 (m, 4H), 2.92-2.94 (m, 4H), 6.74 (d, J = 8.4 Hz, 2H), 6.94-6.97 (m, 1H), 7.19-7.28 (m, 5H), 7.45 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 9.0 Hz, 2H), 7.73 (br s, 1H), 7.83 (s, 1H), 8.23 (s, 1H), 8.68 (s, 1H), 8.74 (s, 1H), 8.78 (s, 1H). MS (ES+): *m/z* 509 $(M+H)^+$.

EXAMPLE 226. 1-(3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-phenyl)-3-(3-trifluoromethyl-phenyl)-urea (Compound CXLIX)



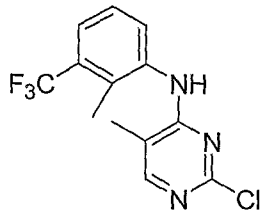
CXLIX

[0437] A suspension of intermediate **79** (0.1 g, 0.26 mmol) in DCM (8 mL) was treated with 1-isocyanato-3-trifluoromethyl-benzene (0.043 mL, 0.31 mmol) and stirred for 1 hour. Reaction solvents then removed and resulting residue purified by HPLC to provide title compound as white solids (0.039 g, 26%).

[0438] ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.16 (s, 3H), 2.82 (s, 3H), 2.86 (br s, 2H), 3.08 (br s, 2H), 3.42 (br s, 2H), 3.69 (br s, 2H), 6.88 (d, J = 8.4 Hz, 2H), 7.20 (br s, 1H), 7.29-7.33

(m, 5H), 7.52 (t, J = 7.9 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H), 7.84 (s, 1H), 8.09 (s, 1H), 9.42 (s, 1H), 9.66 (s, 1H), 9.71 (br s, 1H), 10.1 (br s, 1H). MS (ES+): *m/z* 577 $(M+H)^+$.

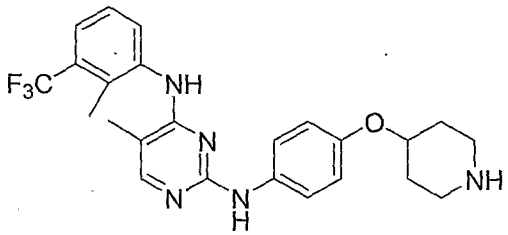
EXAMPLE 227. (2-Chloro-5-methyl-pyrimidin-4-yl)-(2-methyl-3-trifluoromethyl-phenyl)-amine (Intermediate 80)



80

[0439] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.18 g, 5.9 mmol), 1-bromo-2-methyl-3-trifluoromethyl-benzene (0.33 g, 1.4 mmol), $Pd_2(dba)_3$ (0.12 g, 0.13 mmol), Xantphos (0.15 g, 0.25 mmol) and cesium carbonate (1.23 g, 3.8 mmol) were suspended in dioxane (8 mL) microwaved at 160 °C for 18 min. Reaction vessel was then centrifuged down and decanted. Solvents then evaporated and resulting residue was purified by flash chromatography on silica gel to afford title compound as white solids (0.095 g, 25%).

EXAMPLE 228. 5-Methyl-N^4-(2-methyl-3-trifluoromethyl-phenyl)-N^2-[4-(piperidin-4-yloxy)-phenyl]-pyrimidine-2,4-diamine (Compound CL)



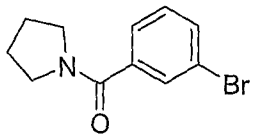
CL

[0440] A mixture of intermediate **80** (0.058 g, 0.2 mmol) and 4-(4-amino-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (0.073 g, 0.25 mmol) were diluted with HOAc (5 mL) and microwaved at 150 °C for 15 min. Solvents then removed and resulting residue purified on HPLC. Title compound isolated as white solids (0.025 g, 30%).

[0441] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.71-1.78 (m, 2H), 2.00-2.04 (m, 2H), 2.18 (s, 3H), 2.25 (s, 3H), 3.08 (br s, 2H), 3.22 (br s, 2H), 4.50-4.52 (m, 1H), 6.70 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.9 Hz, 2H), 7.54 (t, J = 7.8, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 7.8

Hz, 1H), 7.91 (s, 1H), 8.54 (br s, 1H), 8.61 (br s, 1H), 9.88 (s, 1H), 10.34 (br s, 1H). MS (ES+): *m/z* 458 $(M+H)^+$.

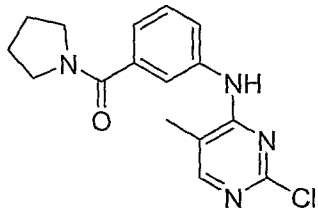
EXAMPLE 229. (3-Bromo-phenyl)-pyrrolidin-1-yl-methanone (Intermediate 81)



81

[0442] A solution of 3-bromo-benzoyl chloride (2.7 g, 12 mmol) in DCM (40 mL) was chilled to zero degrees and treated with pyrrolidine (3 mL, 36.8 mmol). Reaction was allowed to come to room temperature and stir for 4 h. Mixture was then poured onto water and washed once. Organic phase then washed with brine, dried over sodium sulfate, filtered and evaporated to amber oil (3.1g, 100%).

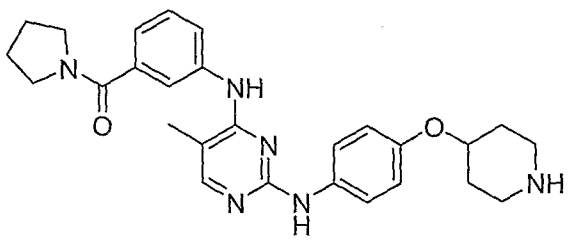
EXAMPLE 230. [3-(2-Chloro-5-methyl-pyrimidin-4-ylamino)-phenyl]-pyrrolidin-1-yl-methanone (Intermediate 82)



82

[0443] A mixture of 2-chloro-5-methyl-pyrimidin-4-ylamine (0.22 g, 1.5 mmol), intermediate **81** (0.46 g, 1.8 mmol), $Pd_2(dba)_3$ (0.14 g, 0.15 mmol), Xantphos (0.17 g, 0.3 mmol) and cesium carbonate (1.5 g, 4.5 mmol) were suspended in dioxane (8 mL) microwaved at 160 °C for 18 min. Reaction vessel was then centrifuged down and decanted. Solvents then evaporated and resulting residue was purified by flash chromatography on silica gel to afford title compound as white solids (0.25 g, 53%).

EXAMPLE 231. (3-{5-Methyl-2-[4-(piperidin-4-yloxy)-phenylamino]-pyrimidin-4-ylamino}-phenyl)-pyrrolidin-1-yl-methanone (Compound CLI)

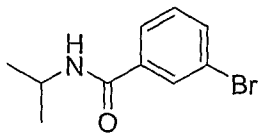


CLI

[0444] A mixture of intermediate **82** (0.1 g, 0.32 mmol) and 4-(4-amino-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (0.12 g, 0.41 mmol) were diluted with HOAc (6 mL) and microwaved at 150 °C for 15 min. Solvents then removed and resulting residue purified on HPLC. Title compound isolated as white solids (0.005 g, 3%).

[0445] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.74-1.81 (m, 4H), 1.83-1.88 (m, 2H), 2.05-2.09 (m, 2H), 2.16 (s, 3H), 2.25 (s, 3H), 3.25 (br s, 2H), 3.34 (t, J = 6.5 Hz, 2H), 3.46 (t, J = 6.9 Hz, 2H), 4.45-4.59 (m, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.9 Hz, 2H), 7.36 (d, J = 7.7 Hz, 1H), 7.43 (t, J = 7.8, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.70 (s, 1H), 7.89 (s, 1H), 8.50 (br s, 1H), 8.56 (br s, 1H), 9.64 (br s, 1H), 10.21 (br s, 1H). MS (ES+): *m/z* 473 $(M+H)^+$.

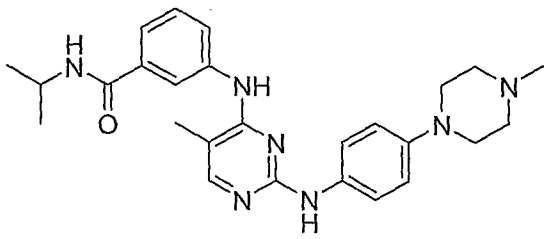
EXAMPLE 232. 3-Bromo-*N*-isopropyl-benzamide (Intermediate 83)



83

[0446] A solution of 3-bromo-benzoyl chloride (0.83 g, 3.8 mmol) in DCM (40 mL) was chilled to zero degrees and treated with isopropylamine (0.96 mL, 11.32 mmol). Reaction was allowed to come to room temperature and stir for 24 h. Mixture was then poured onto water and washed once. Organic phase then washed with brine, dried over sodium sulfate, filtered and evaporated to white solids (0.6 g, 66%).

EXAMPLE 233. *N*-Isopropyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzamide (Compound CLII)



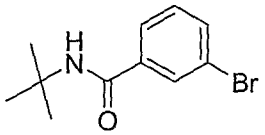
CLII

[0447] A mixture of intermediate **32** (0.1 g, 0.34 mmol), intermediate **83** (0.13 g, 0.54 mmol), $Pd_2(dba)_3$ (0.031 g, 0.034 mmol), Xantphos (0.039 g, 0.067 mmol) and cesium carbonate (0.33 g, 1 mmol) were suspended in dioxane (8 mL) microwaved at 160 °C for 15 min. Reaction vessel was then centrifuged down and decanted. Solvents then evaporated and

resulting residue was purified by HPLC to afford title compound as white solids (0.011 g, 7%).

[0448] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.14 (d, J = 6.7 Hz, 6H), 2.16 (s, 4H), 2.87 (s, 4H), 3.10 (br s, 2H), 3.51 (s, 2H), 4.22 (m, 1H), 6.85 (d, J = 8.8 Hz, 2H), 7.30-7.32 (m, 2H), 7.45 (t, J = 7.8 Hz, 1H), 7.69-7.70 (m, 2H), 7.90 (s, 1H), 7.99 (s, 1H), 8.24 (d, J = 7.7 Hz, 1H), 9.70 (br s, 1H), 9.94 (br s, 1H), 10.2 (br s, 1H). MS (ES+): *m/z* 460 $(M+H)^+$.

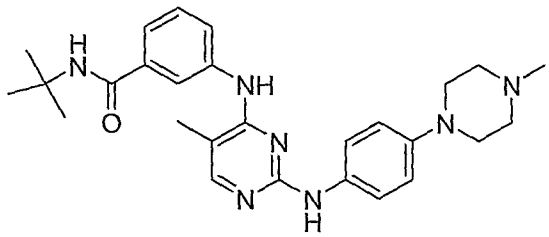
EXAMPLE 234. 3-Bromo-*N*-*tert*-butyl-benzamide (Intermediate 84)



84

[0449] A solution of 3-bromo-benzoyl chloride (0.83 g, 3.8 mmol) in DCM (10 mL) was chilled to zero degrees and treated with *tert*-butylamine (1.2 mL, 11.3 mmol). Reaction was allowed to come to room temperature and stir for 4 h. Mixture was then poured onto water and washed once. Organic phase then washed with brine, dried over sodium sulfate, filtered and evaporated to amber oil (0.9 g, 94%).

EXAMPLE 235. *N*-tert-Butyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzamide (Compound CLIII)



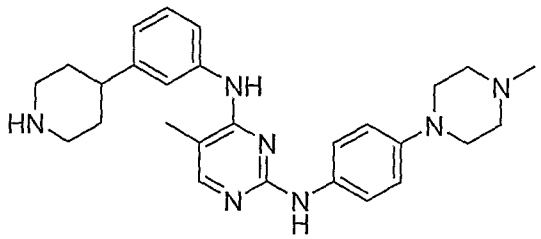
CLIII

[0450] A mixture of intermediate **32** (0.1 g, 0.34 mmol), intermediate **84** (0.1 g, 0.4 mmol), $Pd_2(dba)_3$ (0.031 g, 0.034 mmol), Xantphos (0.039 g, 0.067 mmol) and cesium carbonate (0.33 g, 1 mmol) were suspended in dioxane (8 mL) microwaved at 160 °C for 15 min. Reaction vessel was then centrifuged down and decanted. Solvents then evaporated and resulting residue was purified by HPLC to afford title compound as white solids (0.055 g, 35%).

[0451] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.36 (s, 9H), 2.09 (s, 3H), 2.21 (s, 3H), 2.43 (t, J = 2.8 Hz, 4H), 3.00 (t, J = 2.8 Hz, 4H), 6.74 (d, J = 9.1 Hz, 2H), 7.35 (t, J = 7.9 Hz, 1H),

7.44-7.48 (m, 3H), 7.67 (s, 1H), 7.85 (s, 1H), 7.88-7.92 (m, 2H), 8.36 (s, 1H), 8.74 (s, 1H). MS (ES+): *m/z* 474 $(M+H)^+$.

EXAMPLE 236. 5-Methyl-N^2-[4-(4-methyl-piperazin-1-yl)-phenyl]-N^4-(3-piperidin-4-yl-phenyl)-pyrimidine-2,4-diamine (Compound CLIV)

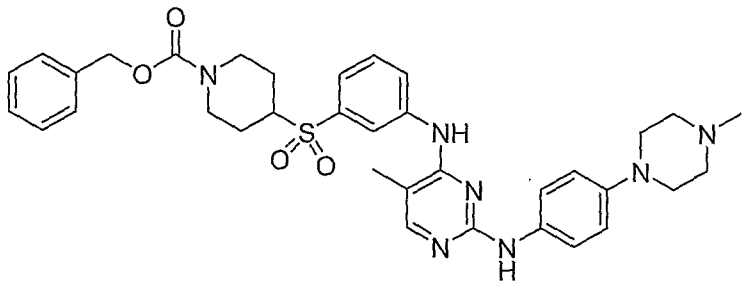


CLIV

[0452] A mixture of intermediate **32** (0.08 g, 0.27 mmol), 4-(3-bromo-phenyl)-piperidine (0.084 g, 0.35 mmol), $Pd_2(dba)_3$ (0.025 g, 0.027 mmol), Xantphos (0.031 g, 0.054 mmol) and cesium carbonate (0.26 g, 0.81 mmol) were suspended in dioxane (8 mL) microwaved at 160 °C for 15 min. Reaction vessel was then centrifuged down and decanted. Solvents then evaporated and resulting residue was purified by HPLC to afford title compound as white solids (0.007 g, 6%).

[0453] ^1H NMR (500 MHz, DMSO-d_6): δ 1.74-1.79 (m, 3H), 2.09 (s, 3H), 2.21 (s, 3H), 2.43 (t, J = 2.8 Hz, 4H), 3.00 (t, J = 2.8 Hz, 4H), 6.76 (d, J = 9.1 Hz, 2H), 6.90 (d, J = 7.7 Hz, 1H), 7.24 (t, J = 7.9 Hz, 1H), 7.47-7.53 (m, 3H), 7.68 (d, J = 8.2 Hz, 1H), 7.82 (s, 1H), 8.18 (s, 1H), 8.67 (s, 1H). MS (ES+): *m/z* 458 $(M+H)^+$.

EXAMPLE 237. 4-(3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonyl)-piperidine-1-carboxylic acid benzyl ester (Intermediate 85)

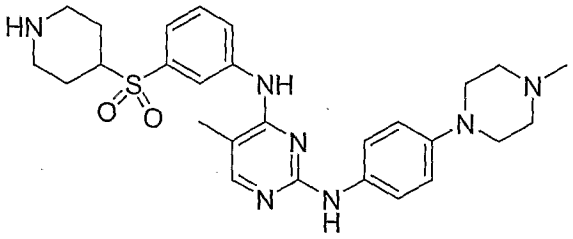


85

[0454] A mixture of intermediate **32** (0.17 g, 0.58 mmol), 4-(3-bromo-benzenesulfonyl)-piperidine-1-carboxylic acid benzyl ester (0.28 g, 0.64 mmol), $Pd_2(dba)_3$ (0.053 g, 0.058 mmol), Xantphos (0.067 g, 0.12 mmol) and cesium carbonate (0.57 g, 1.74 mmol) were

suspended in dioxane (8 mL) microwaved at 160 °C for 15 min. Reaction vessel was then centrifuged down and decanted onto ice. Yellow solids collected, dried and used without further purification (0.4 g, 100%).

EXAMPLE 238. 5-Methyl-N^2-[4-(4-methyl-piperazin-1-yl)-phenyl]-N^4-[3-(piperidine-4-sulfonyl)-phenyl]-pyrimidine-2,4-diamine (Compound CLV)

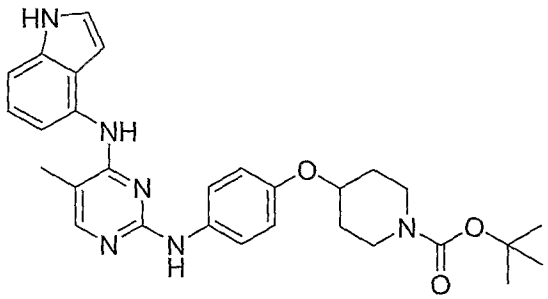


CLV

[0455] A stirring solution of intermediate **85** (0.17 g, 0.26 mmol) in DCM (15 mL) was treated with 1M BBr_3 in DCM (2 mL, 2 mmol). After 4 h, reaction was quenched by slow addition of MeOH (4 mL) followed by removal of solvents. Residue purified by HPLC to provide title compound as purple powder (0.008 g, 6%).

[0456] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.31-1.40 (m, 2H), 1.75 (d, J = 10.8 Hz, 2H), 2.12 (s, 3H), 2.21 (s, 3H), 2.36-2.41 (m, 2H), 2.44 (t, J = 4.9 Hz, 4H), 2.95 (d, J = 12.5 Hz, 2H), 3.02 (t, J = 4.9 Hz, 4H), 3.24 (tt, J = 11.7 Hz, J = 3.8 Hz, 1H), 6.81 (d, J = 9.0 Hz, 2H), 7.44 (m, 3H), 7.56 (t, J = 8.0 Hz, 1H), 7.90-7.91 (m, 2H), 8.49 (d, J = 7.6 Hz, 1H), 8.60 (s, 1H), 8.74 (s, 1H). MS (ES+): *m/z* 522 $(M+H)^+$.

EXAMPLE 239. *tert*-Butyl 4-(4-(4-(1*H*-indol-4-ylamino)-5-methylpyrimidin-2-ylamino)phenoxy)piperidine-1-carboxylate (Intermediate 86)

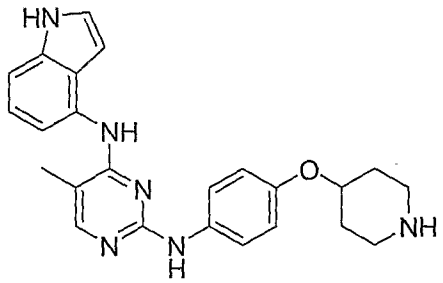


86

[0457] A mixture of 4-bromo-1*H*-indole (41 μL, 0.33 mmol), intermediate **42** (131 mg, 0.33 mmol), $Pd_2(dba)_3$ (30 mg, 0.03 mmol), Xantphos (60 mg, 0.10 mmol) and cesium carbonate (428 mg, 1.31 mmol) in dioxane (3 mL) was irradiated in the microwaved at 160

°C for 20 min. The reaction mixture was cooled to room temperature and filtered rinsing with DCM. The filtrate was concentrated and purified by gradient flash chromatography (0-15% MeOH in DCM) to afford the title compound as a white solid (30 mg, 17%).

EXAMPLE 240. N^4-(1*H*-Indol-4-yl)-5-methyl-N^2-(4-(piperidin-4-yloxy)phenyl)pyrimidine-2,4-diamine (Compound CLVI)

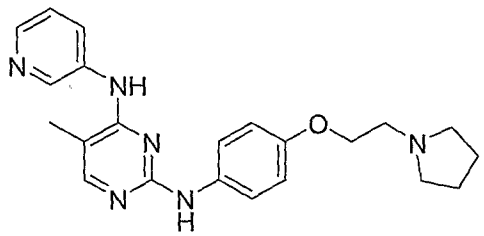


CLVI

[0458] A mixture of intermediate **86** (27 mg, 0.05 mmol) in 30% TFA/DCM (1 mL) was stirred for 3 h. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC. The resulting fractions were concentrated *in vacuo* to obtain the TFA salt of the title compound as a tan solid (11 mg, 43%).

[0459] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.71-1.77 (m, 2H), 1.98-2.06 (m, 2H), 2.22 (s, 3H), 3.03-3.12 (m, 2H), 3.19-3.27 (m, 2H), 4.44-4.53 (m, 1H), 6.34-6.37 (m, 1H), 6.64 (br d, J = 8.3 Hz, 2H), 7.08 (t, J = 7.2 Hz, 3H), 7.14 (t, J = 7.8 Hz, 1H), 7.36 (t, J = 2.7 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.84 (s, 1H), 8.48 (br s, 1H), 8.55 (br s, 1H), 9.85 (br s, 1H), 9.98 (br s, 1H), 11.27 (s, 1H).

EXAMPLE 241. 2-Chloro-*N*-{2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-5-yl}-5 (3-trifluoromethyl-benzoylamino)-benzamide (Compound CLVII)



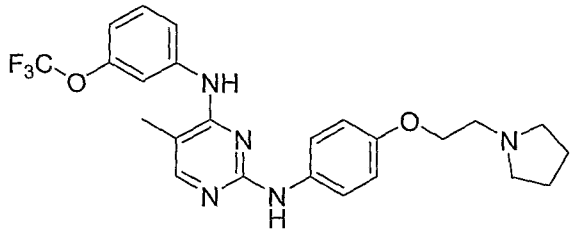
CLVII

[0460] A mixture of 3-bromopyridine (379 mg, 2.4 mmol), 4-amino-2-chloro-5-methylpyrimidine (287 mg, 2.0 mmol), $Pd_2(dba)_3$ (18 mg, 0.02 mmol), xantphos (23 mg, 0.04 mmol) and cesium carbonate (975 mg, 3.0 mmol) in dioxane (15 mL) was heated under refluxed for 1 h under argon. The solvent was removed and the residue on purification by

HPLC gave an intermediate, 2-chloro-5-methyl-*N*-(pyridin-3-yl)pyrimidin-4-amine as yellow solid (252 mg, 57%). For second Buckwald, a mixture of 2-chloro-5-methyl-*N*-(pyridin-3-yl)pyrimidin-4-amine (80 mg, 0.36 mmol), 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (74 mg, 0.34 mmol), $Pd_2(dba)_3$ (3.2 mg, 0.003 mmol), xantphos (4.2 mg, 0.007 mmol) and cesium carbonate (234 mg, 0.72 mmol) in dioxane (5 mL) was heated under refluxed for 1 h under argon. The crude reaction mixture on purification using HPLC gave the title compound as light brown solid (28 mg, 20%).

[0461] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.85-1.95 (m, 2H), 2.0-2.09 (m, 2H), 2.18 (s, 3H), 3.09-3.18 (m, 2H), 3.55-3.65 (m, 4H), 4.27 (dd, J = 5.2, 4.7 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 7.35 (d, J = 8.9 Hz, 2H), 7.50 (dd, J = 8.2, 4.8 Hz, 1H),7.92-7.96 (m, 1H), 8.08-8.15 (m, 1H), 8.45 (dd, J = 4.8, 1.4, 1H), 8.84, 9.75, 9.85, 10.24 (4 br s, 1H each). MS (ES+): *m/z* 329 $(M+H)^+$.

EXAMPLE 242. N^2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-5-methyl-N^4-(3-(trifluoromethoxy)phenyl) pyrimidine-2,4-diamine (Compound CLVIII)



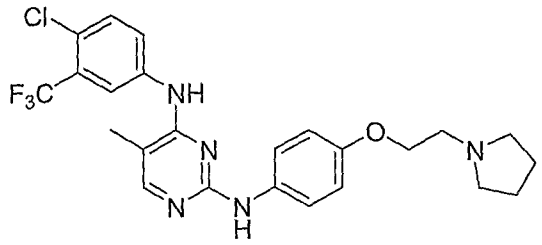
CLVIII

[0462] A mixture of 1-bromo-3-(trifluoromethoxy)benzene (241 mg, 1.0 mmol), 4-amino-2-chloro-5-methylpyrimidine (143 mg, 1.0 mmol), $Pd_2(dba)_3$ (9 mg, 0.01 mmol), xantphos (14 mg, 0.02 mmol) and cesium carbonate (650 mg, 2.0 mmol) in dioxane (15 mL) was heated under refluxed for 10 h under argon. The solvent was removed and the residue on purification by HPLC gave an intermediate, 2-chloro-5-methyl-*N*-(pyridin-3-yl)pyrimidin-4-amineas brown solid (260 mg, 85 %). A mixture of this intermediate (100 mg, 0.33 mmol) and 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (67 mg, 0.33 mmol) in glacial acetic acid (5 mL) was heated under refluxed for 3 h under argon. The crude reaction mixture on purification using HPLC gave the title compound as white solid (11 mg, 7 %).

[0463] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.65-1.72 (m, 4H), 2.11 (s, 3H), 2.51-2.55 (m, 2H, superimposed with solvent peak), 2.75 (t, J = 5.9 Hz, 2H), 3.25-3.34 (m, 2H, superimposed with water peak), 3.99 (t, J = 5.9 Hz, 2H), 6.79 (d, J = 8.9 Hz, 2H), 6.98 (d, J =

8.0 Hz, 1H), 7.40 (dd, J = 7.6, 7.4 Hz, 1H), 7.50 (d, J = 8.9 Hz, 2H), 7.76 (br s, 1H), 7.87 (d, J = 8.4 1H), 7.90, 8.31, 8.41, 8.84 (4 s, 1H each). MS (ES+): *m/z* 474 $(M+H)^+$.

EXAMPLE 243. N^2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N^4-(4-chloro-3-(trifluoromethyl)phenyl)-5-methylpyrimidine-2,4-diamine (Compound CLIX)



CLIX

[0464] A mixture of 4-bromo-1-chloro-2-(trifluoromethyl)benzene (259 mg, 1.0 mmol), 4-amino-2-chloro-5-methylpyrimidine (143 mg, 1.0 mmol), $Pd_2(dba)_3$ (9 mg, 0.01 mmol), xantphos (14 mg, 0.02 mmol) and cesium carbonate (650 mg, 2.0 mmol) in dioxane (15 mL) was heated under refluxed for 10 h under argon. The solvent was removed and the residue was purified by HPLC to give an intermediate 2-chloro-*N*-(4-chloro-3-(trifluoromethyl) phenyl)-5-methylpyrimidin-4-amine as brown solid (200 mg, 62 %). A mixture of this intermediate (161 mg, 0.5 mmol) and 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (103 mg, 0.5 mmol) in glacial acetic acid (5 mL) was heated under refluxed for 3 h under argon. The crude reaction mixture on purification using HPLC gave the title compound as brown solid (75 mg, 31 %).

[0465] ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.65-1.72 (m, 4H), 2.10 (s, 3H), 2.51-2.55 (m, 4H, superimposed with solvent peak), 2.75 (t, J = 6.0 Hz, 2H), 4.0 (t, J = 5.9 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 9.0 Hz, 2H), 7.58 (d, J = 9.0 Hz, 2H), 7.93 (s, 1H), 8.01 (d, J = 2.5 Hz, 1H), 8.22 (d, J = 8.5 Hz, 2H), 8.60, 8.88 (2 s, 1H each). MS (ES+): *m/z* 492 $(M+H)^+$.

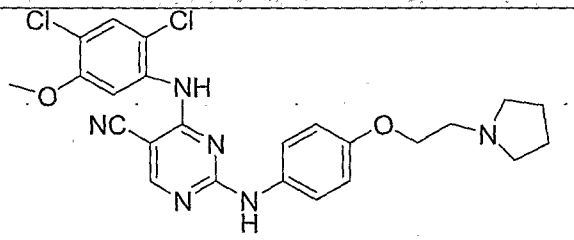
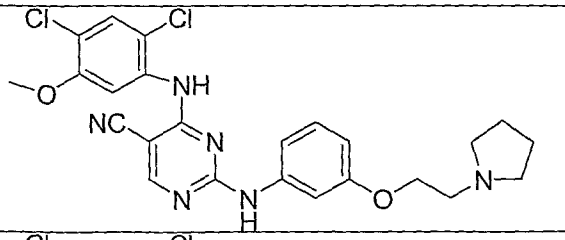
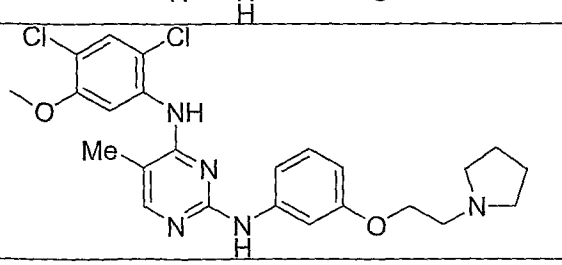
EXAMPLE 244. IC_{50} Value Determinations for Jak2 Kinase

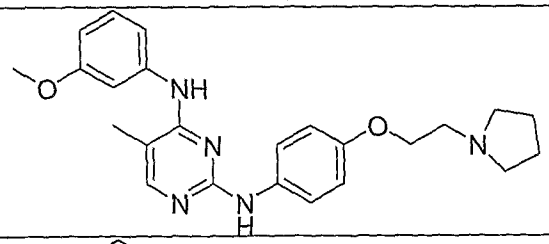
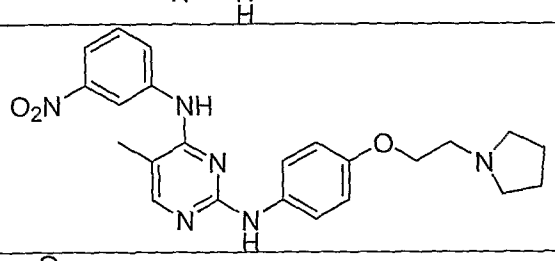
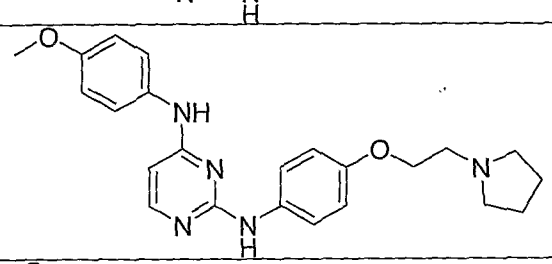
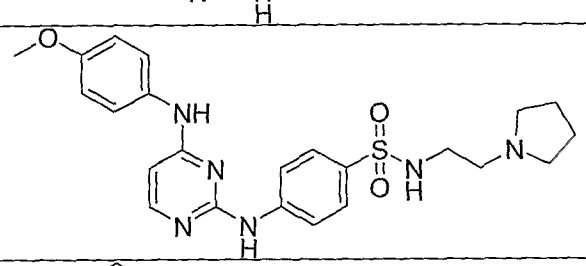
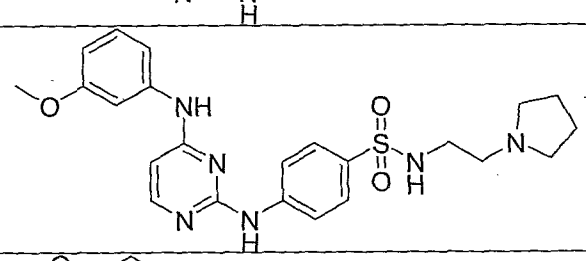
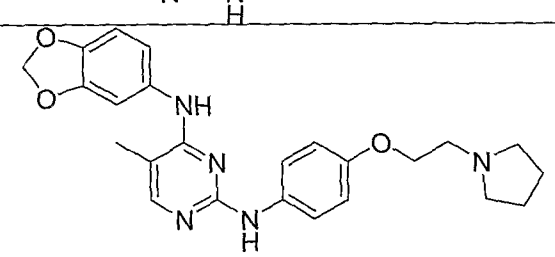
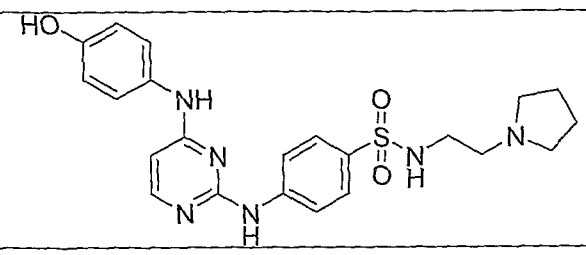
[0466] The IC_{50} values for compounds were determined using a luminescence-based kinase assay with recombinant JAK2 obtained from Upstate Cell Signaling Solutions. In white, flat-bottom, 96-well plates (Nunc) parallel assays were run at room temperature at a final volume of 50 µL. Each well contained 40 µL of buffer consisting of 40 mM Tris buffer, pH 7.4, containing 50 mM $MgCl_2$, 800 µM EGTA, 350 µM Triton X-100, 2 mM β-

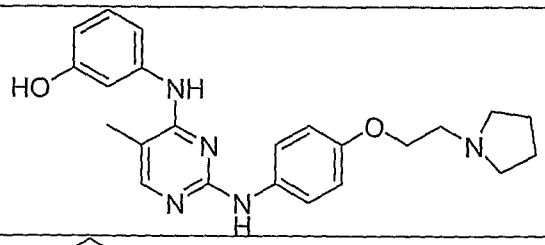
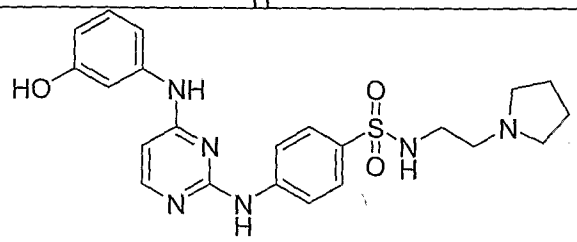
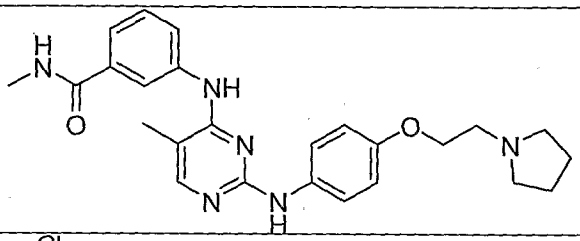
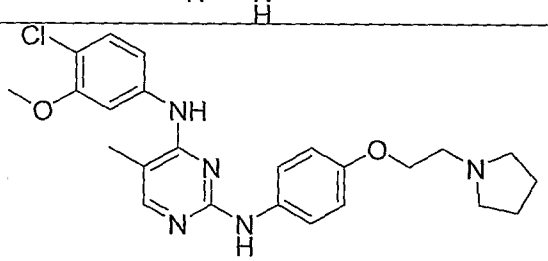
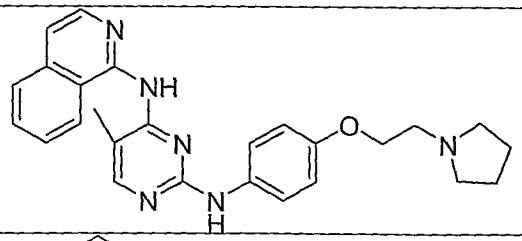
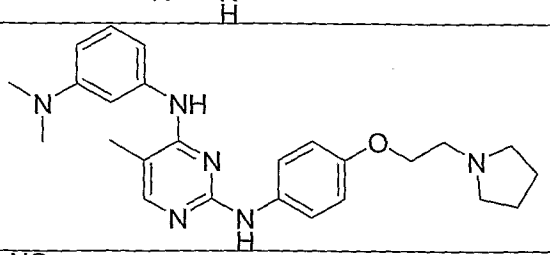
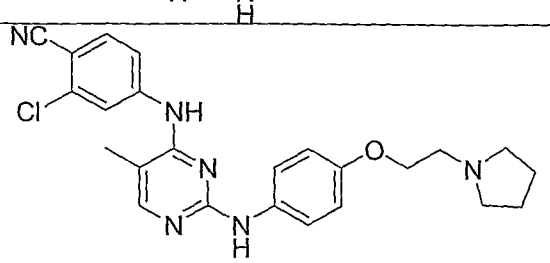
mercaptoethanol, 100 μM peptide substrate (PDKtide; Upstate Cell Signaling Solutions) and an appropriate amount of JAK2 (75 – 25 ng/well) such that the assay was linear over 60 min. The final concentrations of TargeGen compounds for IC_{50} value determinations ranged from 1000 to 0.01 μM by adding the appropriate amount of compound in 2.5 μL of DMSO; the DMSO present in each assay was constant at 5%. The reaction was initiated by the addition of 10 μL of ATP to a final assay concentration of 3 μM. After the reaction had proceeded for 60 min, 50 μL of Kinase-Glo reagent (Promega) was added to terminate the reaction. This solution was then allowed to proceed for an additional 10 min to maximize the luminescence reaction.

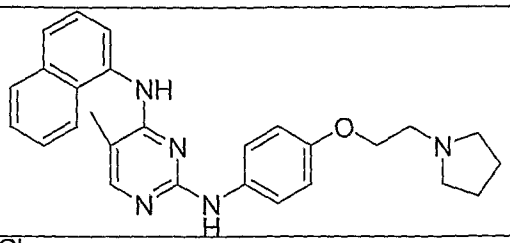
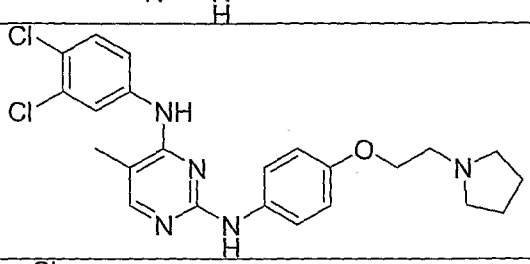
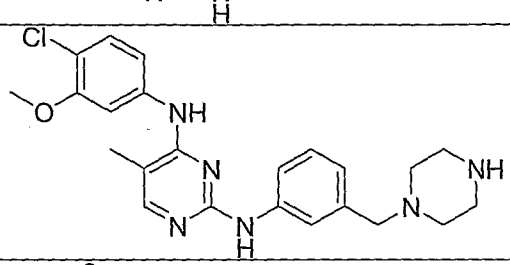
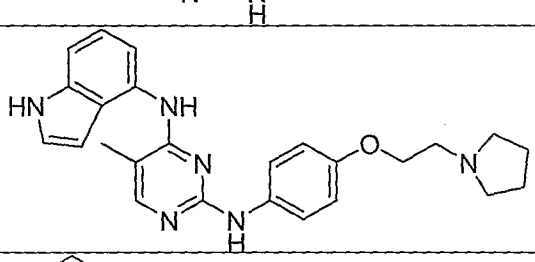
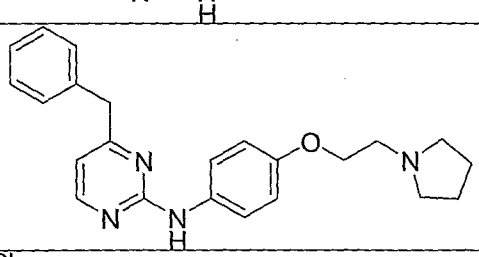
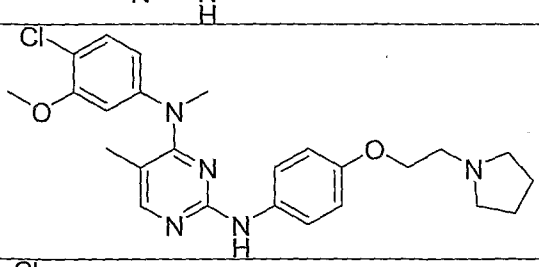
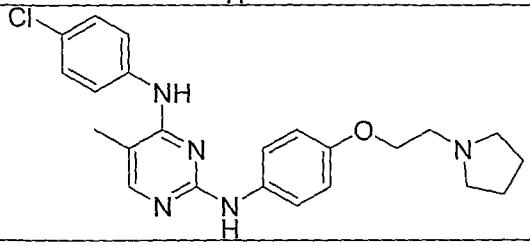
[0467] Values were then measured using an Ultra 384 instrument (Tecan) set for luminosity measurements. Two control reactions were also ran: one reaction containing no compound and the second containing neither inhibitor nor peptide substrate. IC_{50} values were derived from experimental data using the non-linear curve fitting capabilities of Prism (Version 4; GraphPad Software). The results are shown in Table 1.

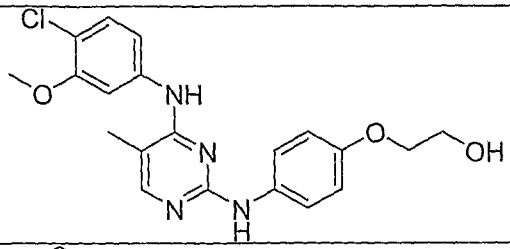
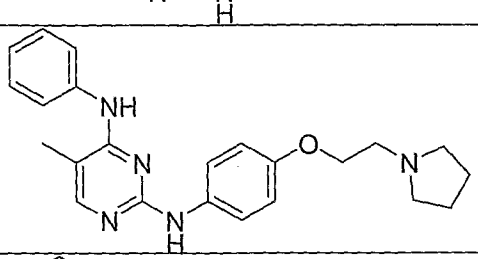
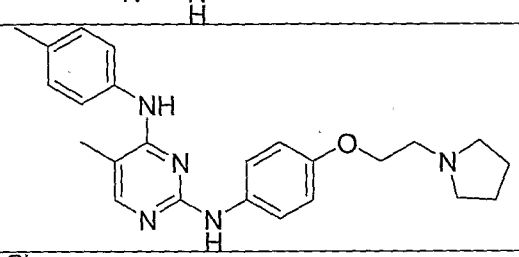
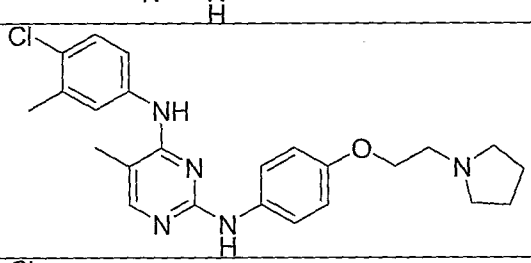
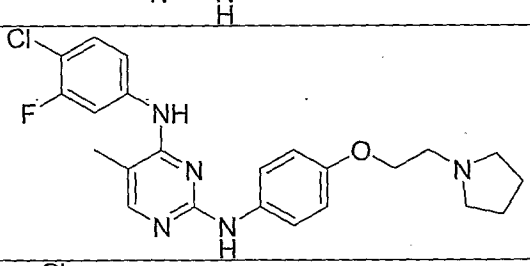
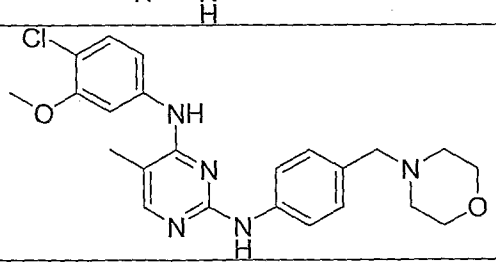
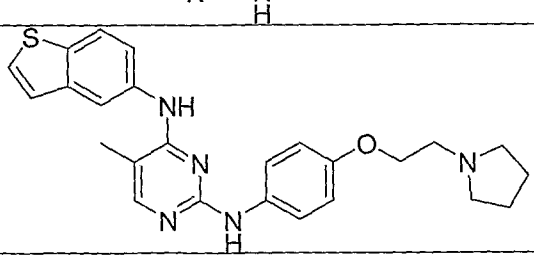
TABLE 1. Compounds of the Invention And Their IC Values for Jak2 Kinase

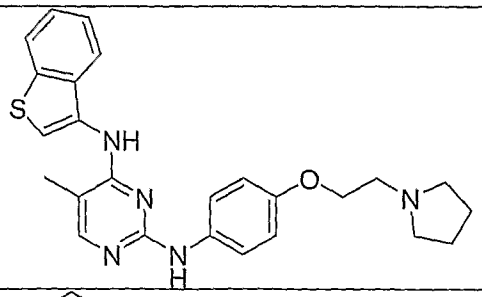
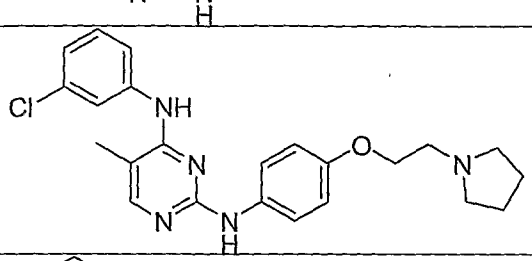
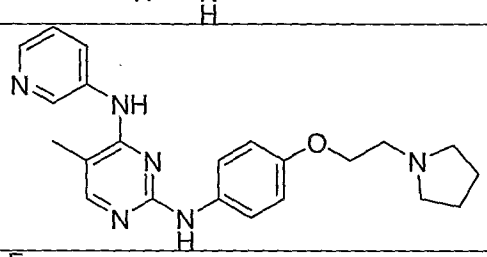
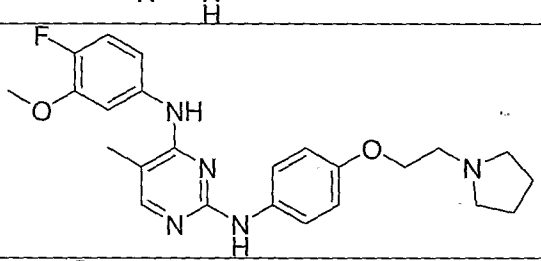
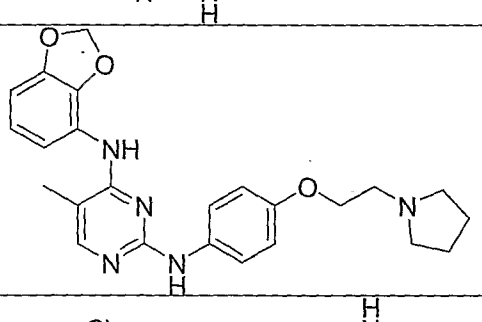
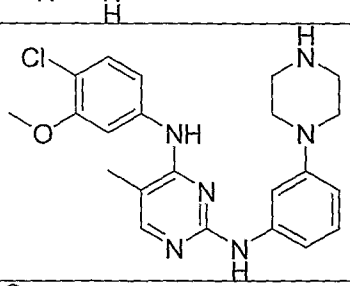
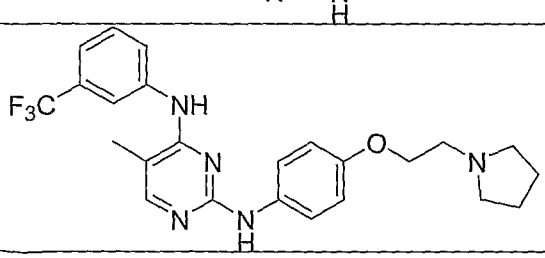
Structure	Name	JAK2 IC50
	4-(2,4-Dichloro-5-methoxy-phenylamino)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidine-5-carbonitrile	6240
	4-(2,4-Dichloro-5-methoxy-phenylamino)-2-[3-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidine-5-carbonitrile	10500
	N4-(2,4-Dichloro-5-methoxy-phenyl)-5-methyl-N2-[3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine	2040

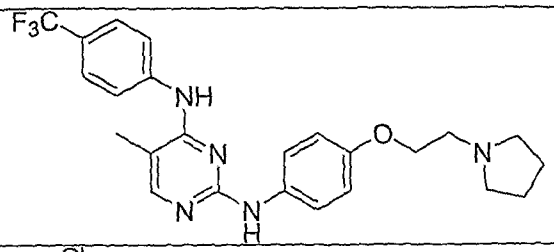
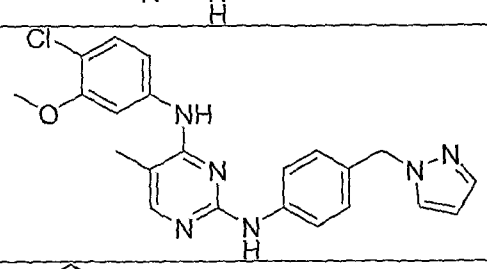
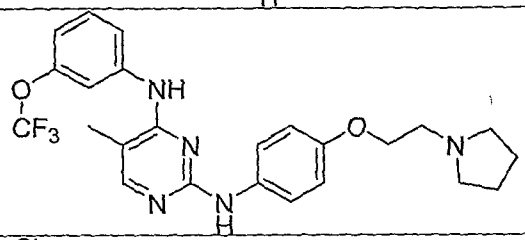
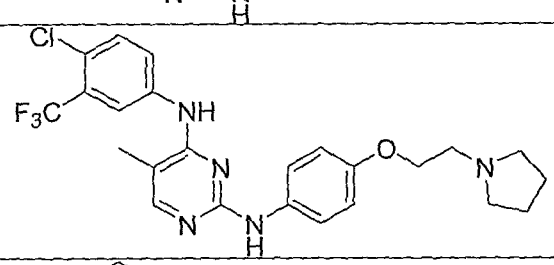
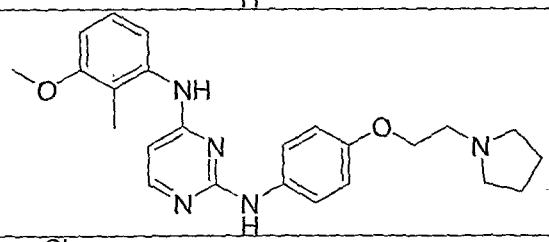
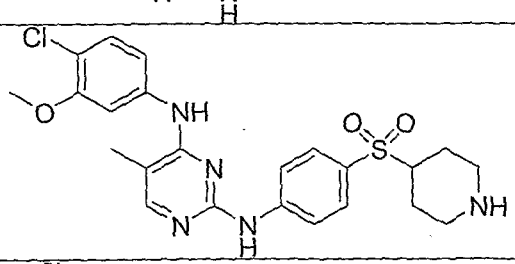
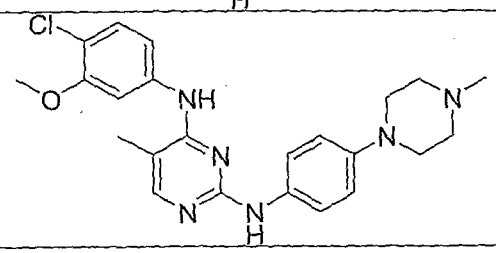
Structure	Name	JAK2 IC50
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N4-(3-methoxyphenyl)-5-methylpyrimidine-2,4-diamine Hydrochloride	52.8
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-5-methyl-N4-(3-nitrophenyl)pyrimidine-2,4-diamine Hydrochloride	61.1
	N4-(4-Methoxy-phenyl)-N2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine trifluoroacetate	4330
	4-[4-(4-Methoxy-phenylamino)-pyrimidin-2-ylamino]-N-(2-pyrrolidin-1-yl-ethyl)-benzenesulfonamide trifluoroacetate	10700
	4-[4-(3-Methoxy-phenylamino)-pyrimidin-2-ylamino]-N-(2-pyrrolidin-1-yl-ethyl)-benzenesulfonamide trifluoroacetate	638
	N4-Benzo[1,3]dioxol-5-yl-5-methyl-N2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine trifluoroacetate	87.2
	4-[4-(4-Hydroxy-phenylamino)-pyrimidin-2-ylamino]-N-(2-pyrrolidin-1-yl-ethyl)-benzenesulfonamide	9740

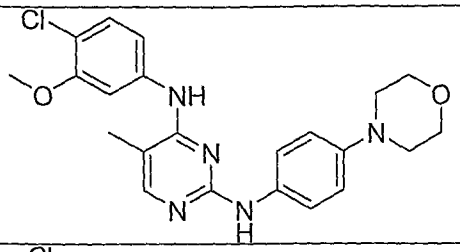
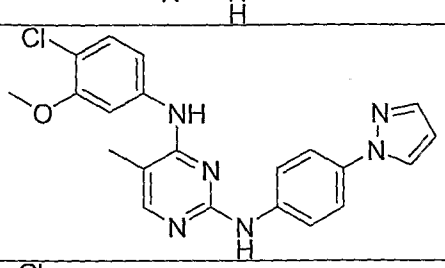
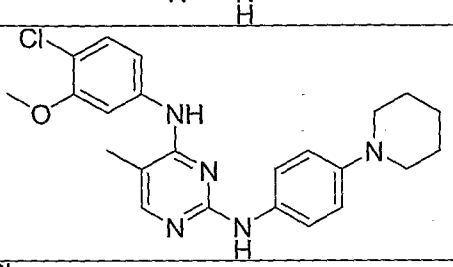
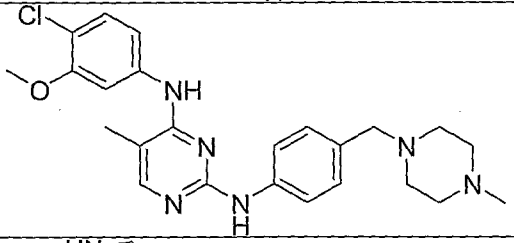
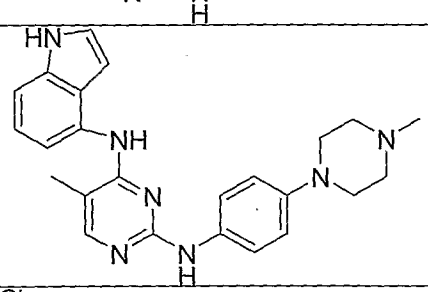
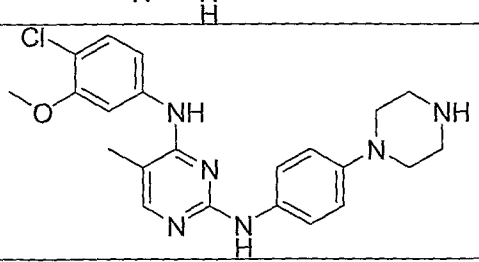
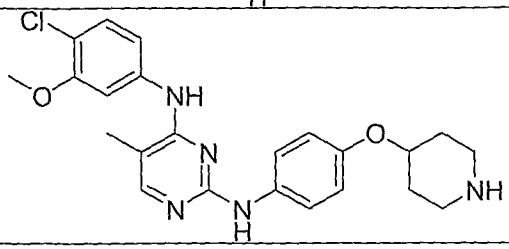
Structure	Name	JAK2 IC50
	3-(2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)-5-methylpyrimidin-4-ylamino)phenol Hydrochloride	203
	4-[4-(3-Hydroxy-phenylamino)-pyrimidin-2-ylamino]-N-(2-pyrrolidin-1-yl-ethyl)-benzenesulfonamide trifluoroacetate	3620
	N-Methyl-3-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-ylamino}-benzamide	257
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine	7.96
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N4-(isoquinolin-1-yl)-5-methylpyrimidine-2,4-diamine	1050
	N4-(3-Dimethylamino-phenyl)-5-methyl-N2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine	19.7
	4-(2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)-5-methylpyrimidin-4-ylamino)-2-chlorobenzonitrile Hydrochloride	67.5

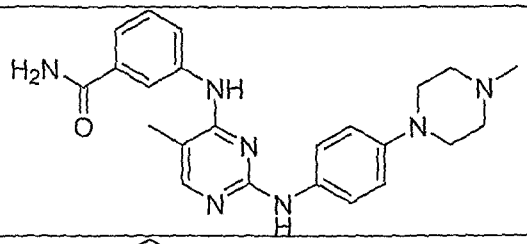
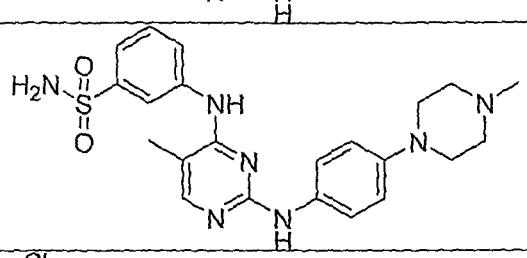
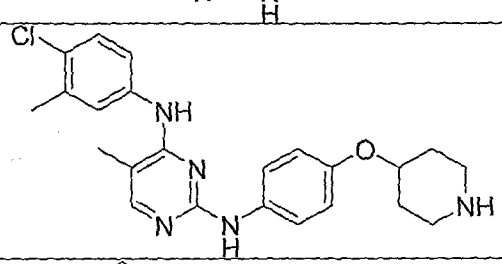
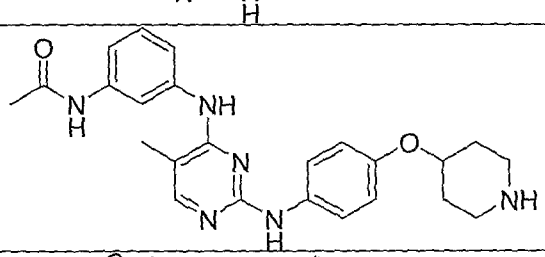
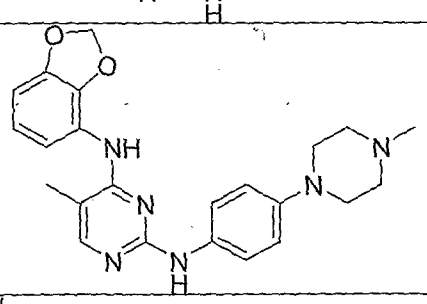
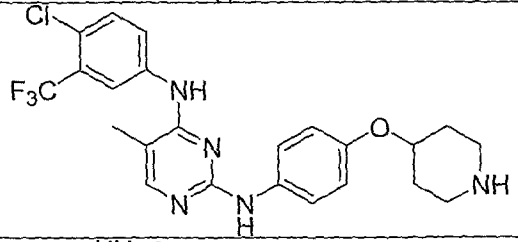
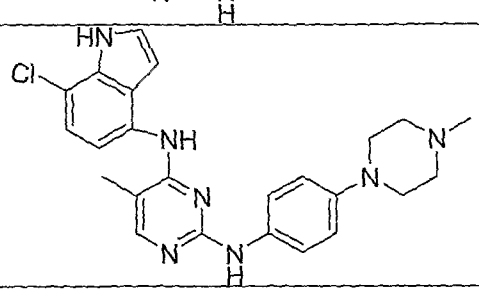
Structure	Name	JAK2 IC50
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-5-methyl-N4-(naphthalen-1-yl)pyrimidine-2,4-diamine Hydrochloride	20
	N4-(3,4-Dichloro-phenyl)-5-methyl-N2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine	25.7
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-(3-piperazin-1-ylmethyl-phenyl)-pyrimidine-2,4-diamine	15.8
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N4-(1H-indol-4-yl)-5-methylpyrimidine-2,4-diamine Hydrochloride	19.2
	N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-4-benzylpyrimidin-2-amine	702.000000
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N4-(4-chloro-3-methoxyphenyl)-N4,5-dimethylpyrimidine-2,4-diamine trifluoroacetate	4900
	N4-(4-Chloro-phenyl)-5-methyl-N2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine trifluoroacetate	18.2

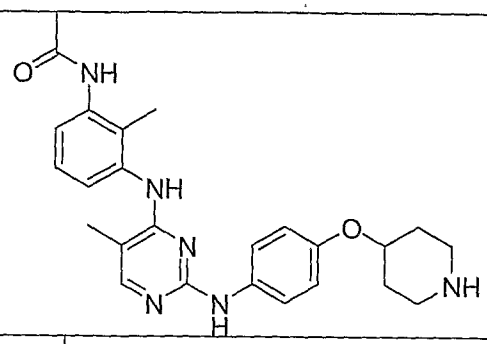
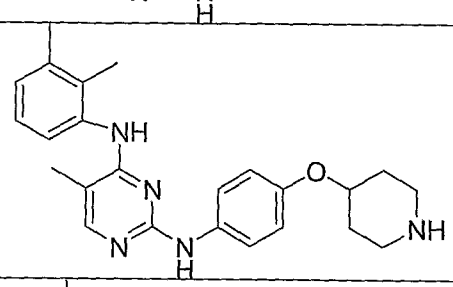
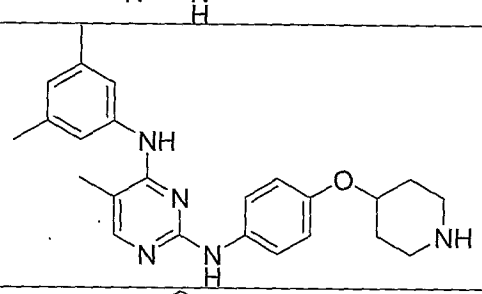
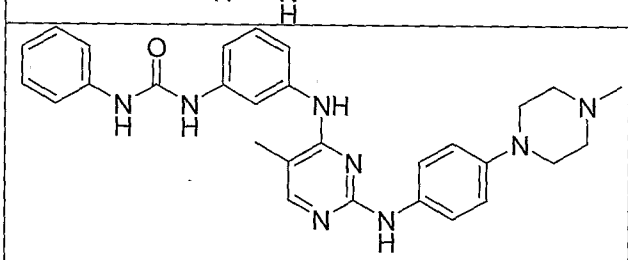
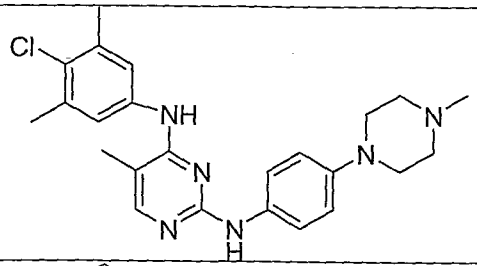
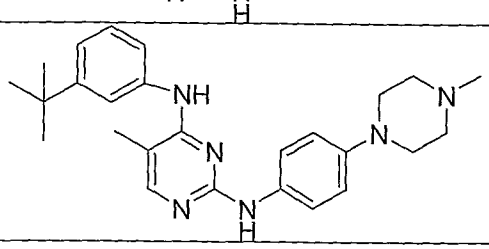
Structure	Name	JAK2 IC50
	2-{4-[4-(4-Chloro-3-methoxy-phenylamino)-5-methyl-pyrimidin-2-ylamino]-phenoxy}-ethanol	9.14
	5-Methyl-N4-phenyl-N2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine	16.7
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-5-methyl-N4-p-tolylpyrimidine-2,4-diamine Hydrochloride	35.7
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N4-(4-chloro-3-methylphenyl)-5-methylpyrimidine-2,4-diamine Hydrochloride	12.4
	N4-(4-Chloro-3-fluoro-phenyl)-5-methyl-N2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine	40.1
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-(4-morpholin-4-ylmethyl-phenyl)-pyrimidine-2,4-diamine trifluoroacetate	13.3
	N4-Benzo[b]thiophen-5-yl-5-methyl-N2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine	28.5

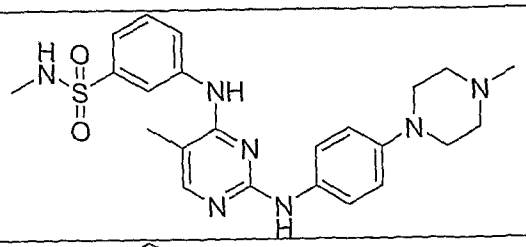
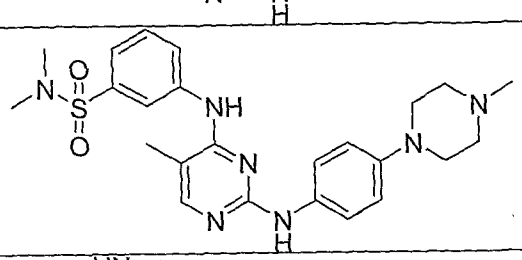
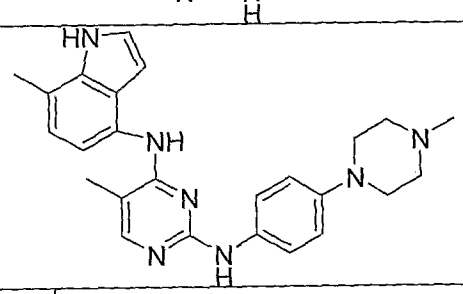
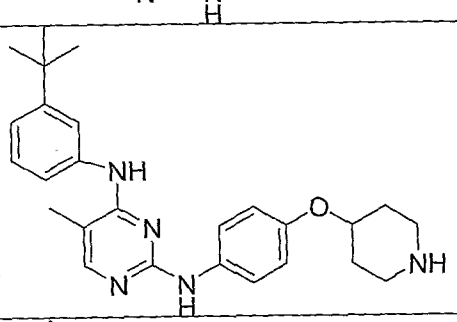
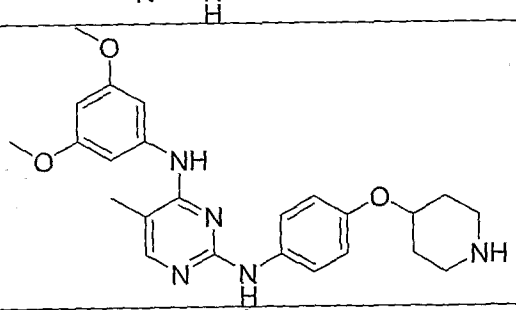
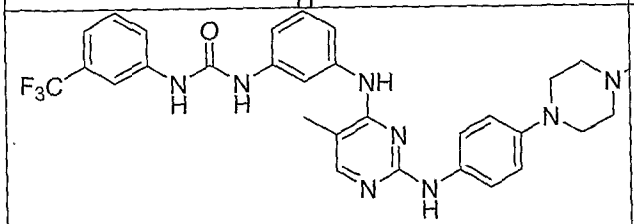
Structure	Name	JAK2 IC50
	N4-Benzo[b]thiophen-3-yl-5-methyl-N2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine	12.4
	N4-(3-Chloro-phenyl)-5-methyl-N2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine	20.8
	2-Chloro-N-{2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-5-yl}-5-(3-trifluoromethyl-benzoylamino)-benzamide	304
	N4-(4-Fluoro-3-methoxy-phenyl)-5-methyl-N2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine	14.8
	N4-Benzo[1,3]dioxol-4-yl-5-methyl-N2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine	16.9
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-(3-piperazin-1-yl-phenyl)-pyrimidine-2,4-diamine	9.52
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N4-(3-(trifluoromethyl)phenyl)-5-methylpyrimidine-2,4-diamine	17.6

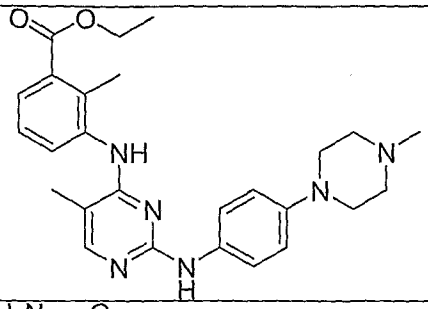
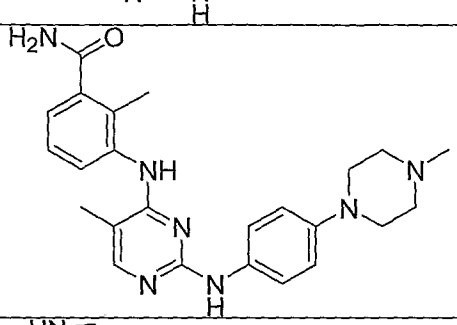
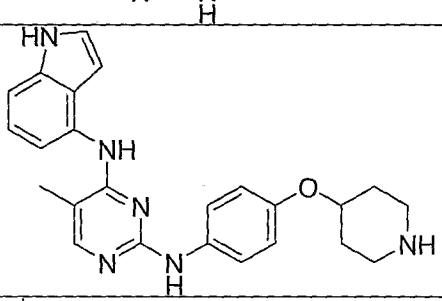
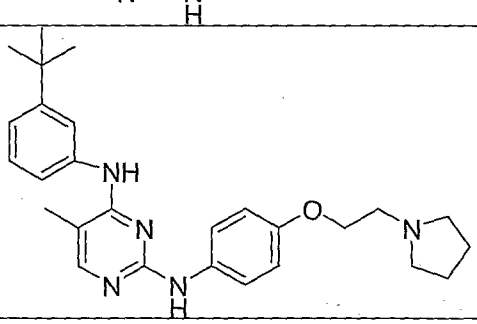
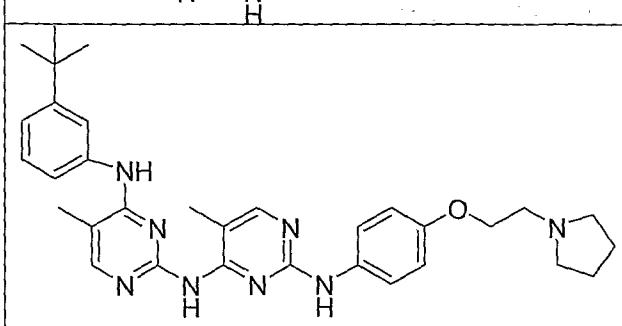
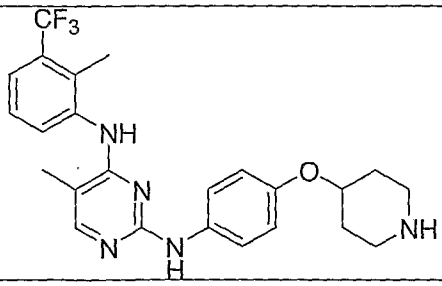
Structure	Name	JAK2 IC50
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N4-(4-(trifluoromethyl)phenyl)-5-methylpyrimidine-2,4-diamine hydrochloride	39.8
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-(4-pyrazol-1-ylmethyl-phenyl)-pyrimidine-2,4-diamine	18.9
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-5-methyl-N4-(3-(trifluoromethoxy)phenyl)pyrimidine-2,4-diamine	20.7
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N4-(4-chloro-3-(trifluoromethyl)phenyl)-5-methylpyrimidine-2,4-diamine	23.4
	N4-(3-Methoxy-2-methyl-phenyl)-N2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrimidine-2,4-diamine	371
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-[4-(piperidine-4-sulfonyl)-phenyl]-pyrimidine-2,4-diamine	13
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-[4-(4-methyl-piperazin-1-yl)-phenyl]-pyrimidine-2,4-diamine	5.5

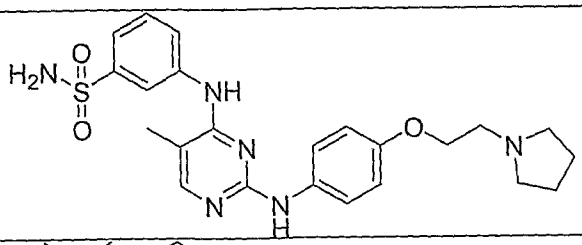
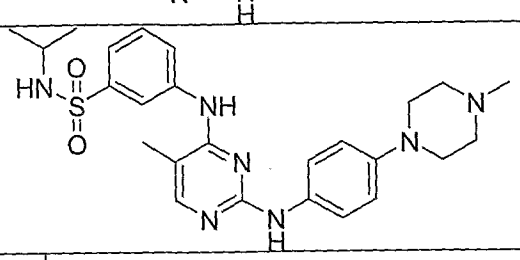
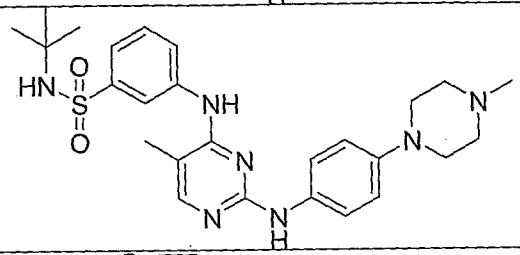
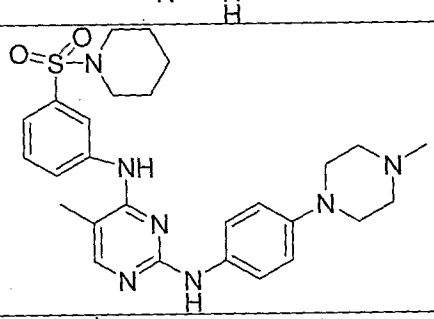
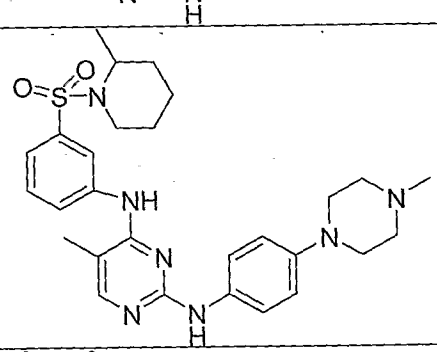
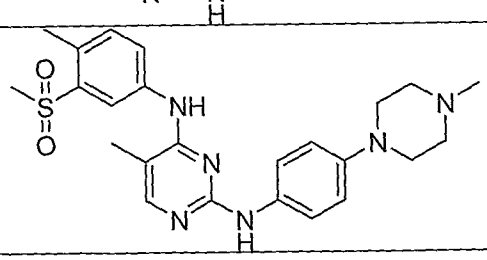
Structure	Name	JAK2 IC50
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-(4-morpholin-4-yl-phenyl)-pyrimidine-2,4-diamine	130
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-(4-pyrazol-1-yl-phenyl)-pyrimidine-2,4-diamine trifluoroacetate	35.3
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-(4-piperidin-1-yl-phenyl)-pyrimidine-2,4-diamine	35.3
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-pyrimidine-2,4-diamine	12
	N4-(1H-indol-4-yl)-5-methyl-N2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine Hydrochloride	9.53
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-(4-piperazin-1-yl-phenyl)-pyrimidine-2,4-diamine	6.15
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-[4-(piperidin-4-yloxy)-phenyl]-pyrimidine-2,4-diamine	4.14

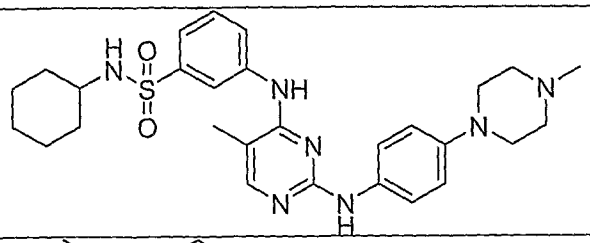
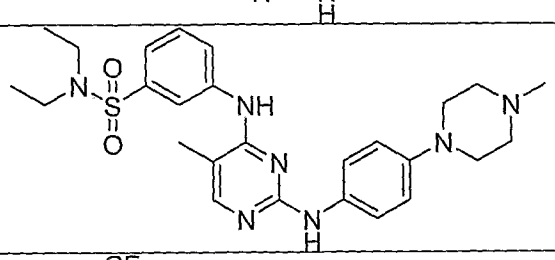
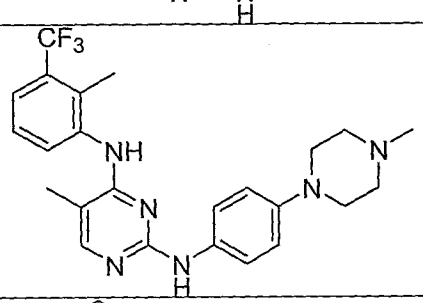
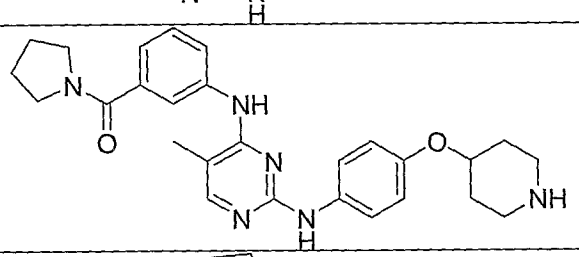
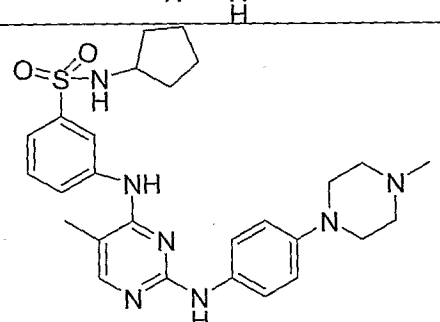
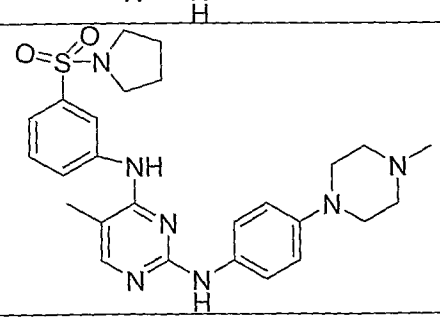
Structure	Name	JAK2 IC50
	3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzamide	23
	3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	13.6
	N4-(4-Chloro-3-methyl-phenyl)-5-methyl-N2-[4-(piperidin-4-yloxy)-phenyl]-pyrimidine-2,4-diamine	8.41
	N-(3-{5-Methyl-2-[4-(piperidin-4-yloxy)-phenylamino]-pyrimidin-4-ylamino}-phenyl)-acetamide	137
	N4-Benzo[1,3]dioxol-4-yl-5-methyl-N2-[4-(4-methyl-piperazin-1-yl)-phenyl]-pyrimidine-2,4-diamine	14.2
	N4-(4-Chloro-3-trifluoromethyl-phenyl)-5-methyl-N2-[4-(piperidin-4-yloxy)-phenyl]-pyrimidine-2,4-diamine	11.4
	N4-(7-chloro-1H-indol-4-yl)-5-methyl-N2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine	5.36

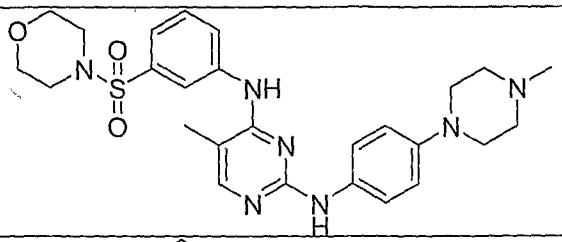
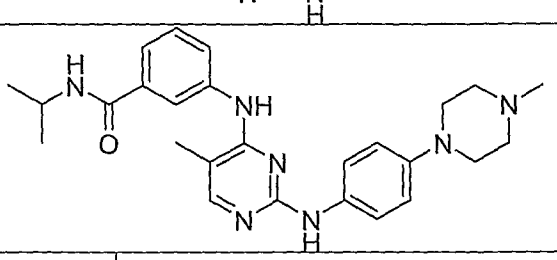
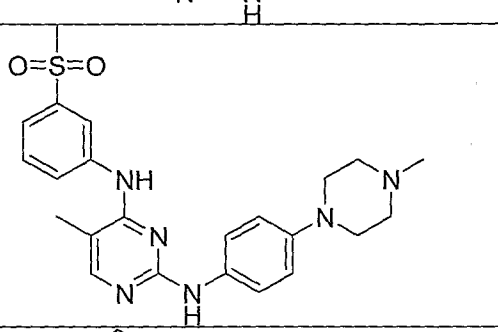
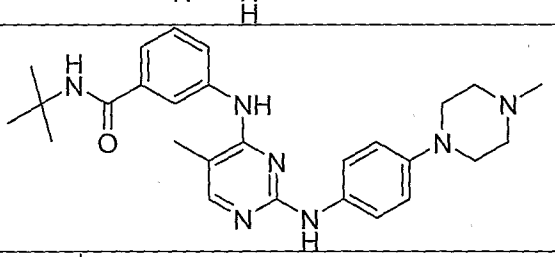
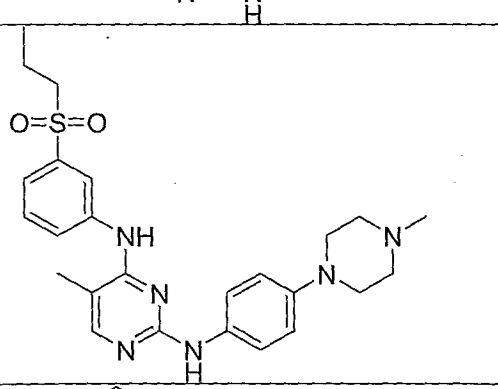
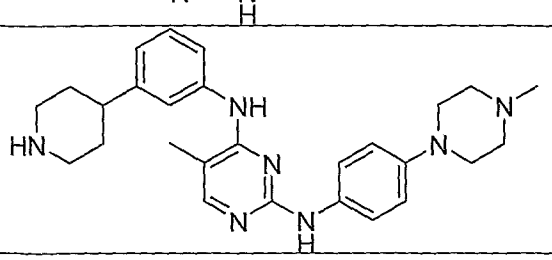
Structure	Name	JAK2 IC50
	N-(2-Methyl-3-{5-methyl-2-[4-(piperidin-4-yloxy)-phenylamino]-pyrimidin-4-ylamino}-phenyl)-acetamide	146
	5-methyl-N4-(2,3-dimethylphenyl)-N2-(4-(piperidin-4-yloxy)phenyl)pyrimidine-2,4-diamine Hydrochloride	4.38
	5-methyl-N4-(3,5-dimethylphenyl)-N2-(4-(piperidin-4-yloxy)phenyl)pyrimidine-2,4-diamine hydrochloride	37.2
	1-(3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-phenyl)-3-phenyl-urea	63.6
	N4-(4-chloro-3,5-dimethylphenyl)-5-methyl-N2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine Hydrochloride	38
	N4-(3-tert-butylphenyl)-5-methyl-N2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine Hydrochloride	4.7

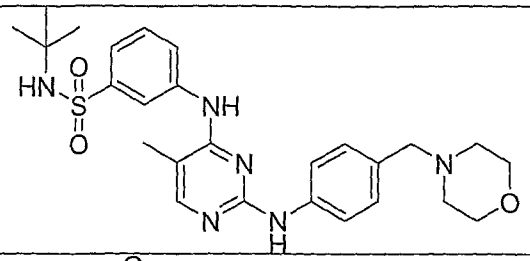
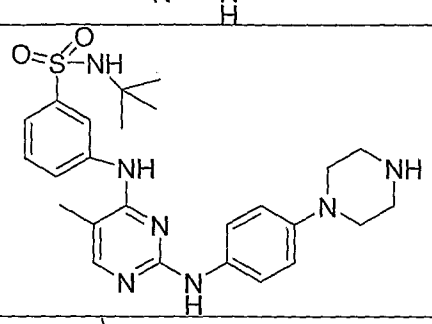
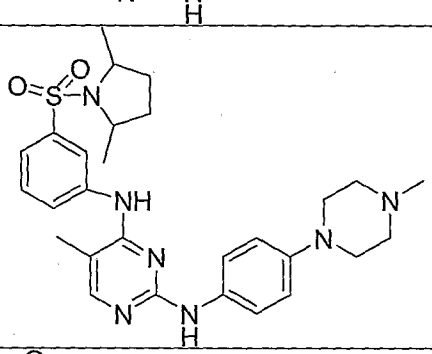
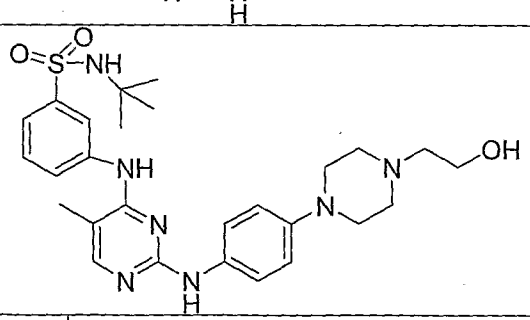
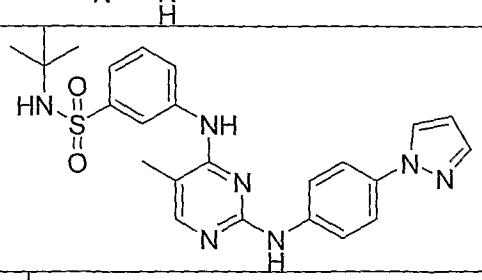
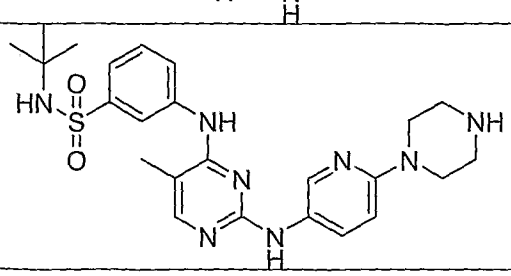
Structure	Name	JAK2 IC50
	N-Methyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	16.1
	N,N-Dimethyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	9.5
	5-methyl-N4-(7-methyl-1H-indol-4-yl)-N2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine Hydrochloride	3.84
	N4-(3-tert-butylphenyl)-5-methyl-N2-(4-(piperidin-4-yloxy)phenyl)pyrimidine-2,4-diamine Hydrochloride	2.73
	N4-(3,5-dimethoxyphenyl)-5-methyl-N2-(4-(piperidin-4-yloxy)phenyl)pyrimidine-2,4-diamine trifluoroacetate	137
	1-(3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-phenyl)-3-(3-trifluoromethyl-phenyl)-urea	126

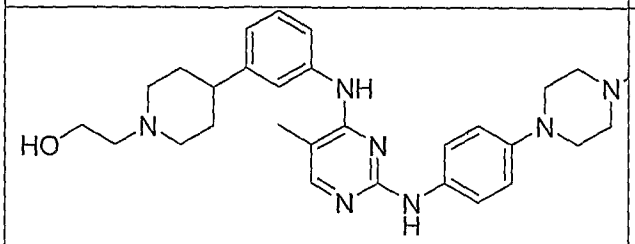
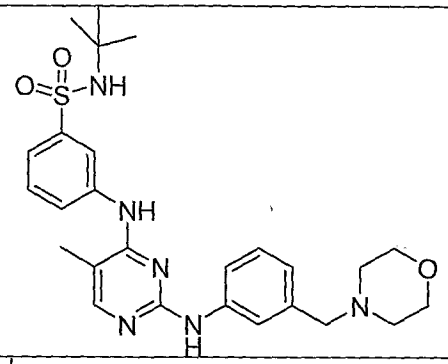
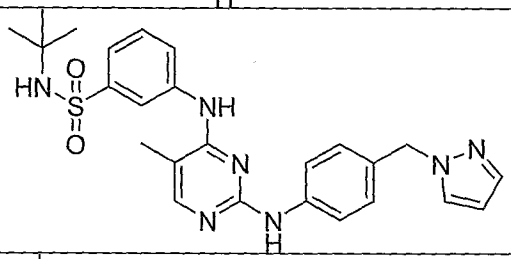
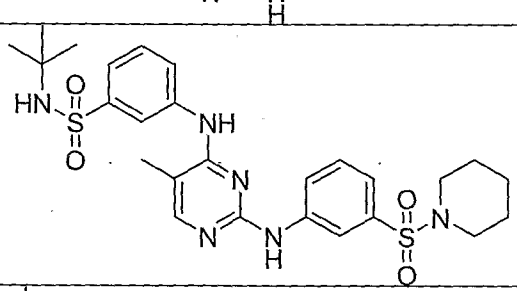
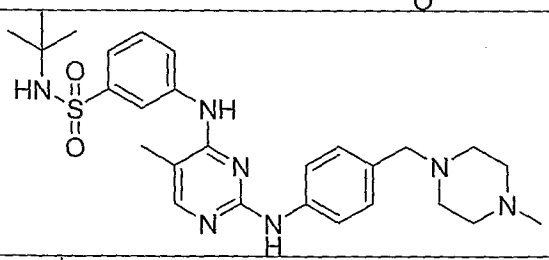
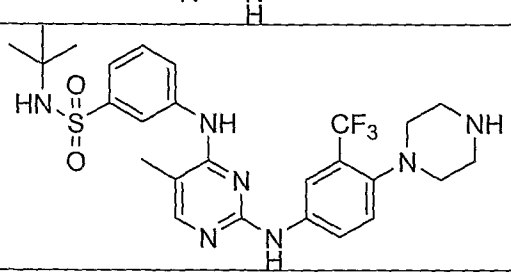
Structure	Name	JAK2 IC50
	2-Methyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzoic acid ethyl ester	27.8
	2-Methyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzamide	26.2
	N4-(1H-indol-4-yl)-5-methyl-N2-(4-(piperidin-4-yloxy)phenyl)pyrimidine-2,4-diamine trifluoroacetic acid salt	4.27
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N4-(3-tert-butylphenyl)-5-methylpyrimidine-2,4-diamine Hydrochloride	6.71
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N4-(4-(3-tert-butylphenylamino)-5-methylpyrimidin-2-yl)-5-methylpyrimidine-2,4-diamine Hydrochloride	153
	5-Methyl-N4-(2-methyl-3-trifluoromethyl-phenyl)-N2-[4-(piperidin-4-yloxy)-phenyl]-pyrimidine-2,4-diamine	52.9

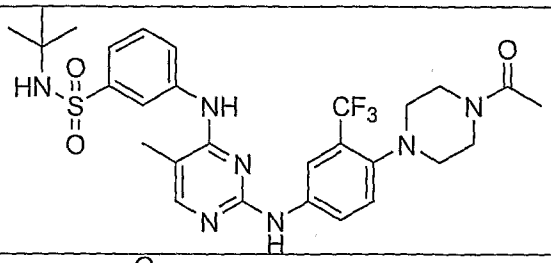
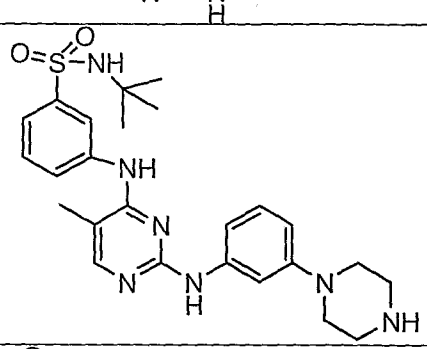
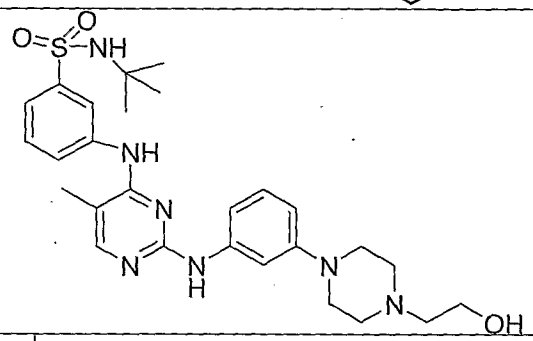
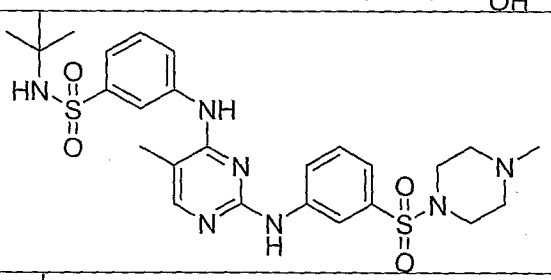
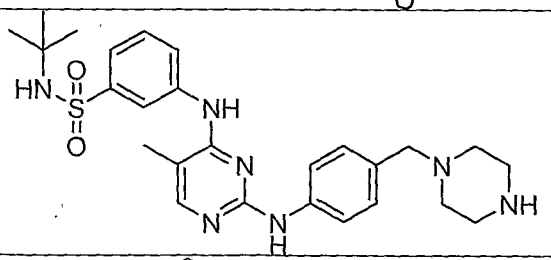
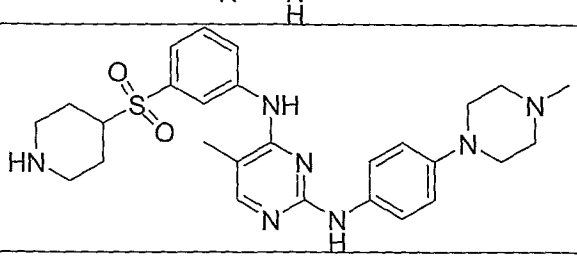
Structure	Name	JAK2 IC50
	3-{5-Methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	72.2
	N-Isopropyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	11.8
	N-tert-Butyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	6.06
	5-Methyl-N2-[4-(4-methyl-piperazin-1-yl)-phenyl]-N4-[3-(piperidine-1-sulfony)-phenyl]-pyrimidine-2,4-diamine Hydrochloride	24.8
	5-Methyl-N2-[4-(4-methyl-piperazin-1-yl)-phenyl]-N4-[3-(2-methyl-piperidine-1- sulfony)-phenyl]-pyrimidine-2,4-diamine Hydrochloride	33.5
	N4-(3-Methanesulfonyl-4-methyl-phenyl)-5-methyl-N2-[4-(4-methyl-piperazin-1-yl)-phenyl]-pyrimidine-2,4-diamine	160

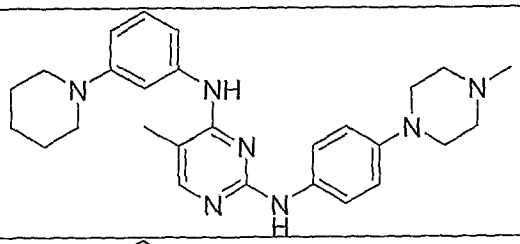
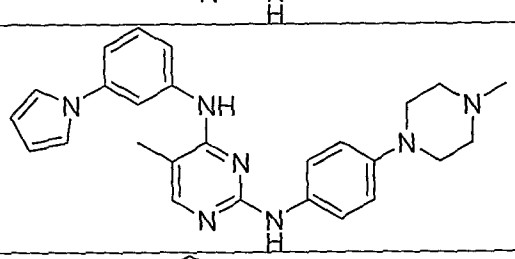
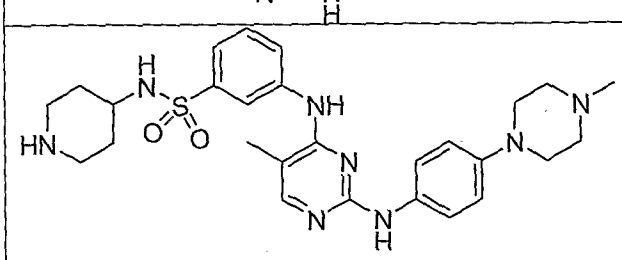
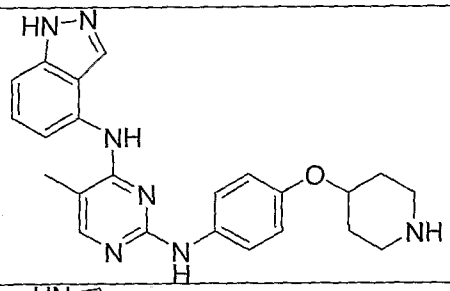
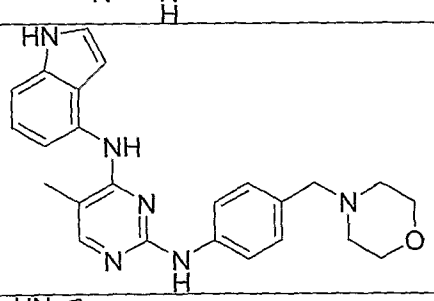
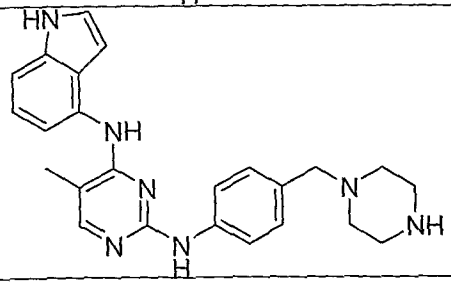
Structure	Name	JAK2 IC50
	N-Cyclohexyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	39.4
	N,N-Diethyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	60.3
	N4-(3-(trifluoromethyl)-2-methylphenyl)-5-methyl-N2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine hydrochloride	87.1
	(3-{5-Methyl-2-[4-(piperidin-4-yloxy)-phenylamino]-pyrimidin-4-ylamino}-phenyl)-pyrrolidin-1-yl-methanone	113
	N-Cyclopentyl3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidine-4-ylamino}-benzenesulfonamide Hydrochloride	19.8
	5-Methyl-N2-[4-(4-methyl-piperazin-1-yl)-phenyl]-N4-[3-(pyrrolidine-1-sulfony)-phenyl]-pyrimidine-2,4-diamine Hydrochloride	17.1

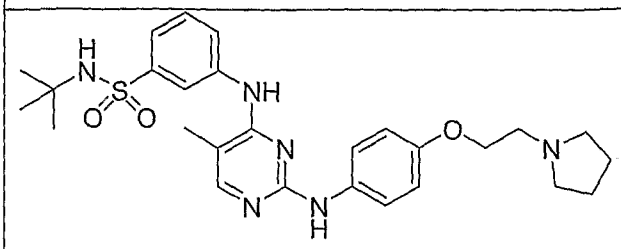
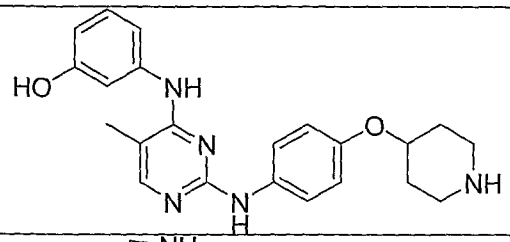
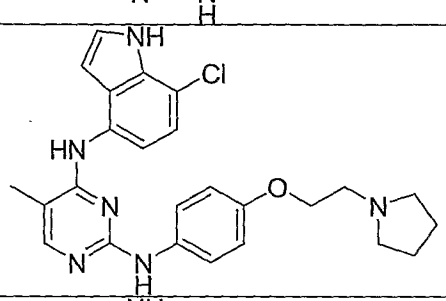
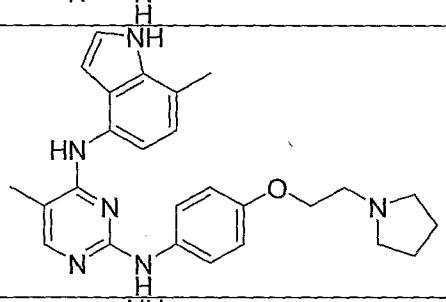
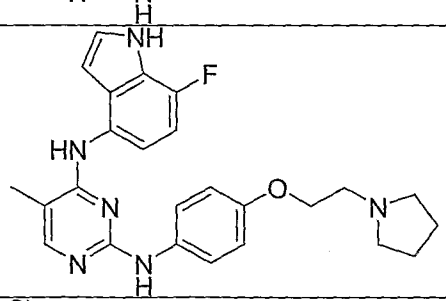
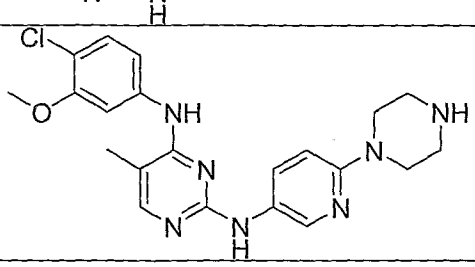
Structure	Name	JAK2 IC50
	5-Methyl-N2-[4-(4-methyl-piperazin-1-yl)-phenyl]-N4-[3-(morpholine-4-sulfonyl)-phenyl]-pyrimidine-2,4-diamine	20.7
	N-Isopropyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzamide	541
	5-methyl-N2-(4-(4-methylpiperazin-1-yl)phenyl)-N4-(3-(methylsulfonyl)phenyl)pyrimidine-2,4-diamine	215
	N-tert-Butyl-3-{5-methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzamide	890
	5-methyl-N2-(4-(4-methylpiperazin-1-yl)phenyl)-N4-(3-(propylsulfonyl)phenyl)pyrimidine-2,4-diamine	8
	5-Methyl-N2-[4-(4-methyl-piperazin-1-yl)-phenyl]-N4-(3-piperidin-4-yl-phenyl)-pyrimidine-2,4-diamine	42.5

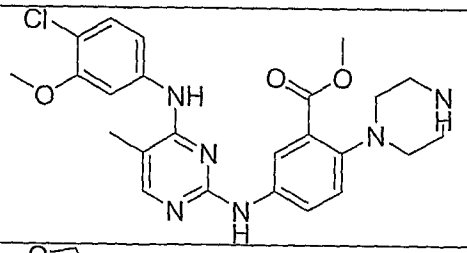
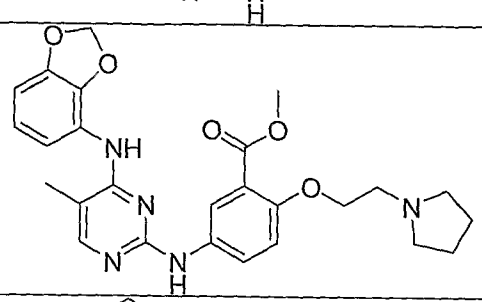
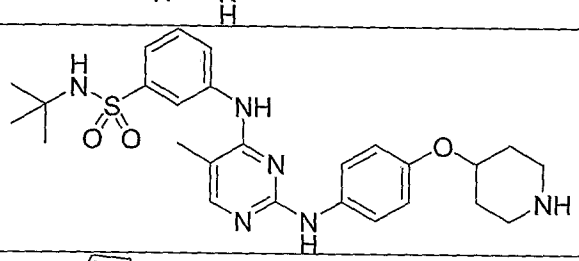
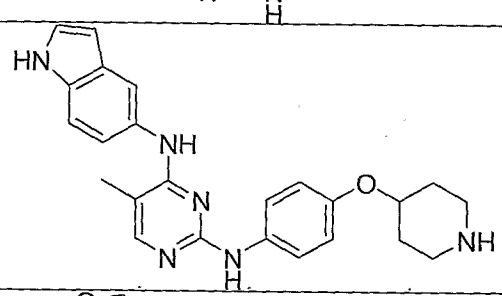
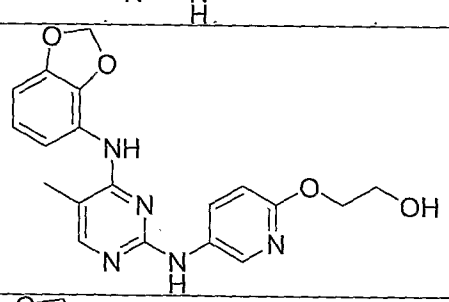
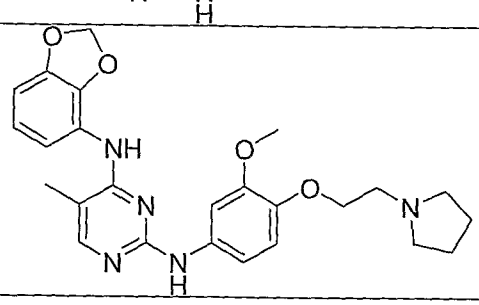
Structure	Name	JAK2 IC50
	N-tert-Butyl-3-[5-methyl-2-(4-morpholin-4-ylmethyl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide	12.5
	N-tert-Butyl-3-[5-methyl-2-(4-piperazin-1-yl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide Hydrochloride	7.59
	N4-[3-(2,5-Dimethyl-pyrrolidine-1-sulfonyl)-phenyl]-5-methyl-N2-[4-(4-methyl-piperazin-1-yl)-phenyl]-pyrimidine-2,4-diamine Hydrochloride	18.8
	N-tert-Butyl-3-(2-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-phenylamino}-[5-methyl-pyrimidin-4-ylamino]-benzenesulfonamide Hydrochloride	7.09
	N-tert-Butyl-3-[5-methyl-2-(4-pyrazol-1-yl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide	19
	N-tert-Butyl-3-[5-methyl-2-(6-piperazin-1-yl-pyridin-3-ylamino)-pyrimidin-4-ylamino]-benzenesulfonamide	10

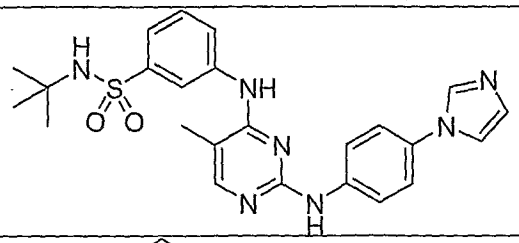
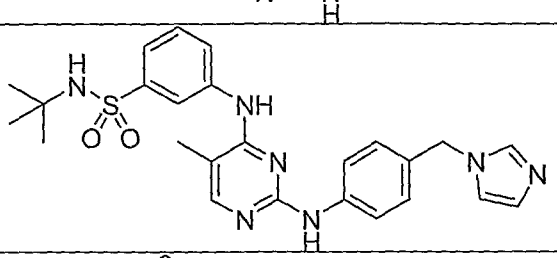
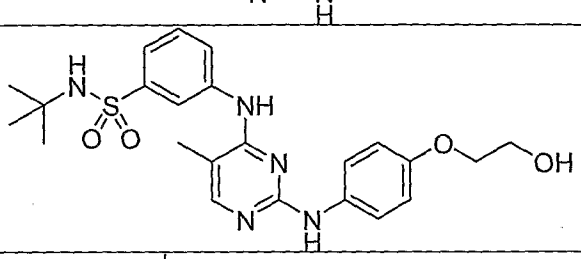
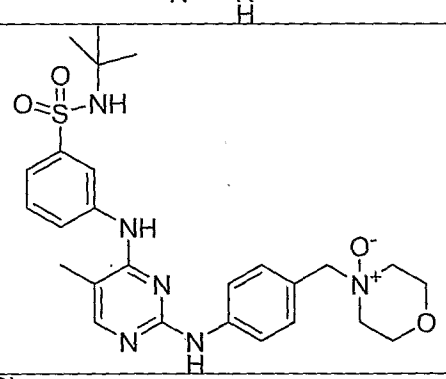
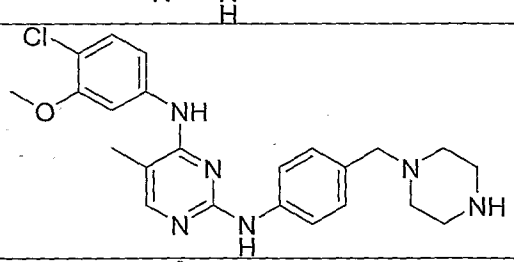
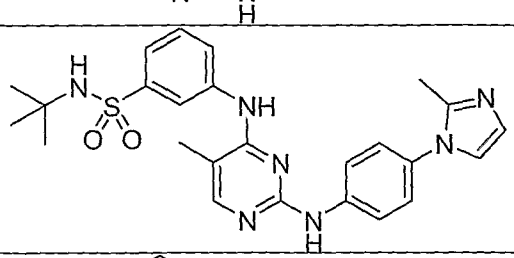
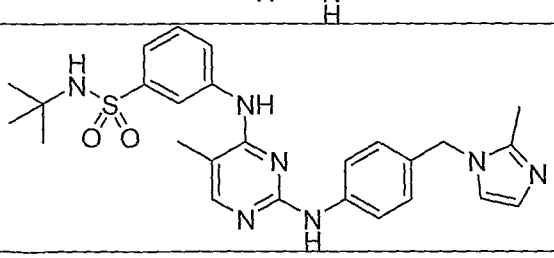
Structure	Name	JAK2 IC50
	2-[4-(3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-phenyl)-piperidin-1-yl]-ethanol	8.46
	N-tert-Butyl-3-[5-methyl-2-(3-morpholin-4-ylmethyl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide	7.06
	N-tert-Butyl-3-[5-methyl-2-(4-pyrazol-1-ylmethyl-phenylamino)-pyrimidin-4-ylamino}-benzenesulfonamide	18.6
	N-tert-Butyl-3-{5-methyl-2-[3-(piperidine-1-sulfonyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	316
	N-tert-butyl-3-{[5-methyl-2-({4-[(4-methylpiperazin-1-yl)methyl]phenyl}amino)pyrimidin-4-yl]amino}benzenesulfonamide	29.8
	N-tert-butyl-3-[(5-methyl-2-{[4-piperazin-1-yl-3-(trifluoromethyl)phenyl]amino}pyrimidin-4-yl)amino]benzenesulfonamide	22.5

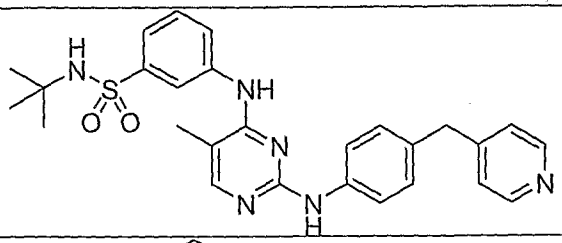
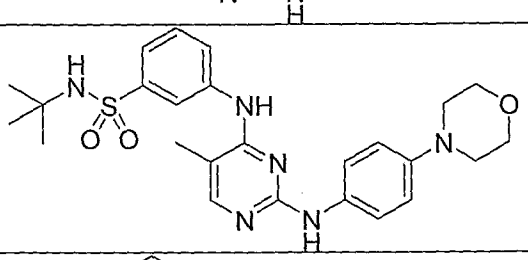
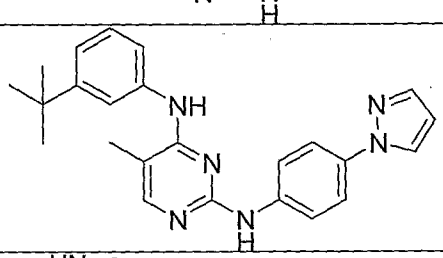
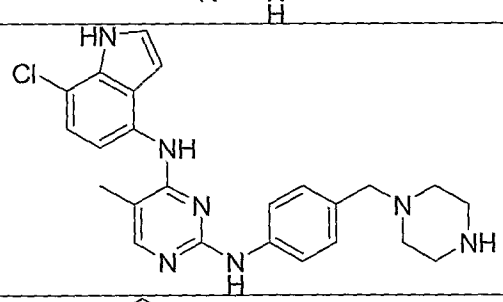
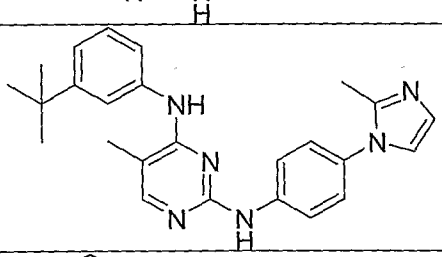
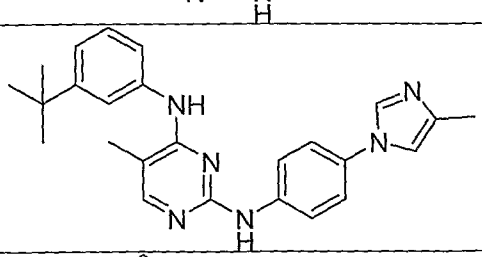
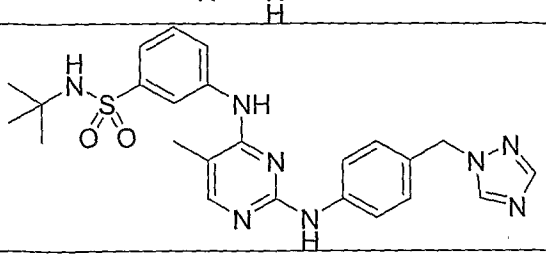
Structure	Name	JAK2 IC50
	3-[(2-{[4-(4-acetylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}-5-methylpyrimidin-4-yl)amino]-N-tert-butylbenzenesulfonamide	35.7
	N-tert-Butyl-3-[5-methyl-2-(3-piperazin-1-yl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide Hydrochloride	18
	N-tert-Butyl-3-(2-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-phenylamino}-[5-methyl-pyrimidin-4-ylamino]-benzenesulfonamide Hydrochloride	40.5
	N-tert-butyl-3-{[5-methyl-2-({3-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}amino)pyrimidin-4-yl]amino}benzenesulfonamide	650
	N-tert-butyl-3-[(5-methyl-2-{[4-(piperazin-1-ylmethyl)phenyl]amino}pyrimidin-4-yl)amino]benzenesulfonamide	4.6
	5-Methyl-N2-[4-(4-methyl-piperazin-1-yl)-phenyl]-N4-[3-(piperidine-4-sulfonyl)-phenyl]-pyrimidine-2,4-diamine	198

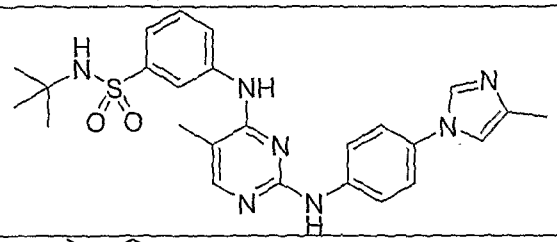
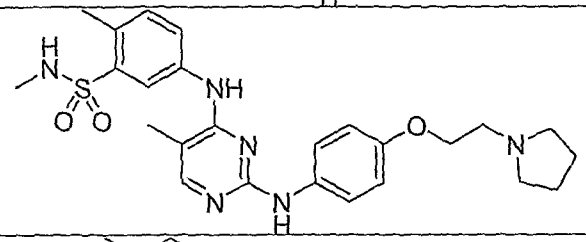
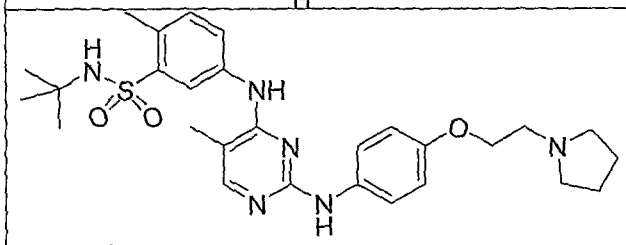
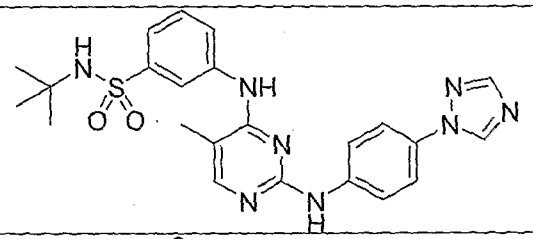
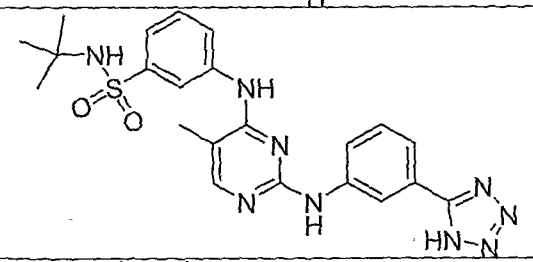
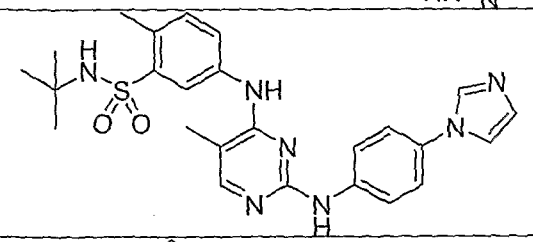
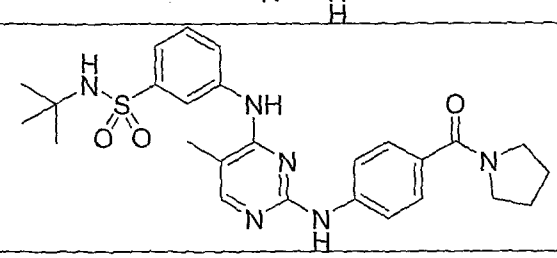
Structure	Name	JAK2 IC50
	5-methyl-N2-(4-(4-methylpiperazin-1-yl)phenyl)-N4-(3-(piperidin-1-yl)phenyl)pyrimidine-2,4-diamine	46.3
	N4-(3-(1H-pyrrol-1-yl)phenyl)-5-methyl-N2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine	33.8
	3-{5-Methyl-2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-N-piperidin-4-yl-benzenesulfonamide	543
	N4-(1H-indazol-4-yl)-5-methyl-N2-(4-(piperidin-4-yloxy)phenyl)pyrimidine-2,4-diamine Hydrochloride	
	N4-(1H-Indol-4-yl)-5-methyl-N2-(4-morpholin-4-ylmethyl-phenyl)-pyrimidine-2,4-diamine	7.42
	N4-(1H-Indol-4-yl)-5-methyl-N2-(4-piperazin-1-ylmethyl-phenyl)-pyrimidine-2,4-diamine	10.1

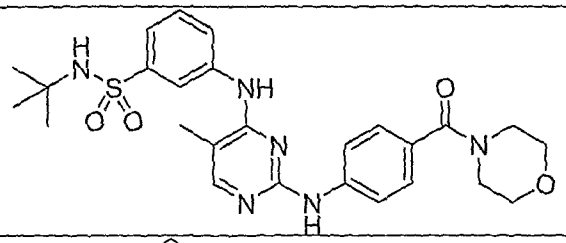
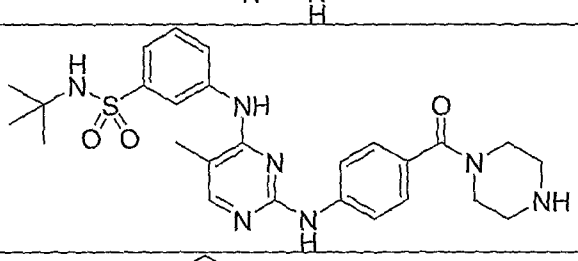
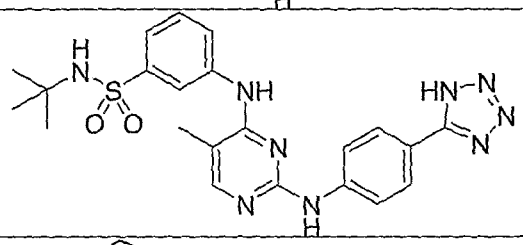
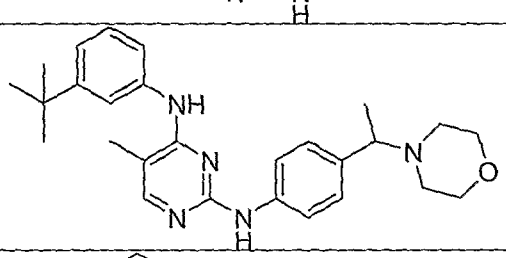
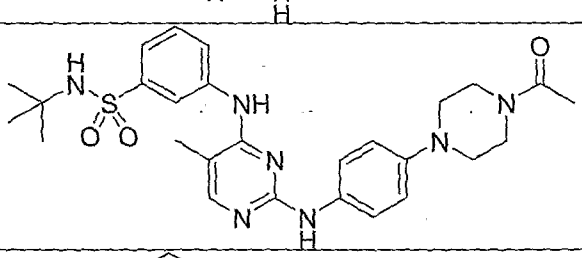
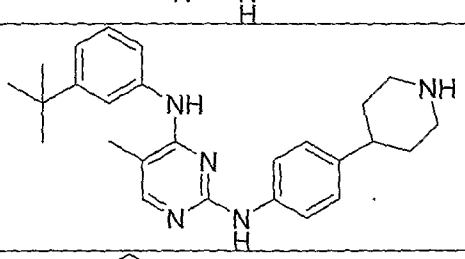
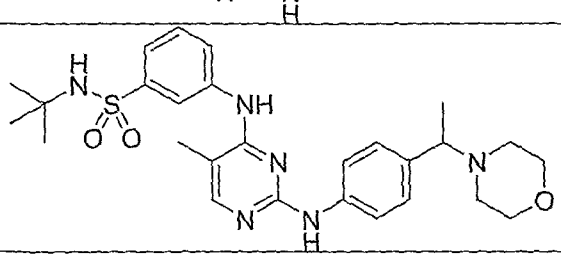
Structure	Name	JAK2 IC50
	N-tert-Butyl-3-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	12.5
	3-(2-(4-(piperidin-4-yloxy)phenylamino)-5-methylpyrimidin-4-ylamino)phenol	51.9
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N4-(7-chloro-1H-indol-4-yl)-5-methylpyrimidine-2,4-diamine Hydrochloride	1.16
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-5-methyl-N4-(7-methyl-1H-indol-4-yl)pyrimidine-2,4-diamine Hydrochloride	6.98
	N2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N4-(7-fluoro-1H-indol-4-yl)-5-methylpyrimidine-2,4-diamine Hydrochloride	9.28
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-(6-piperazin-1-yl-pyridin-3-yl)-pyrimidine-2,4-diamine	12.1

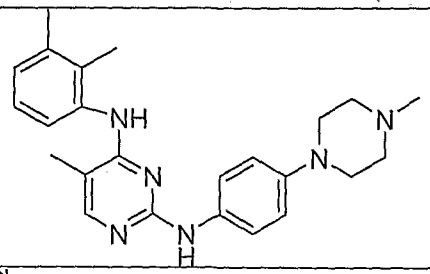
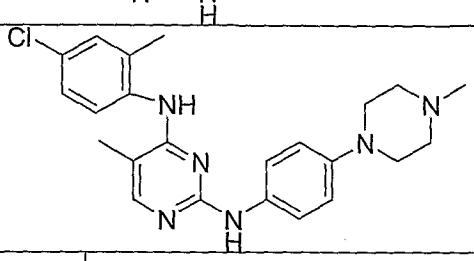
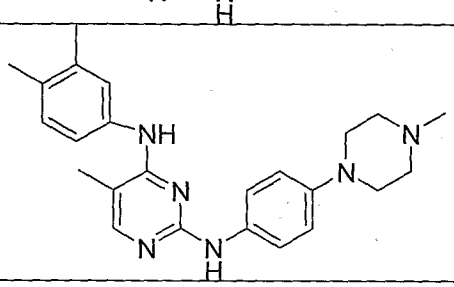
Structure	Name	JAK2 IC50
	5-[4-(4-Chloro-3-methoxy-phenylamino)-5-methyl-pyrimidin-2-ylamino]-2-piperazin-1-yl-benzoic acid methyl ester	5.12
	5-[4-(Benzo[1,3]dioxol-4-ylamino)-5-methyl-pyrimidin-2-ylamino]-2-(2-pyrrolidin-1-yl-ethoxy)-benzoic acid methyl ester	16.4
	N-tert-Butyl-3-{5-methyl-2-[4-(piperidin-4-yloxy)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	7.3
	N4-(1H-Indol-5-yl)-5-methyl-N2-[4-(piperidin-4-yloxy)-phenyl]-pyrimidine-2,4-diamine	
	2-{5-[4-(Benzo[1,3]dioxol-4-ylamino)-5-methyl-pyrimidin-2-ylamino]-pyridin-2-yloxy}-ethanol	116
	N4-Benzo[1,3]dioxol-4-yl-N2-[3-methoxy-4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5-methyl-pyrimidine-2,4-diamine	9.34

Structure	Name	JAK2 IC50
	N-tert-Butyl-3-[2-(4-imidazol-1-yl-phenylamino)-5-methyl-pyrimidin-4-ylamino]-benzenesulfonamide	12.3
	N-tert-Butyl-3-[2-(4-imidazol-1-ylmethyl-phenylamino)-5-methyl-pyrimidin-4-ylamino]-benzenesulfonamide	8.42
	N-tert-Butyl-3-{2-[4-(2-hydroxy-ethoxy)-phenylamino]-5-methyl-pyrimidin-4-ylamino}-benzenesulfonamide	20.3
	N-tert-Butyl-3-{5-methyl-2-[4-(4-oxy-morpholin-4-ylmethyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	48.6
	N4-(4-Chloro-3-methoxy-phenyl)-5-methyl-N2-(4-piperazin-1-ylmethyl-phenyl)-pyrimidine-2,4-diamine	15.2
	N-tert-Butyl-3-{5-methyl-2-[4-(2-methyl-imidazol-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	34.3
	N-tert-Butyl-3-{5-methyl-2-[4-(2-methyl-imidazol-1-ylmethyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	21.9

Structure	Name	JAK2 IC50
	N-tert-Butyl-3-[5-methyl-2-(4-pyridin-4-ylmethyl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide	80.7
	N-tert-Butyl-3-[5-methyl-2-(4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide	12.1
	N2-(4-(1H-pyrazol-1-yl)phenyl)-N4-(3-tert-butylphenyl)-5-methylpyrimidine-2,4-diamine	151
	N4-(7-chloro-1H-indol-4-yl)-5-methyl-N2-(4-((piperazin-1-yl)methyl)phenyl)pyrimidine-2,4-diamine Hydrochloride	694
	N4-(3-tert-butylphenyl)-5-methyl-N2-(4-(2-methyl-1H-imidazol-1-yl)phenyl)pyrimidine-2,4-diamine Hydrochloride	38.4
	N4-(3-tert-butylphenyl)-5-methyl-N2-(4-(2-methyl-1H-imidazol-1-yl)phenyl)pyrimidine-2,4-diamine Hydrochloride	94.1
	N-tert-Butyl-3-[5-methyl-2-(4-[1,2,4]triazol-1-ylmethyl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide	35.4

Structure	Name	JAK2 IC50
	N-tert-Butyl-3-{5-methyl-2-[4-(4-methyl-imidazol-1-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	41.7
	2,N-Dimethyl-5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	127
	N-tert-Butyl-2-methyl-5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	44.4
	N-tert-Butyl-3-[5-methyl-2-(4-[1,2,4]triazol-1-yl-phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide	41.4
	N-tert-Butyl-3-{5-methyl-2-[3-(1H-tetrazol-5-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	55.9
	N-tert-Butyl-5-[2-(4-imidazol-1-yl-phenylamino)-5-methyl-pyrimidin-4-ylamino]-2-methyl-benzenesulfonamide	88.2
	N-tert-Butyl-3-{5-methyl-2-[4-(pyrrolidine-1-carbonyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	33.5

Structure	Name	JAK2 IC50
	N-tert-Butyl-3-{5-methyl-2-[4-(morpholine-4-carbonyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	32.9
	N-tert-Butyl-3-{5-methyl-2-[4-(piperazine-1-carbonyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	69
	N-tert-Butyl-3-{5-methyl-2-[4-(1H-tetrazol-5-yl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	96.7
	N4-(3-tert-butylphenyl)-5-methyl-N2-(4-(1-morpholinoethyl)-phenyl)pyrimidine-2,4-diamine Hydrochloride	19.9
	3-{2-[4-(4-Acetyl-piperazin-1-yl)-phenylamino]-5-methyl-pyrimidin-4-ylamino}-N-tert-butyl-benzenesulfonamide	18.6
	N4-(3-tert-butylphenyl)-5-methyl-N2-(4-(piperidin-4-yl)phenyl)pyrimidine-2,4-diamine Hydrochloride	20.9
	N-tert-Butyl-3-{5-methyl-2-[4-(1-morpholin-4-yl-ethyl)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide	29.7

Structure	Name	JAK2 IC50
	5-methyl-N4-(2,3-dimethylphenyl)-N2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine Hydrochloride	16
	N4-(4-chloro-2-methylphenyl)-5-methyl-N2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine Hydrochloride	15.9
	5-methyl-N4-(3,4-dimethylphenyl)-N2-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4-diamine Hydrochloride	16.6

EXAMPLE 245. Determination Of Efficacy Of Selected Ccompounds

[0468] HEL, CTLL-2 & normal human dermal fibroblasts (NHDF) were from the American Tissue Culture Collection Rockville, MD). BaF/3 cells were obtained from DKFZ Cancer Research Center (Heidelberg, Germany).

[0469] BaF/3, HEL & NHDF cells were grown in RPMI 1640 medium (Gibco BRL, Gaithersburg , MD) supplemented with penicillin, streptomycin, L-glutamine, and 10% fetal bovine serum (FBS). CTLL-2 cells were grown in the same media further supplemented with 20 U/mL recombinant IL-2 (Hoffmann-LaRoche, Nutley, NJ). Plasmid containing the human JAK2 coding sequence was purchased from Invitrogen (Madison, WI). $JAK2^{V617F}$ cDNA was generated by using site-directed mutagenesis to introduce the V617F mutation into the human JAK2 coding sequence followed by verification using two-directional sequencing. This cDNA was subsequently subcloned into a retroviral vector and transduced into BaF/3 cells. Permanently transduced BaF/3 cells expressing $JAK2^{V617F}$ were selected and maintained with 1 mg/ml G418. GFP was introduced into this cells by lentiviral transduction using pLenti6-GFP (Invitrogen) followed by selection with blasticidin and confirmation of GFP expression using FACs analysis.

[0470] Cell proliferation assay was performed using the XTT cell proliferation kit according to the manufacturer's instructions (Roche, Alameda, CA). In brief, approximately 2.5 × 103 cells were plated in triplicate into microtiter-plate wells in 100 μL RPMI growth media plus various doses of XLV. After 72 hour incubation twenty microliters of XTT was added to the wells and allowed to incubate for 4-6 hours. The colored formazan product that is formed was measured spectrophotometrically using the Vmax spectrophotometer (Molecular Devices, Sunnyvale, CA) at 450 nm with correction at 650 nm. IC50 values were determined using the GraphPad Prism 4.0 software (San Diego, CA), wherefore OD values were plotted on y-axis (linear scale) and concentration (mM) on the x-axis (log scale). Data was subjected to a non-linear regression fit analysis and IC_{50} values were determined as the concentration which inhibited proliferation 50%.

[0471] Proliferation EC50:

HEL – 270 nM
Baf3:JAK2V617F – 297 nM
Control data: IL-2-induced JAK3-dependent proliferation – 3395 nM
Control data: Normal human dermal fibroblast control – 6487 nM

Apoptosis assays

[0472] BaF/3-JAK^{V617F} cells cultured in growth medium (RPMI, 10%FBS, 1 mg/ml G418 and 10 μg/ml blasticidin) were treated with XLV at 1, 3 and 10 μM for 24 h. Following harvesting cells by centrifugation at 890 RCF (relative centrifugation force) for 5 min, genomic DNA was isolated from cell pellets using a DNA isolation kit (Puregen, Chino, CA). 5 μg genomic DNA of each sample was subjected to 1.2% agarose gel electrophoresis to detect genomic DNA fragmentation (DNA laddering assay). As a control, adherent normal human dermal fibroblasts (NHDF) cultured in growth medium (Cambrex, Walkersville, MD) at 60% confluence were treated with XLV as described above. Following 2 washes with ice cold PBS, genomic DNA was isolated from the NHDF cells for agarose gel electrophoresis.

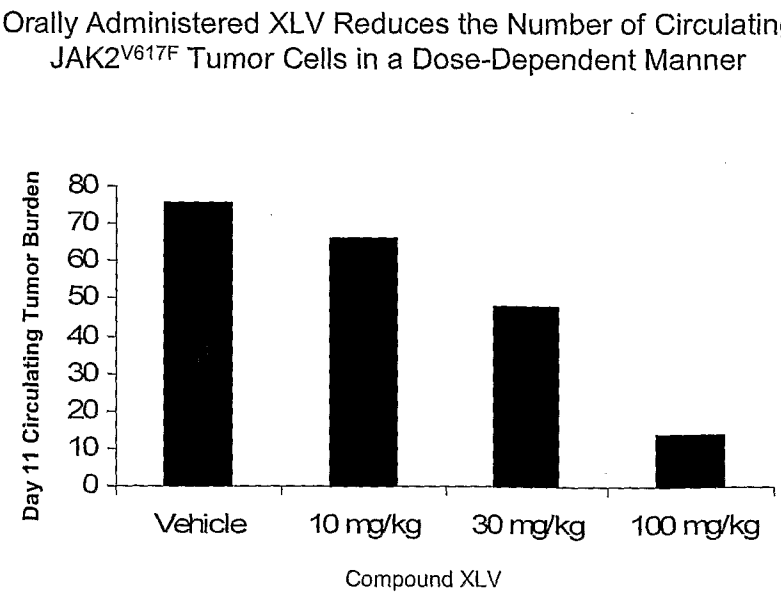
Immunoblotting

[0473] BaF/3-JAK^{V617F} cells treated with XLV or vehicle control were centrifuged, washed 2X with ice-cold PBS and lysed using RIPA buffer. Protein concentration was determined using the BCA method (Pierce, Rockford, IL) and 100 μg of total cellular protein of each sample in 1X Laemmli buffer were subjected to Western blot analysis. The protein blot was probed with an anti-phospho-STAT5 (Tyr694/699) (Upstate Biotechnology,

Charlottesville, VA), subsequently stripped and re-probed with an anti-STAT5 antibody (Cell Signaling Technology, Danvers, MA). The phospho-STAT5 or STAT5 protein was visualized by the enhanced chemoluminescence method (Pierce). In vivo signaling studies were done in a similar fashion. Briefly, on day 11 after cell injection, animals were orally dosed with either vehicle or 100 mg/kg of XLV. Spleens were harvested 7 h after dosing and quickly homogenized in a FastPrep machine (Qbiogen, Irvine, CA). 100 μg of each spleen homogenate were subjected to Western blot analysis. The protein blot was probed with an anti-phospho-STAT5 (Tyr694/699) and subsequently with an anti-STAT5 antibody and visualized by the enhanced chemoluminescence method.

FACs analysis of circulating tumor burden

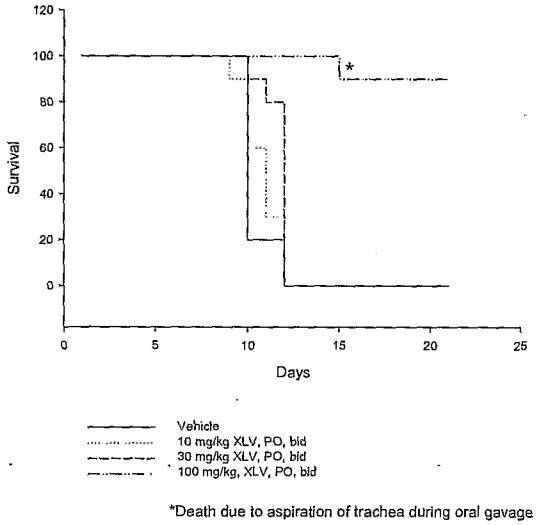
[0474] On day 11 after injection of BaF/3-JAK2^{V617F} cell suspension, 1 mL blood was collected by a terminal cardiac bleeding method from one mouse that received vehicle, moreover, 0.1 mL blood was collected by a non-lethal retro-orbital collection method from 10 mice of each of the three groups dosed with 10, 30 or 100 mg/kg of XLV and pooled together within the dose groups. Blood mono-nucleated cells were isolated by a Ficoll (Sigma-Aldrich, St. Louis, MO) cushion centrifugation method (600 RCF and 30 min). The isolated cells were subjected to FACS analysis to determine the percentage of GFP positive BaF/3:JAK2^{V617F} cells. The results are shown on the following chart.



Circulating Tumor Model

[0475] SCID mice were intravenously injected with BaF/3 cells expressing $JAK2^{V617F}$ and GFP. XLV was dosed orally at the indicated doses beginning 3 days after infusion and ending 20 days after infusion. On day 11 blood was taken from animals in each group and subjected to FACs analysis to determine the percentage of circulating cells which were GFP positive. In a parallel study animals were treated as described above with the exception that they were given a single 100 mg/kg dose of drug on day 11 followed 4 hours later by sacrifice and analysis of STAT5 phosphorylation in the tumor-bearing enlarged spleen. The results are shown on the following chart.

XLV in vivo study data using a circulating tumor model



*Death due to aspiration of trachea during oral gavage

Drug given orally bid beginning on day 3 after tumor injection

Ocular exposure and efficacy data

[0476] Exposure data of compounds at 0.1% via eye drop administration:

[0477] On topical dosing of compounds formulated as 0.1% doses in 0.2% tyloxapol/1% HPMC/4% Mannitol, exposure levels in found in back of the eye tissues of the mouse are shown at two different time points, namely at 2 h and at 7 h. The efficacy data for selected compounds are shown in Table 2.

TABLE 2

Concentration (nM) in mouse ocular tissues following bilateral topical instillation of 0.1% formulation QDX1

Formulation concentration for selected compounds	Time (hr)	Concentration (nM) retina	Sclera/choroid	Cornea
0.1% XVII	2	495	6040	8840
	6	351	2970	3780
0.1% XXXVI	2	816	7250	7870
	7	11200	34800	18600
0.1% XLIV	2	406	4840	103000
	7	321	3180	26600
0.1% LXXXII	2	267	2340	69900
	7	592	2250	45400
0.1% LXXIV	2	2120	6090	45000
	7	2150	7350	21000

EXAMPLE 246. Compound XVII in an Ocular efficacy study in an oxygen-induced retinopathy (OIR) model

[0478] Compound **XVII** was tested using the mouse oxygen-induced retinopathy (OIR) model, in which retinal neovascularization is triggered by cycling mouse pups from normoxia to hyperoxia and then back to normoxia. Litters of C57BL/6 mice were transferred to a hyperoxic environment (70% O_2) starting on postnatal day 7 (P7). After 5 days, litters were returned to a normoxic environment (21% O_2), where they were then maintained for an additional 5 days, during which time they received topical applications of either compound **XVII** or an appropriate vehicle. At the end of this period, retinal whole-mounts were prepared and stained with a fluorescently-labeled lectin (BSL I) that recognizes murine endothelium. Finally, digital images were obtained by fluorescence microscopy and analyzed with an image analysis software program in order to quantify vascular area. In one study, animals dosed with a 0.1% formulation of compound **XVII** twice daily (bid) showed a 29% reduction in vascular area as compared to vehicle-treated animals ($P<0.05$, $n= 11$-15); in a second study, a 22% reduction was observed ($P<0.02$, $n= 6$). The results are summarized in Table 3.

TABLE 3

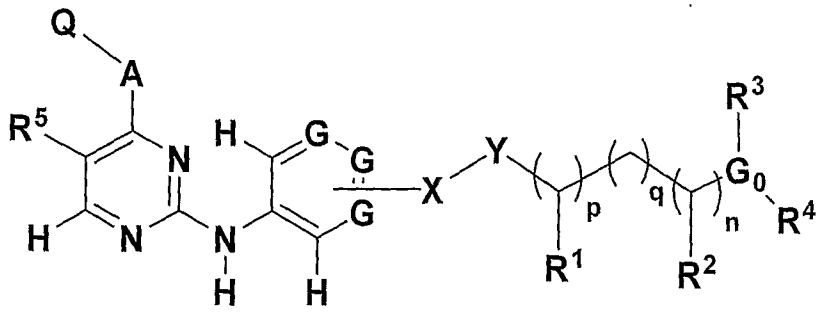
Study #	Treatment Group	Vascular Area (mm^2, mean ± SD)	% Change vs. Vehicle Control
OIR-004	Vehicle	4.9 ± 1.6	---
	0.1% **XVII**	3.5 ± 0.6	-29%
OIR-007	Vehicle	8.3 ± 0.8	---
	0.1% **XVII**	6.4 ± 1.6	-22%

[0479] Although the invention has been described with reference to the above examples, it will be understood that modifications and variations are encompassed within the spirit and scope of the invention. Accordingly, the invention is limited only by the following claims.

CLAIMS

What is claimed is

1. A compound having the structure (A):



(A)

wherein:

X is selected from a group consisting of a bond, O, C=O, SO_2, and CH_2; Y is selected from a group consisting of a bond or NR^9; or X and Y taken together is a bond;

each of R^1 and R^2 is independently selected from a group consisting of H, C_1-C_6 substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; or R^1 and R^2 taken together is a bond; or R^1 and R^2 taken together form a moiety selected from a group consisting of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, and $(CH_2)_r$–O–$(CH_2)_m$;

each of p, q, r, n, m is idependently an integer having the value between 0 and 6,

R^9 is selected from a group consisting of H, C_1-C_6 alkyl, C_1-C_6 cycloalkyl, C_1-C_6 branched alkyl, C_1-C_6 substituted alkyl, C_1-C_6 aminoalkyl, and C_1-C_6 hydroxyalkyl;

G_0 is selected from a group consisting of N, O, H, and CH,

with the proviso that if G_0 is N, then:

each of R^3 and R^4 is independently selected from a group consisting of H, C_1-C_6 alkyl, C_1-C_6 substituted or unsubstituted hydroxyalkyl or aminoalkyl, C_1-C_6 substituted or

unsubstituted branched alkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, or R^3 and R^4 taken together form a moiety selected from a group consisting of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, and $(CH_2)_r$–O–$(CH_2)_m$;

with the additional proviso that if G_0 is N, then:

R^1 and R^9 taken together form a moiety selected from a group consisting of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, and $(CH_2)_r$–O–$(CH_2)_m$; or R^1 and R^4 taken together forms a moiety selected from a group consisting of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, and $(CH_2)_r$–O–$(CH_2)_m$; or R^9 and R^4 taken together form a moiety selected from a group consisting of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, and $(CH_2)_r$–O–$(CH_2)_m$; or R^3 and R^4 taken together form a moiety selected from a group consisting of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^6–$(CH_2)_m$, and $(CH_2)_r$–O–$(CH_2)_m$;

with the further proviso that if G_0 is O, then:

R^3 is is selected from a group consisting of H, C_1-C_6 alkyl and C_1-C_6 substituted or unsubstituted hydroxyalkyl or aminoalkyl, substituted or unsubstituted branched alkyl, substituted or unsubstituted cycloalkyl, substituted heterocyclic connected through carbon or nitrogen, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl connected through carbon or nitrogen, with no group R^4; R^1 and R^9 taken together form a moiety selected from a group consisting of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, and $(CH_2)_r$–O–$(CH_2)_m$; or R^1 and R^3 taken together form a moiety selected from a group consisting of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, and $(CH_2)_r$–O–$(CH_2)_m$; or R^9 and R^3 taken together form a moiety selected from a group consisting of $(CH_2)_m$, $(CH_2)_r$–S–$(CH_2)_m$, $(CH_2)_r$–SO–$(CH_2)_m$, $(CH_2)_r$–SO_2–$(CH_2)_m$, $(CH_2)_r$–NR^9–$(CH_2)_m$, and $(CH_2)_r$–O–$(CH_2)_m$;

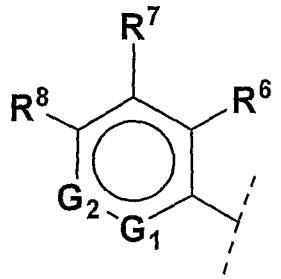
with the further proviso that if G_0 = CH, then each of R^3 and R^4 is independently selected from a group consisting of H, C_1-C_6 alkyl, C_1-C_6 substituted or unsubstituted hydroxyalkyl or aminoalkyl, C_1-C_6 substituted or unsubstituted branched alkyl, substituted or

unsubstituted aryl, C_1-C_6 substituted or unsubstituted heterocycle connected through carbon or nitrogen, and substituted or unsubstituted heteroaryl connected through carbon or nitrogen, or R^3 and R^4 taken together form a moiety selected from a group consisting of $(CHR^9)_r$–$(CHR^9)_m$–$(CHR^9)_p$, $(CHR^9)_r$–S–$(CHR^9)_m$, $(CHR^9)_r$–SO–$(CHR^9)_m$, $(CHR^9)_r$–SO_2–$(CHR^9)_m$, $(CHR^9)_r$–NR^9–$(CHR^9)_m$, and $(CHR^9)_r$–O–$(CHR^9)_m$;

G is N or CR^6, and each G is independent of each other G, with the further proviso that not more than two groups G can be N, with the further proviso that for each CR^6, each R^6 is independent of each other group R^6.

R^5 is methyl;

Q =



wherein each of R^6, R^7, R^8 is independently selected from a group consisting of H, C_1-C_6 substituted or unsubstituted alkyl, C_1-C_6 substituted or unsubstituted alkenyl, C_1-C_6 substituted or unsubstituted alkynyl, C_1-C_6 substituted or unsubstituted hydroxyalkyl or aminoalkyl, C_1-C_6 substituted or unsubstituted branched alkyl, C_1-C_6 substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl connected through carbon or a heteroatom, substituted or unsubstituted heteroaryl connected through carbon or a heteroatom, C_1-C_6 alkoxy, a halogen, CF_3, $-OCF_3$, CHR^3R^4, SR^3, SOR^3, SO_2R^3, $SO_2NR^3R^4$, SO_3R^3, POR^3, PO_2R^3, $PO_2NR^3R^4$, $PO_2CR^3R^4$, PO_3R^3, NR^3R^4, NO_2, CN, OH, $CONR^3R^4$, COR^3, $COOR^3$, N R^3CO R^4, $NR^3CONR^3R^4$, $OCONR^3R^4$, $CSNR^3R^4$, CSR^3, $NR^3CSNR^3R^4$, $SCONR^3R^4$, $SCSNR^3R^4$, and $SCSNR^3R^4$; or any of R^6 and R^7 taken together, or R^7 and R^8 taken together, or R^6 and R^8 taken together form a moeity independently selected from a group consisting of –HN–CH=CH–, –HN–N=CH–, –HN–N=N–, $-O(CH_2)_nO$–, $-S(CH_2)_nS$–, –N=CH–S–, –CH=N–O–, –CH=N–S–, –N=CH–O–, –C=N–O–, –C=N–O–, –CH=CH–CH=CH–, –N=CH–CH=CH–, –CH=N–CH=CH–, –O–CH=CH, and –S–CH=CH–; or R^3 and R^4 taken together form a moiety selected from a group consisting of $(CHR^9)_r$–$(CHR^9)_m$–$(CHR^9)_p$, $(CHR^9)_r$–S–$(CHR^9)_m$, $(CHR^9)_r$–SO–$(CHR^9)_m$, $(CHR^9)_r$–SO_2–$(CHR^9)_m$, $(CHR^9)_r$–NR^9–$(CHR^9)_m$, and $(CHR^9)_r$–O–$(CHR^9)_m$;

A is selected from a group consisting of O, NR^3, CR^3R^4, S, SO, and SO_2;

G_1 is selected from a group consisting of CH, N, NH, S, and O;

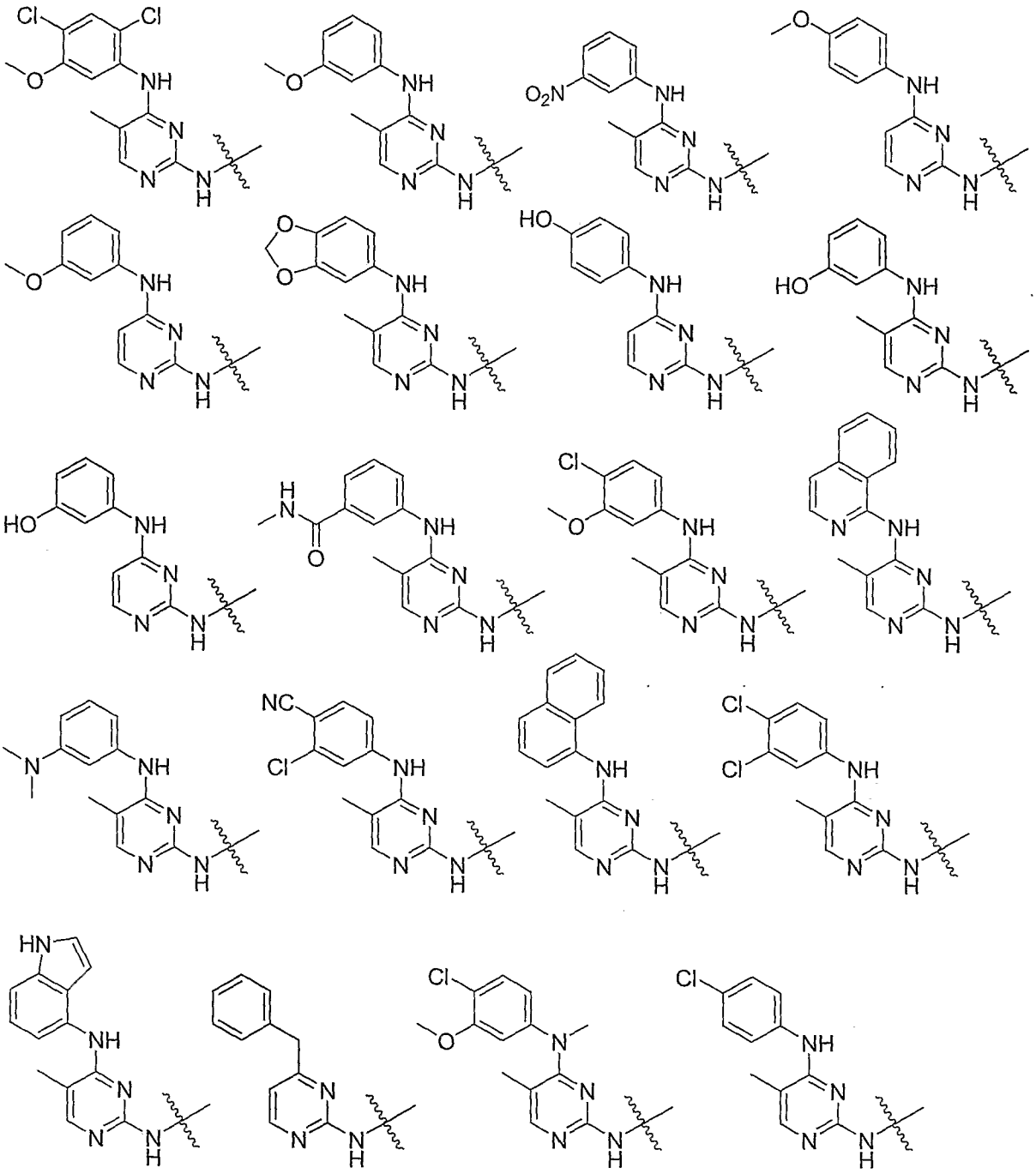
G_2 is selected from a group consisting of CR^7, N, NH, S, and O, with each group R^7 being independent of every other group R^7;

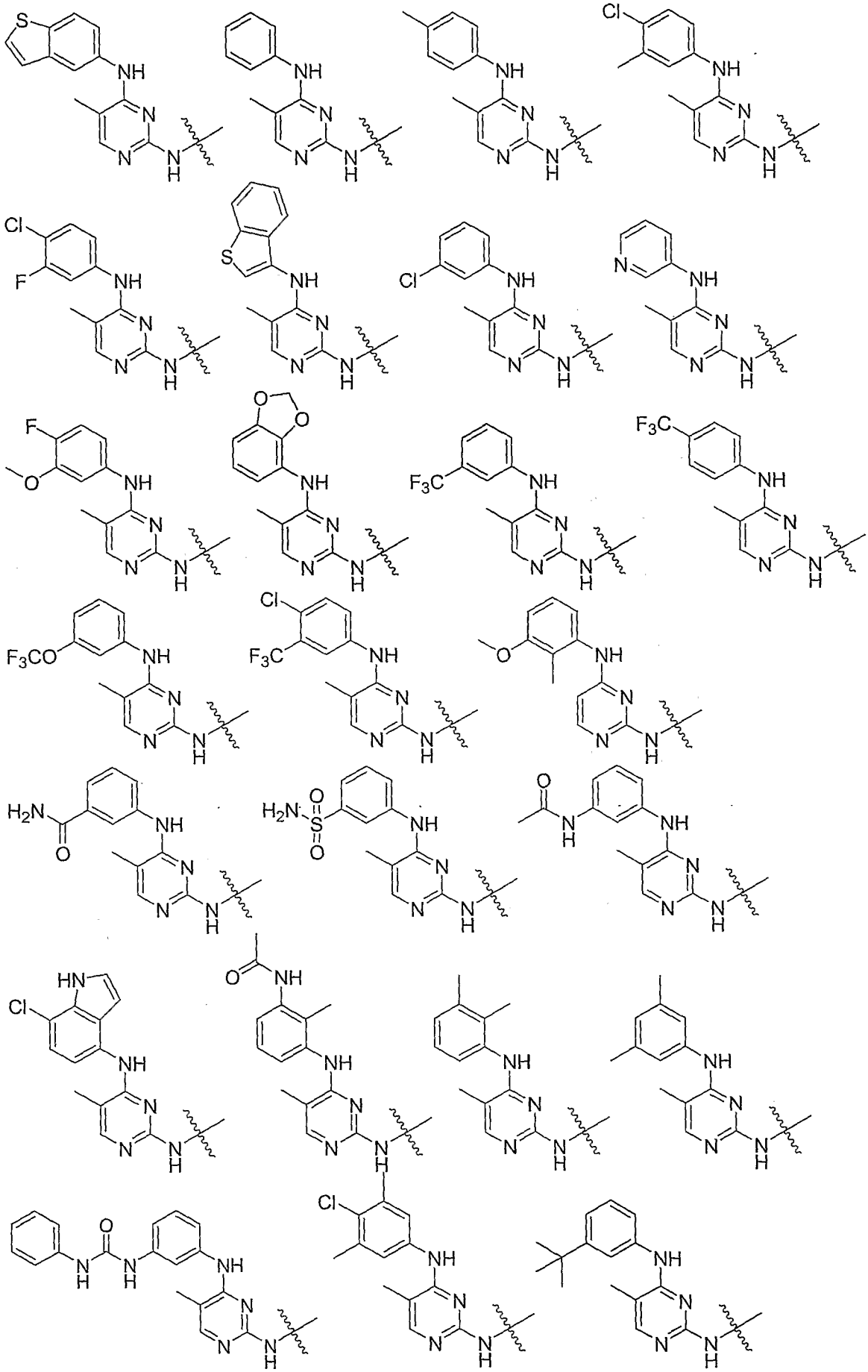
and if G_1 or G_2 is NH, S, or O, then Q is a five membered heteroaromatic ring, optionally fused to a six member aromatic or non-aromatic ring; and if G_1 or G_2 is N, then Q is a five or a six membered aromatic ring, optionally fused to a six member aromatic or non-aromatic ring;

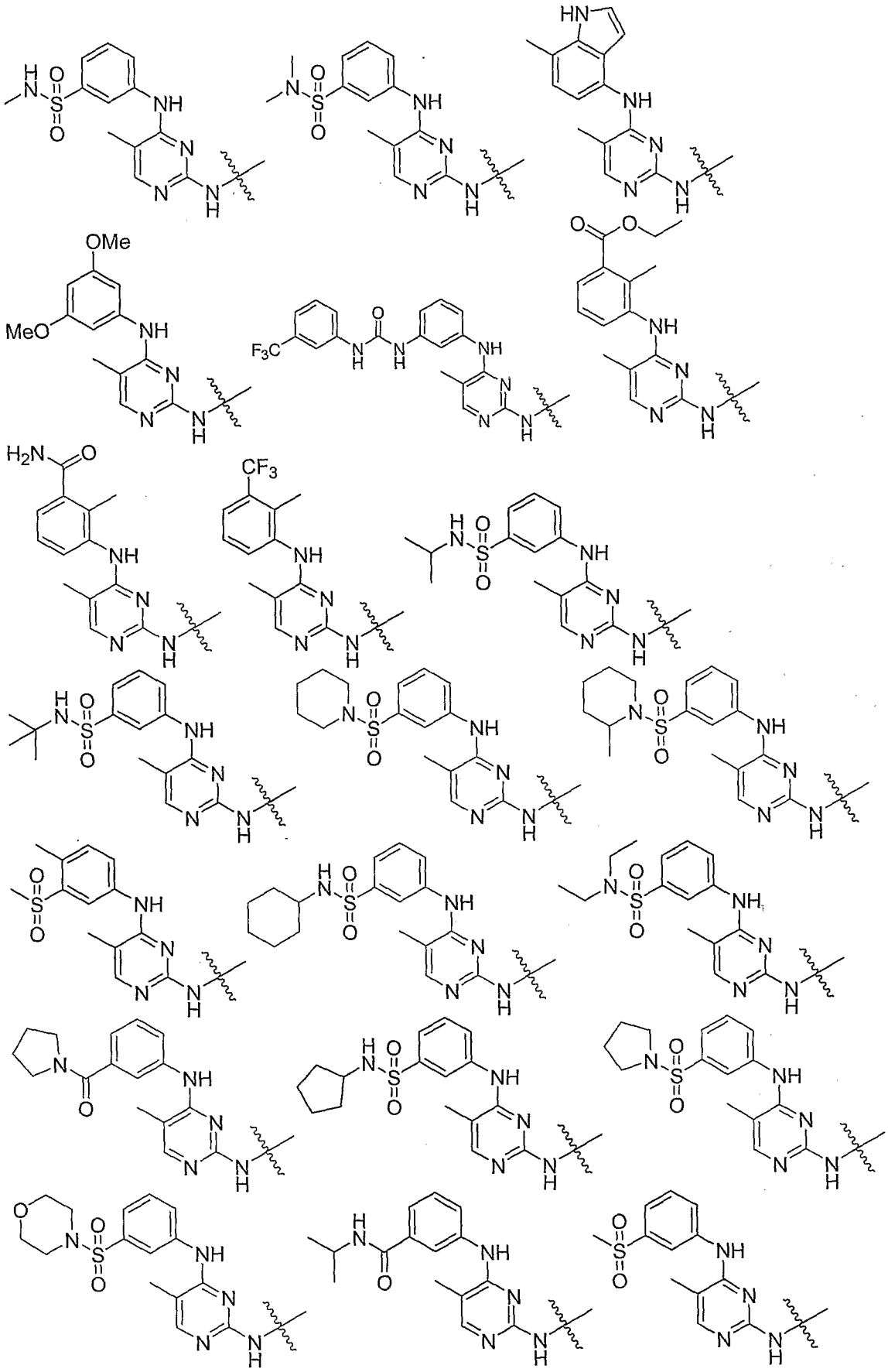
with the further proviso that X or G_0 includes at least one heteroatom included with X and selected from O, S and N, or G_0 comprises at least four non-hydrogen atoms, inclusive of the heteroatom, and R^3 and R^4, or R^1 and R^9, or R^1 and R^4, or R^9 and R^4 taken together form an aromatic, heteroaromatic, cyclic or heterocyclic ring system, or if a noncyclic system is present, then more than one heteroatom is present, and if A is NR_3, then any of R_6, R_7 or R_8, or any combination thereof independently includes at least two non-hydrogen substituents, or if A is NR_3, then Q forms a fused ring from R_6 to R_7, or from R_7 to R_8,

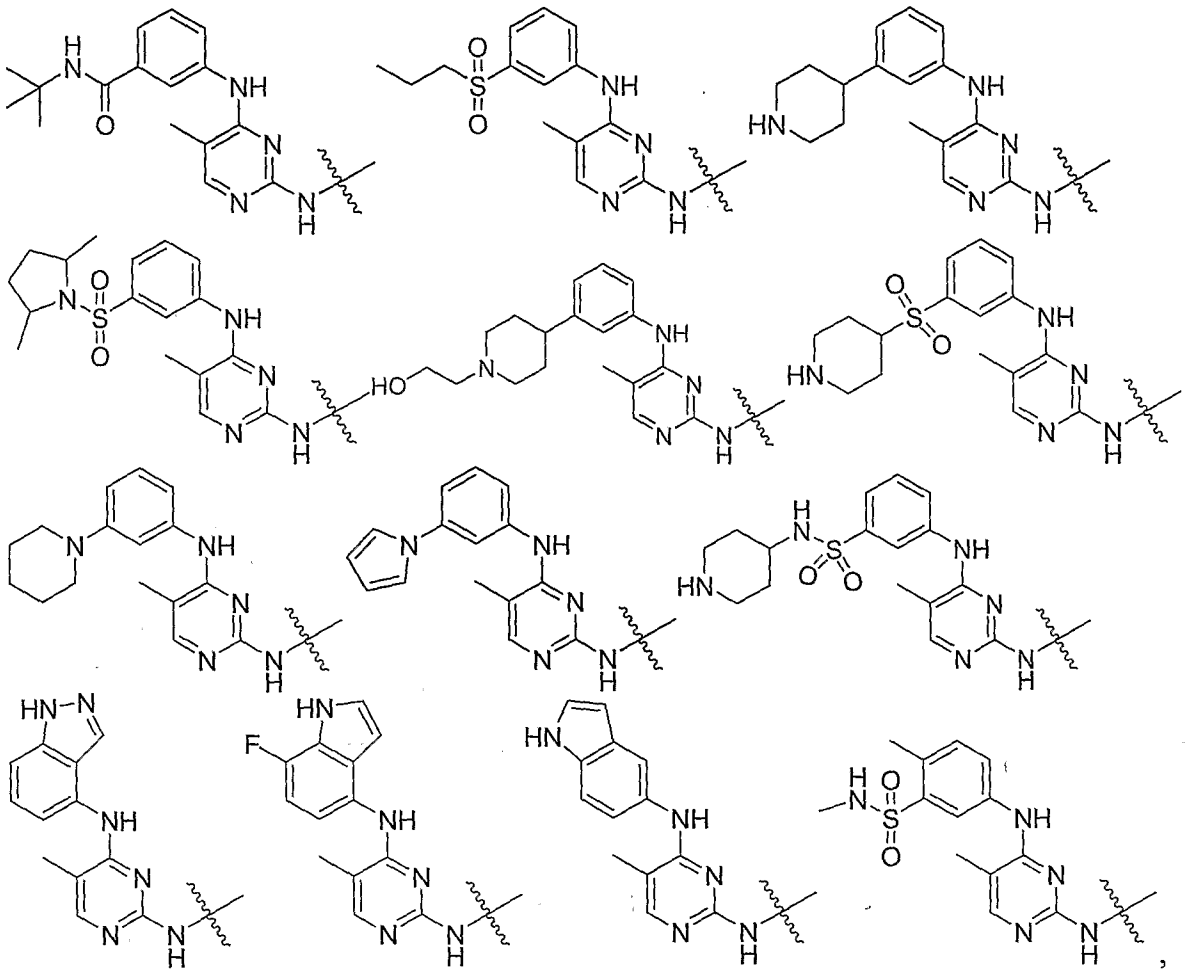
or pharmaceutically acceptable salts, hydrates, solvates, crystal forms, N-oxides, and individual diastereomers of the compound (A).

2. A compound comprising a first moiety chemically connected to a second moiety, or pharmaceutically acceptable salts, hydrates, solvates, crystal forms, N-oxides, and individual diastereomers thereof, wherein the first moiety is selected from the group consiting of:



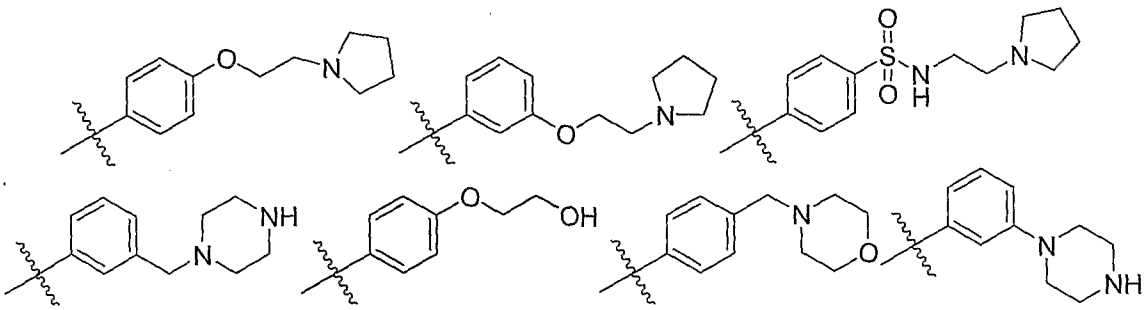


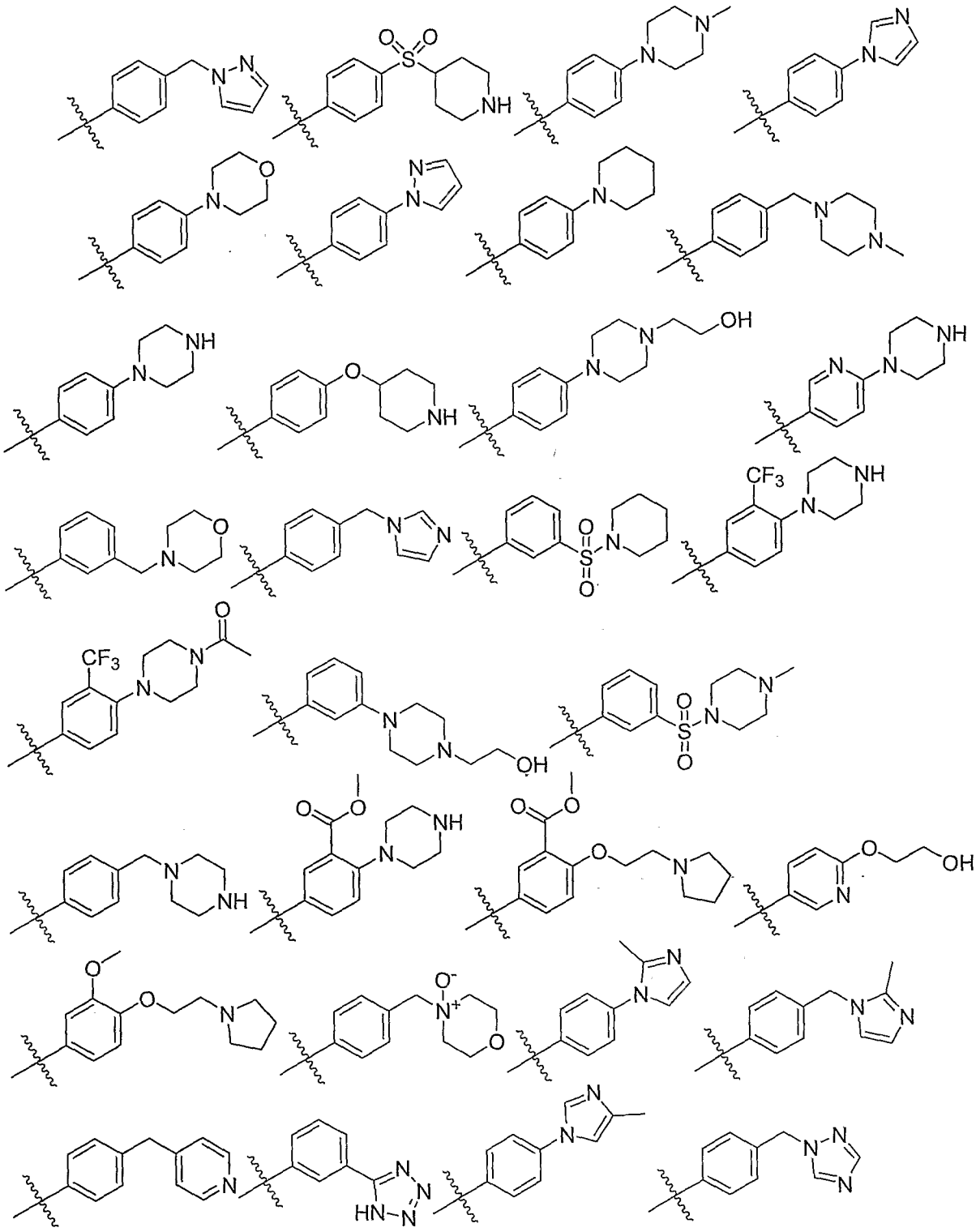


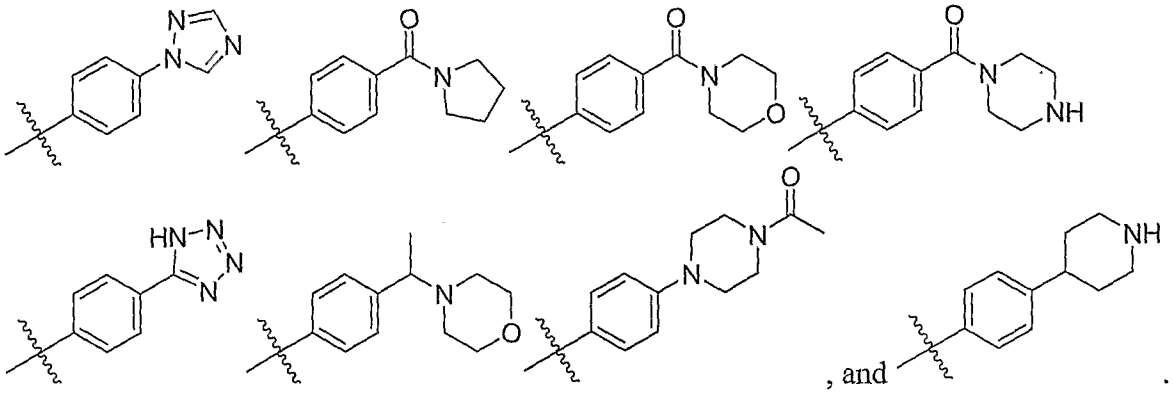


and

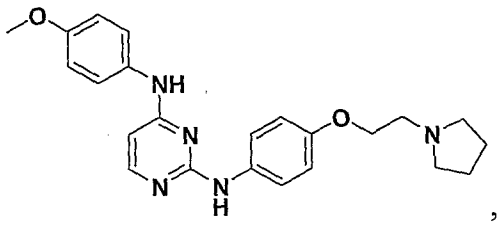
and wherein the second moiety is selected from the group consiting of:






, and .

3. The compound of claim 1, wherein the compound is selected from the group consisting of compounds having formulas I-CLXII: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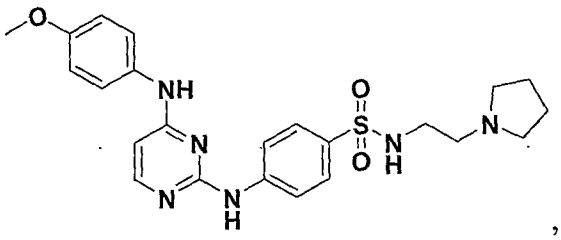
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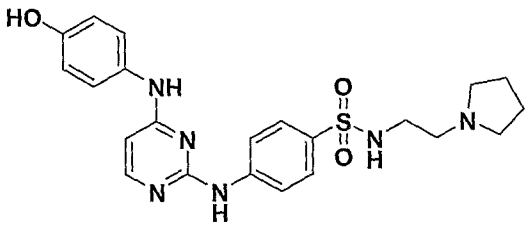
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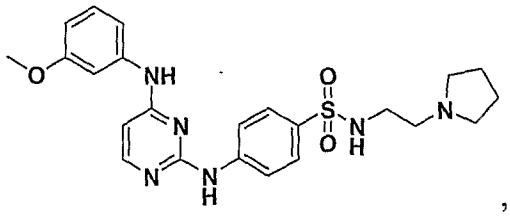

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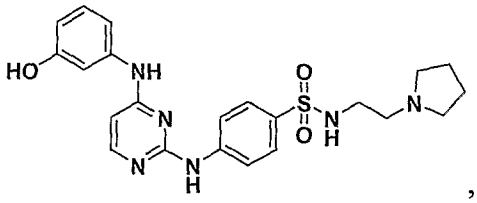

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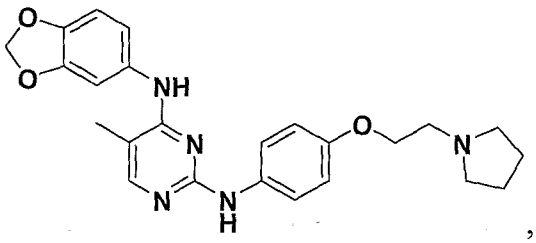

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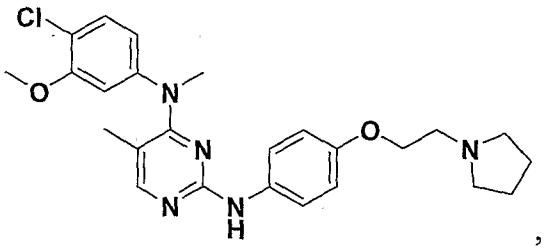
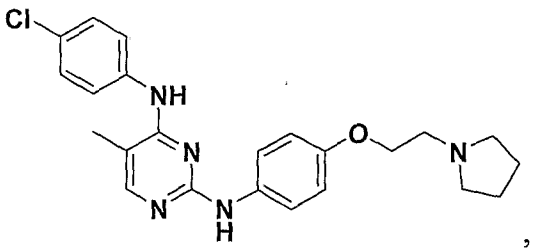


VII



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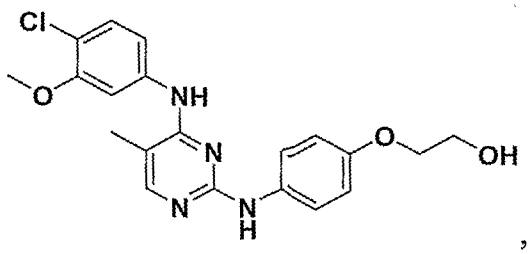

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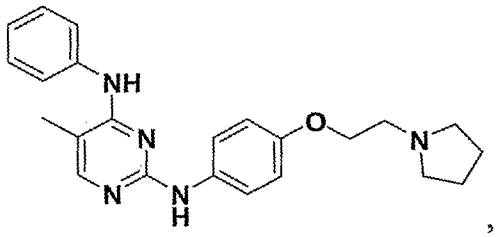

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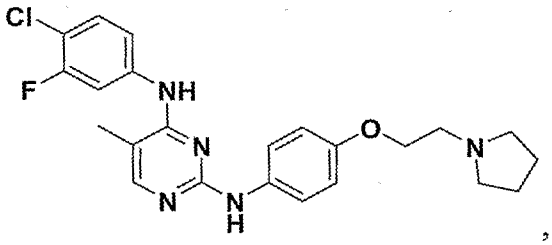

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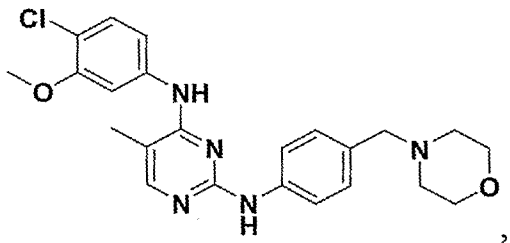

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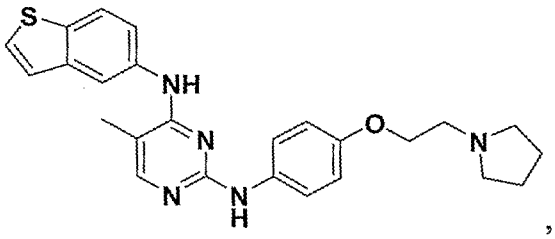

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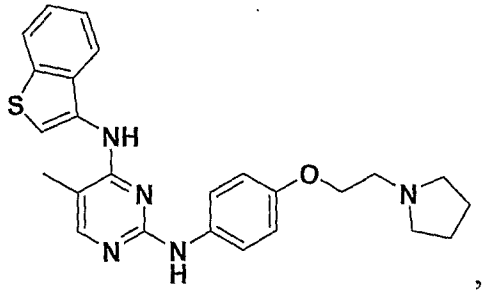

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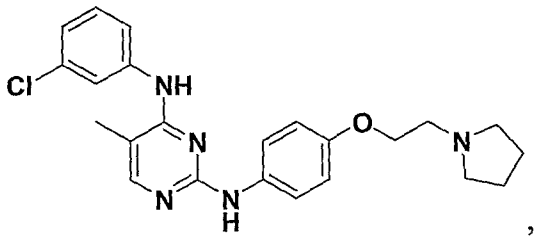

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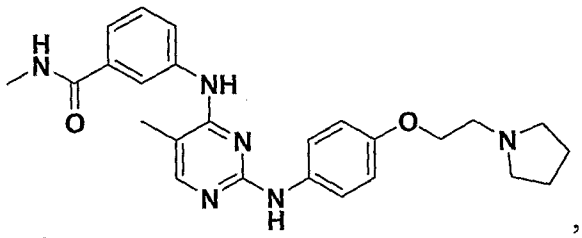

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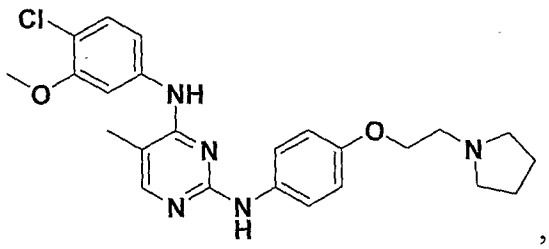

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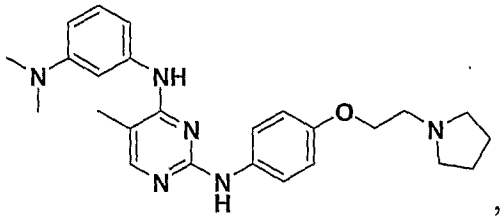

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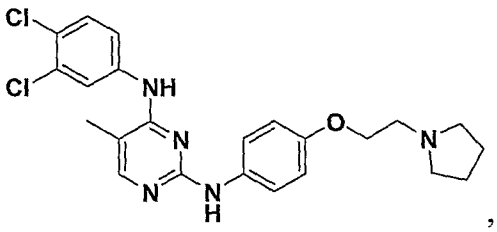

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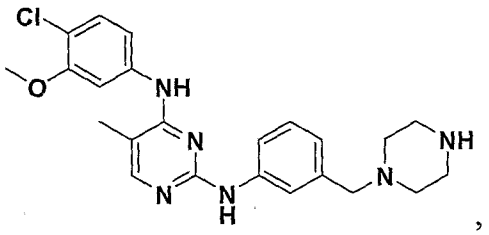

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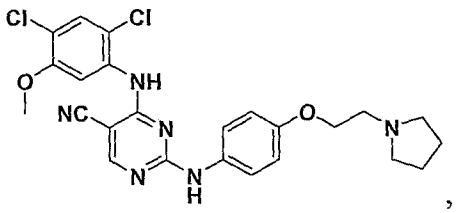

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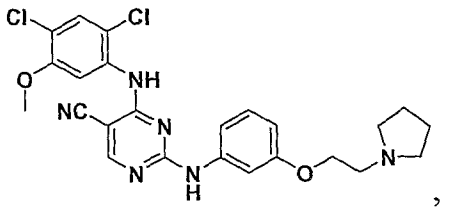

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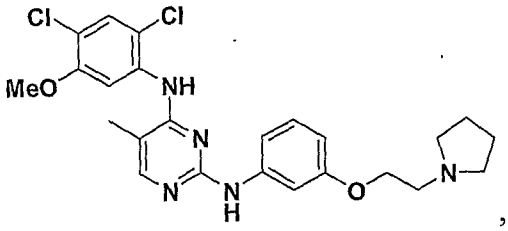

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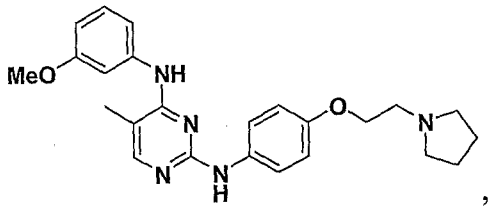

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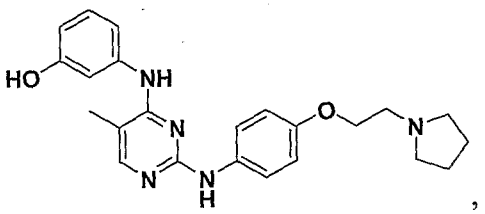

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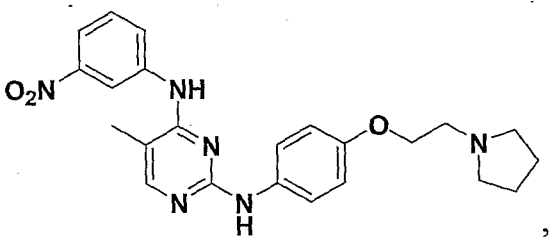

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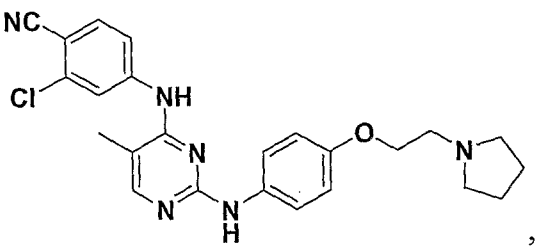

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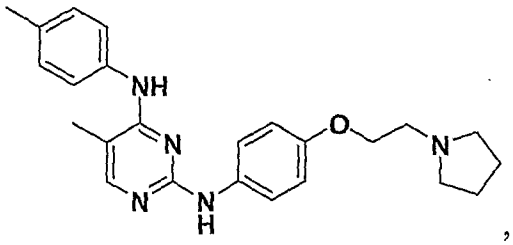

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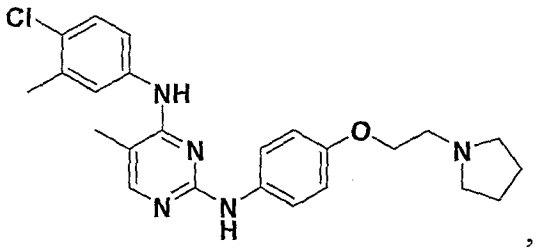

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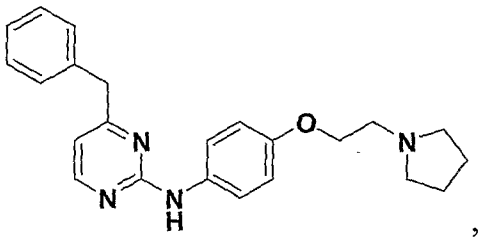

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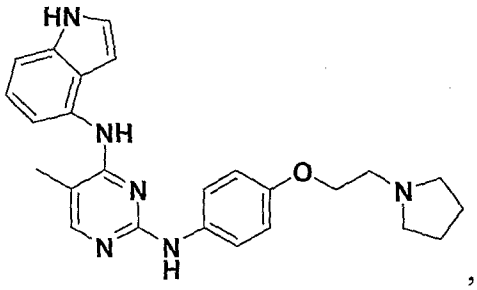

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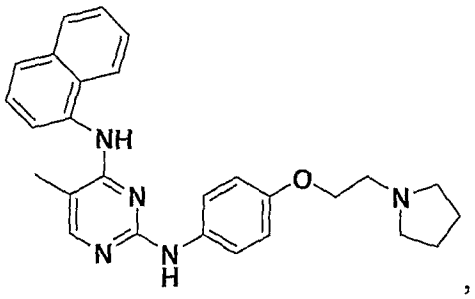

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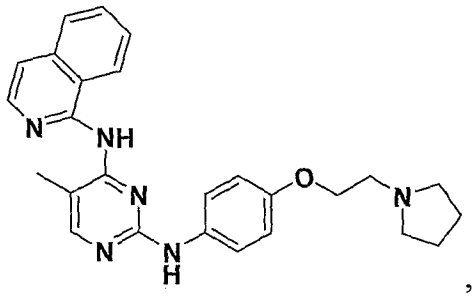

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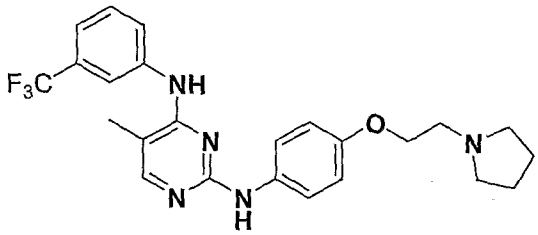

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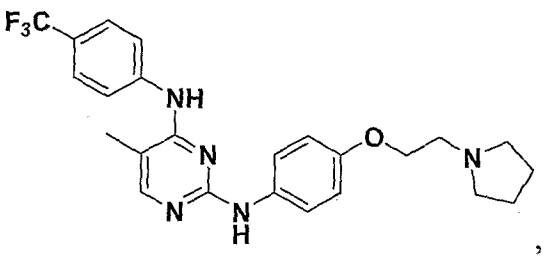

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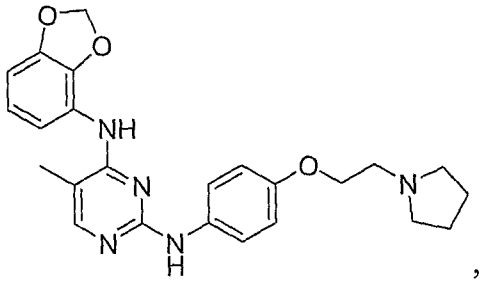

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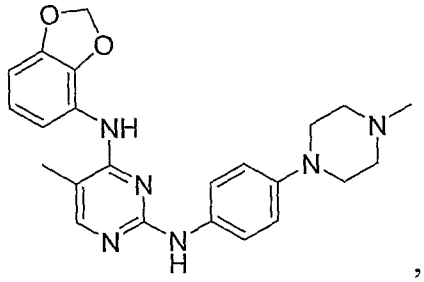

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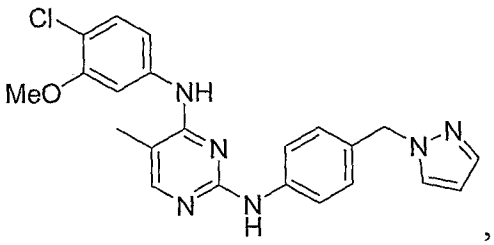

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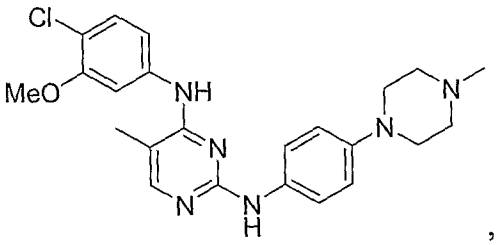

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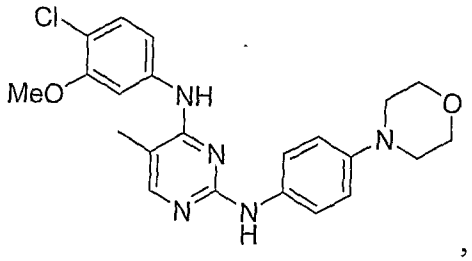

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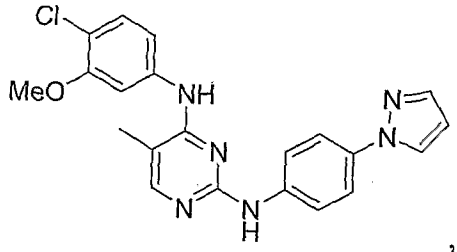

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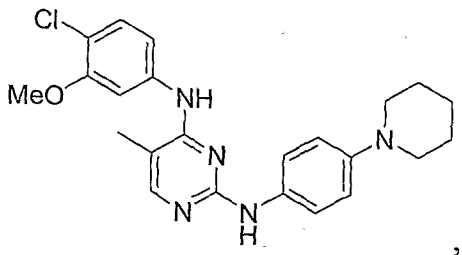

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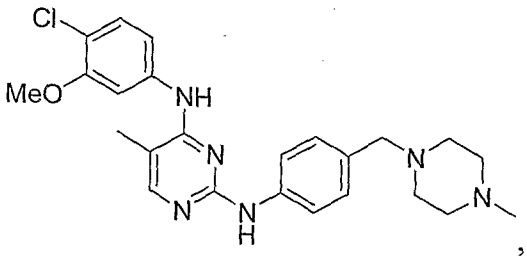

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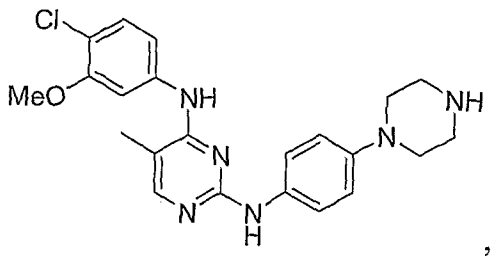

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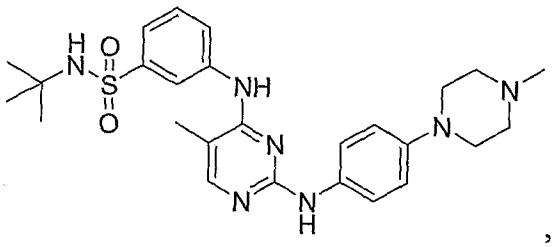

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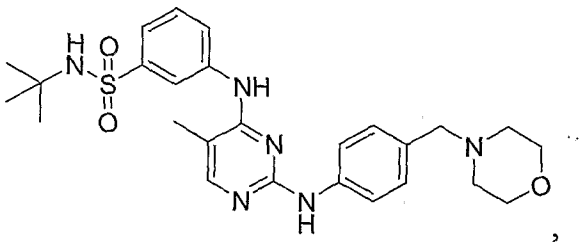

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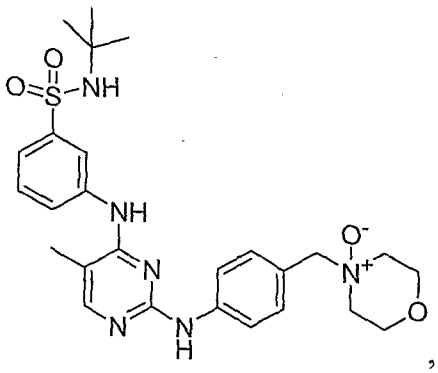

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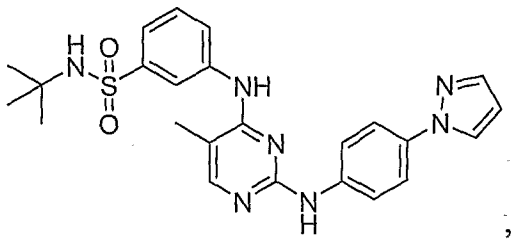

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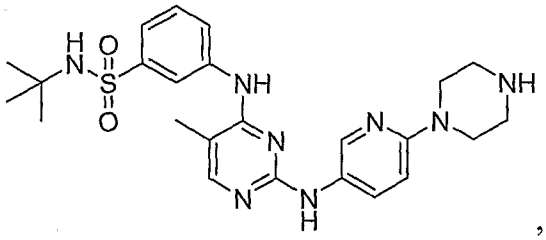

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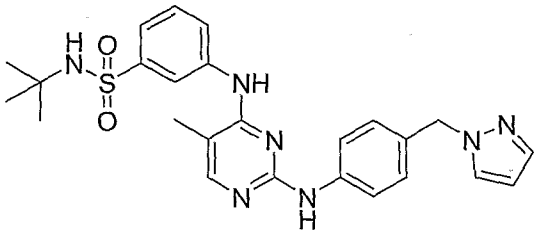

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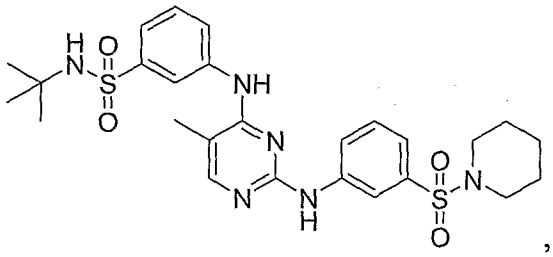

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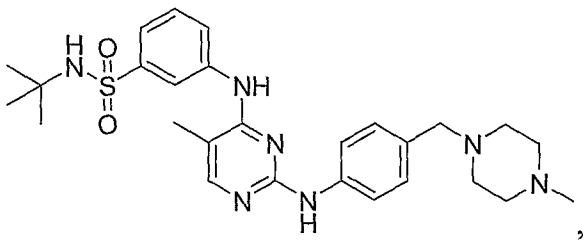

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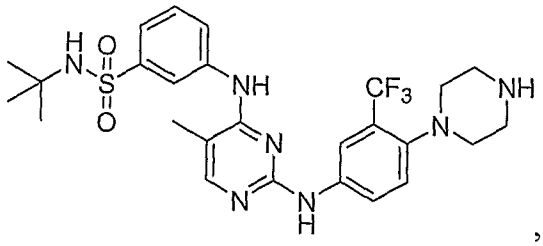

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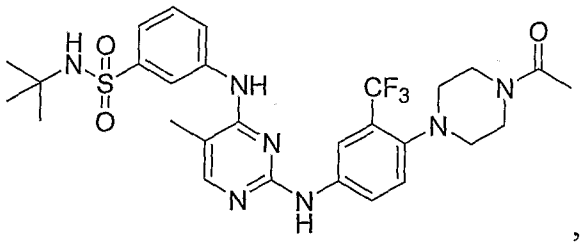

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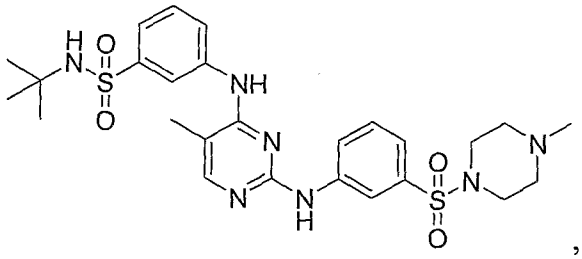

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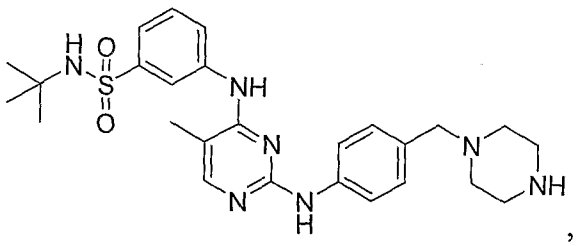

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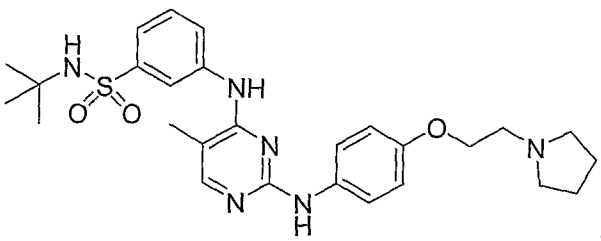

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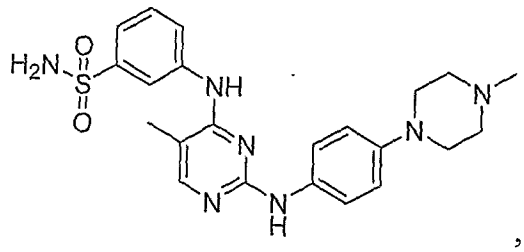

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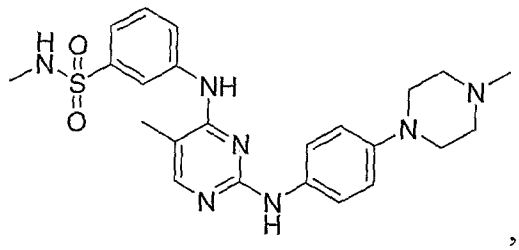

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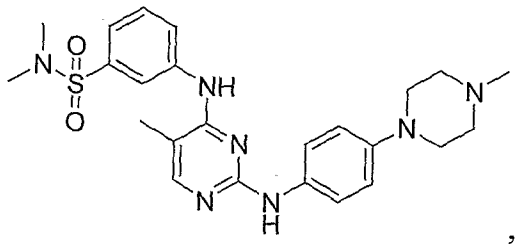

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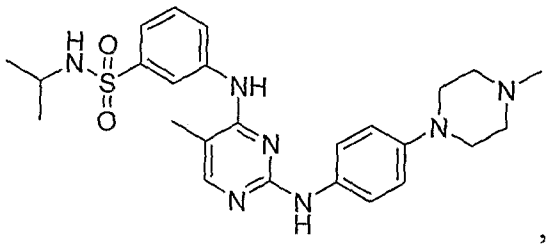

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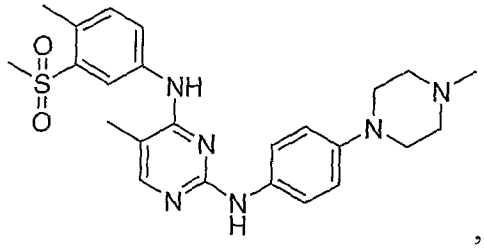

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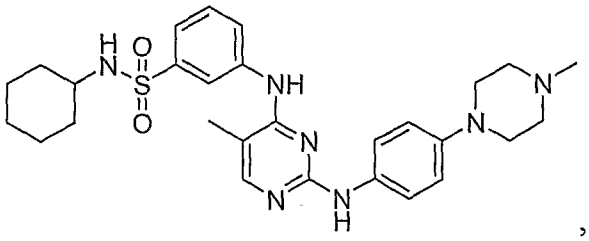

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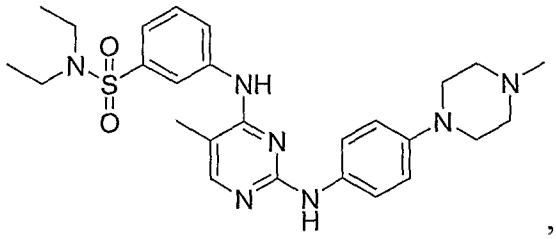

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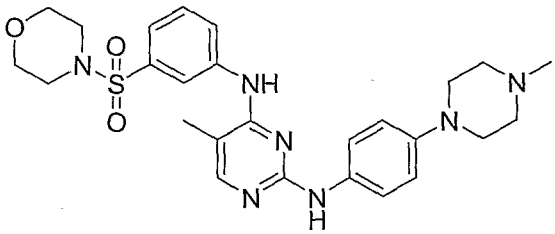

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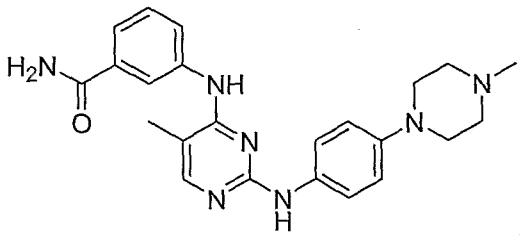

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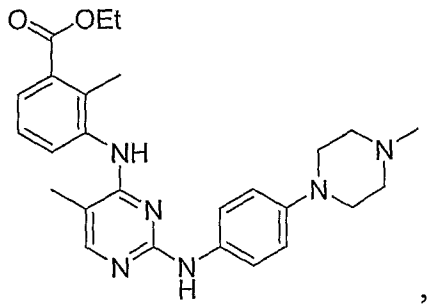

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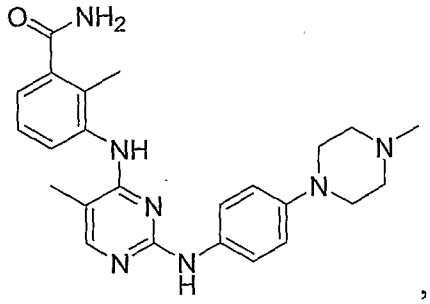

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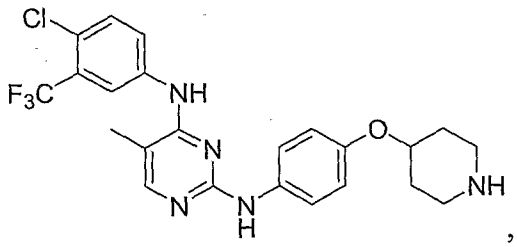

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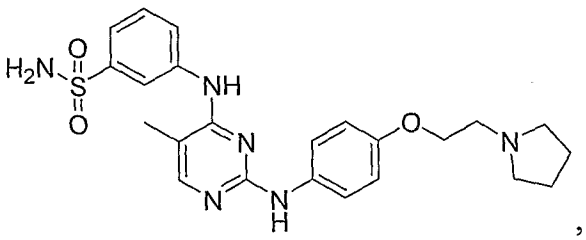

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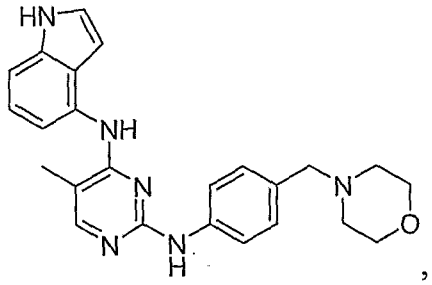

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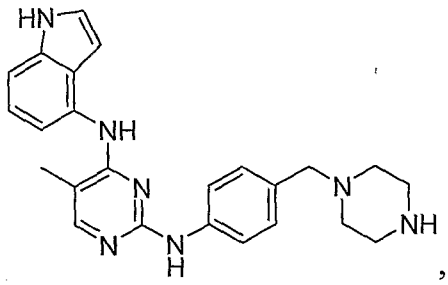

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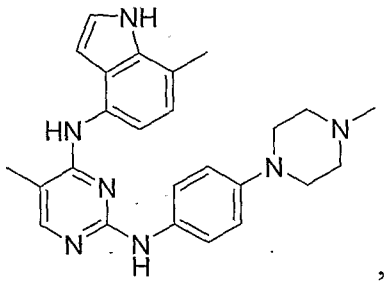

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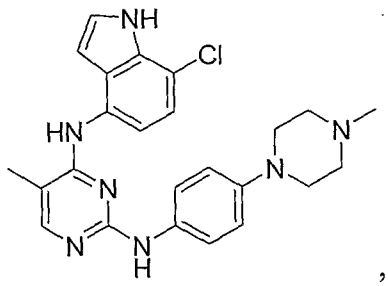

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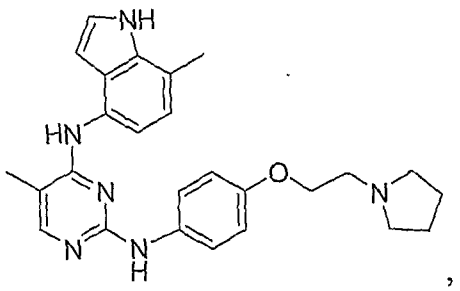

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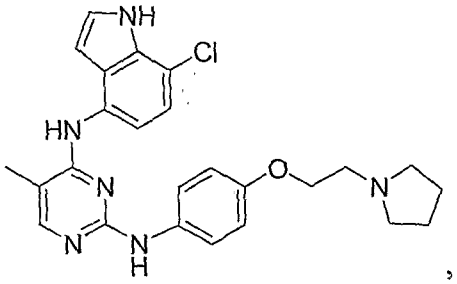

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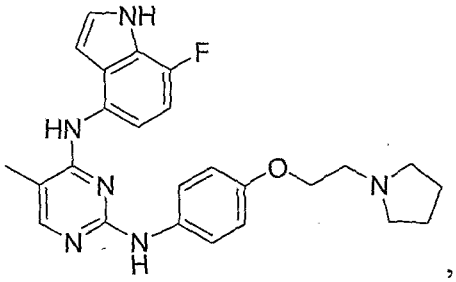

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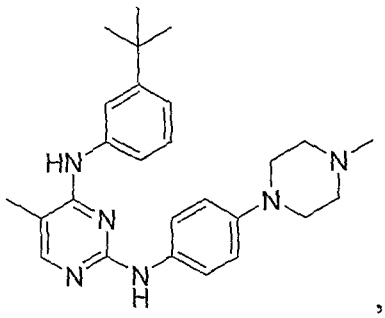

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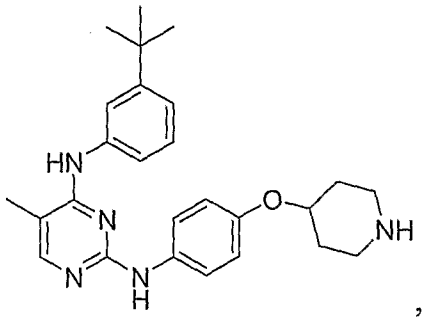

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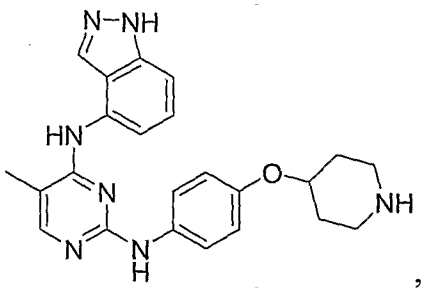

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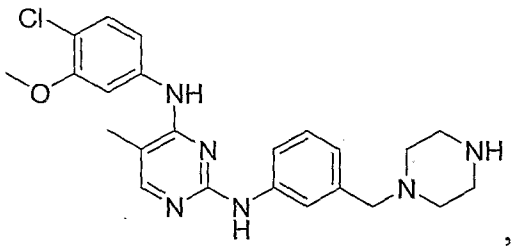

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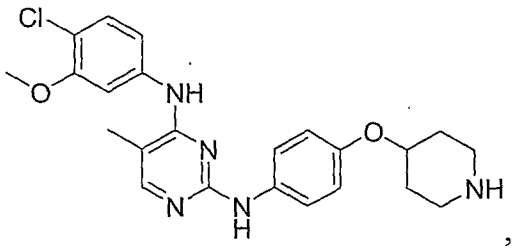

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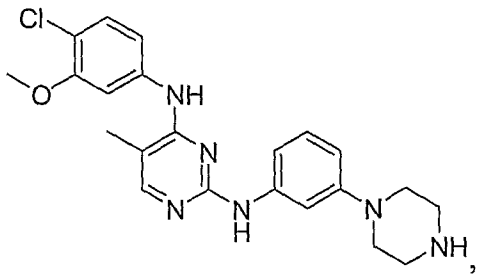

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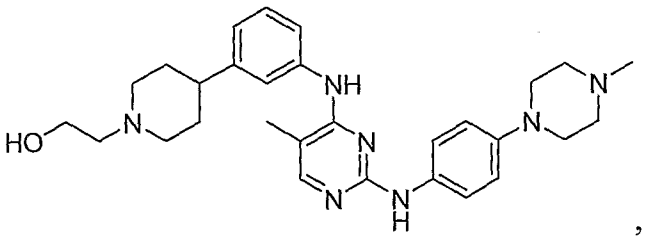

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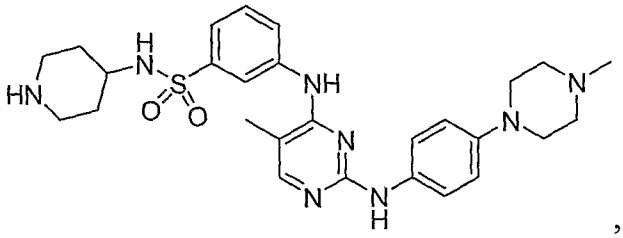

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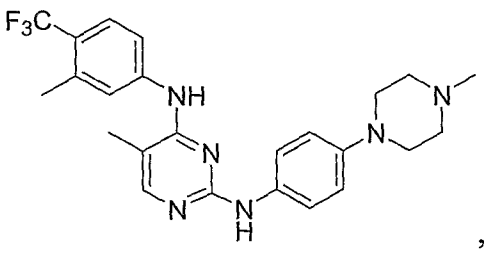

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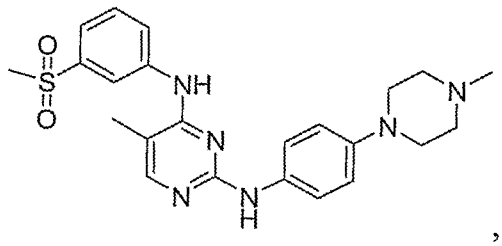

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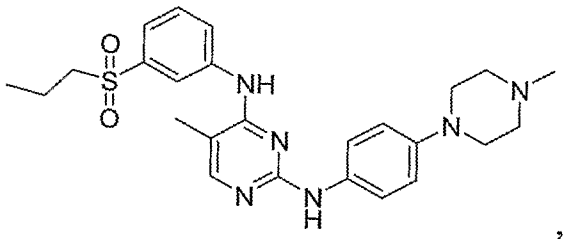

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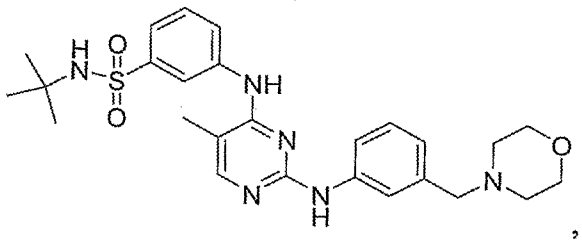

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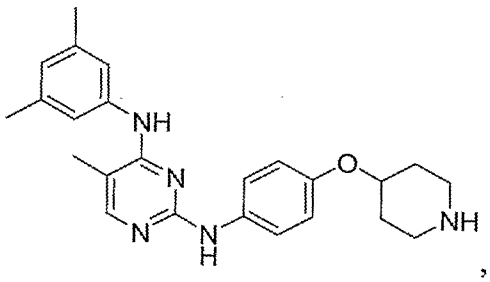

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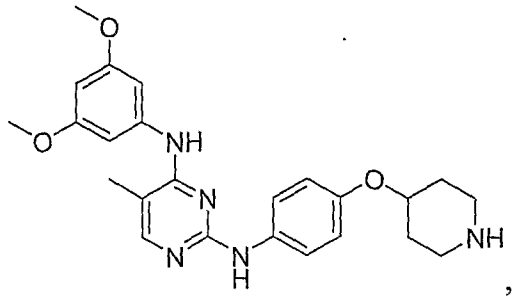

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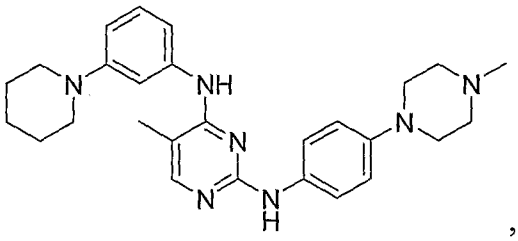

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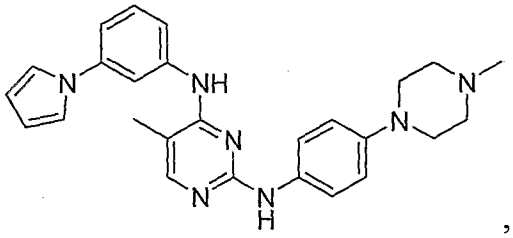

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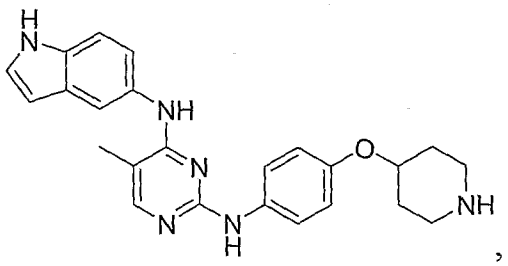

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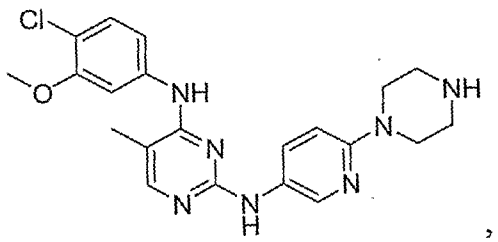

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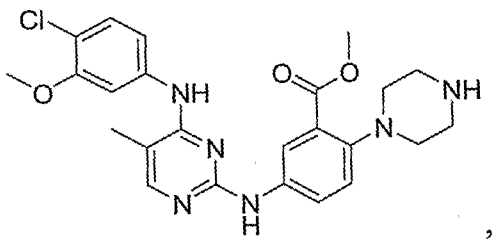

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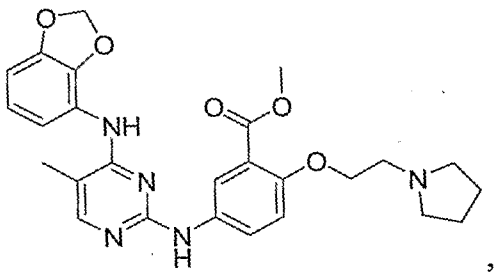

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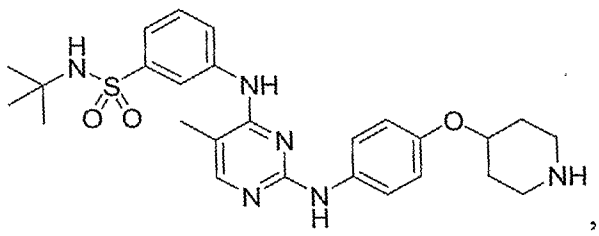

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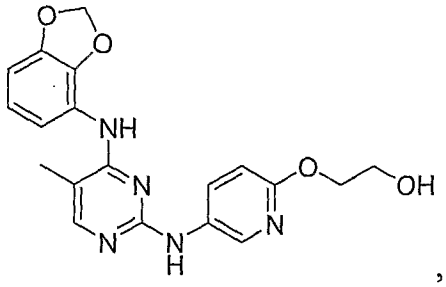

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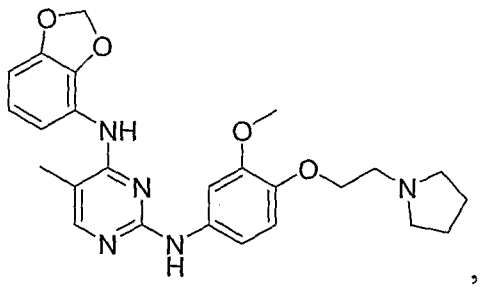

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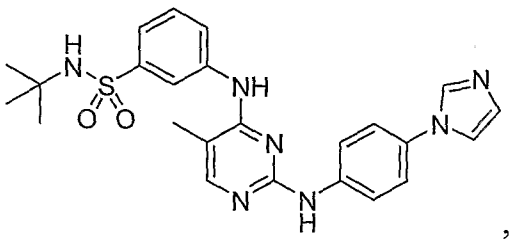

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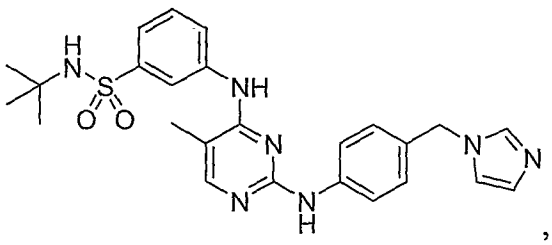

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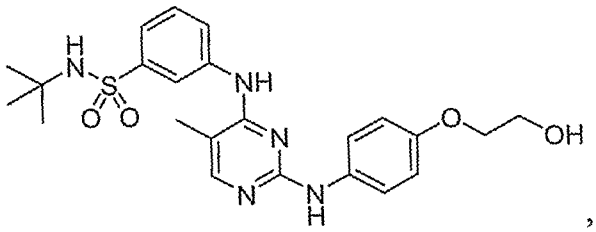

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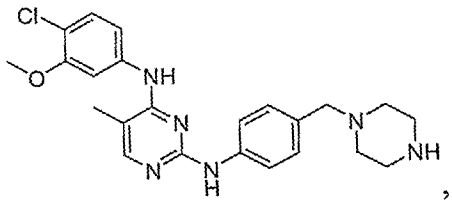

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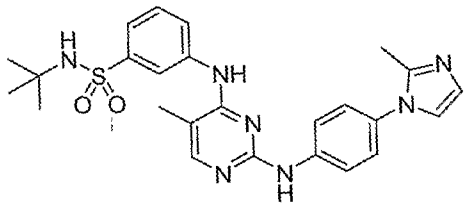

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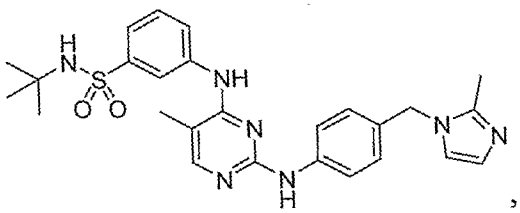

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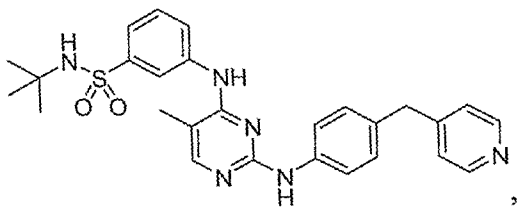

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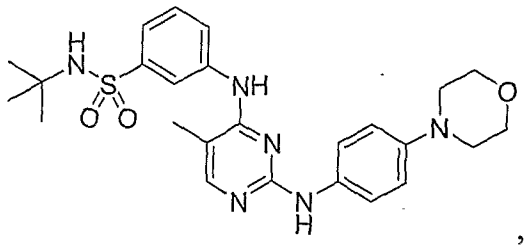

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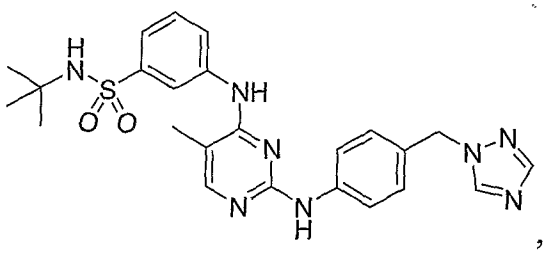

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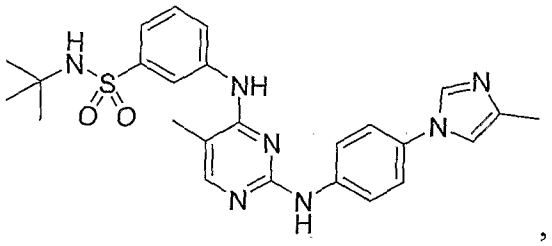

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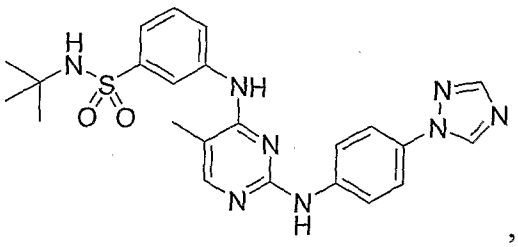

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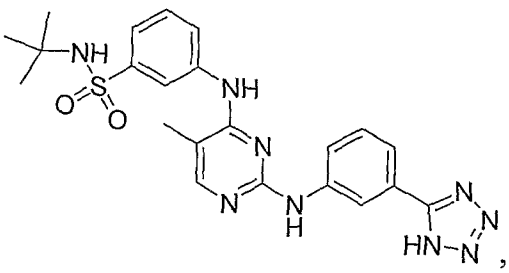

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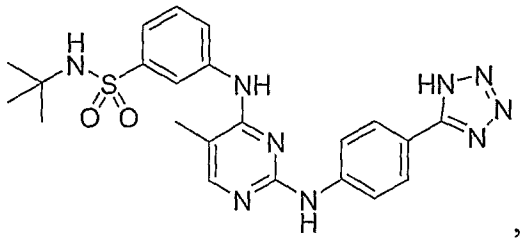

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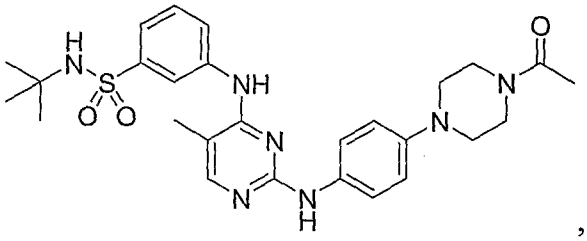

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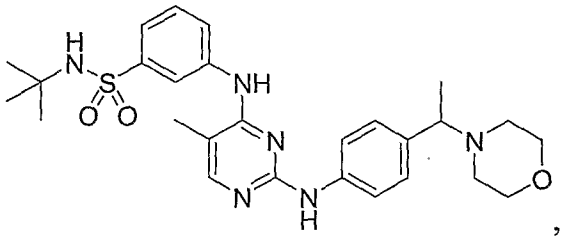

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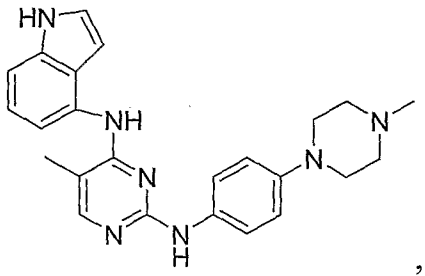

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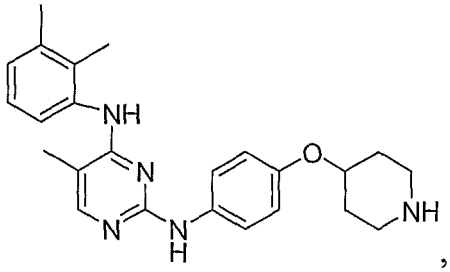

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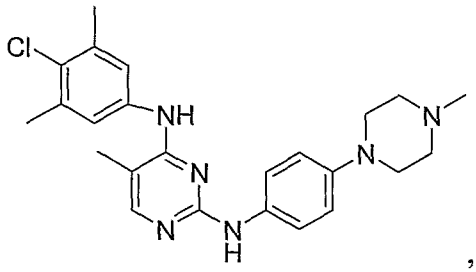

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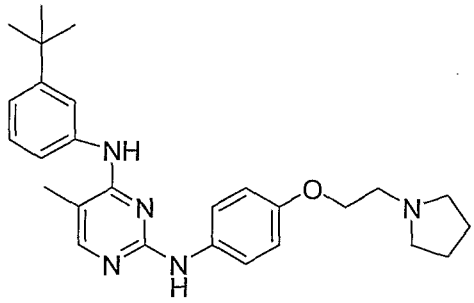

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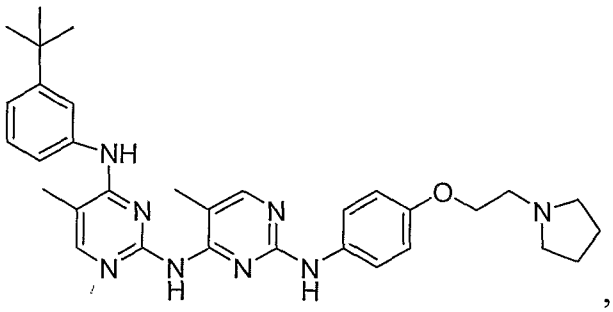

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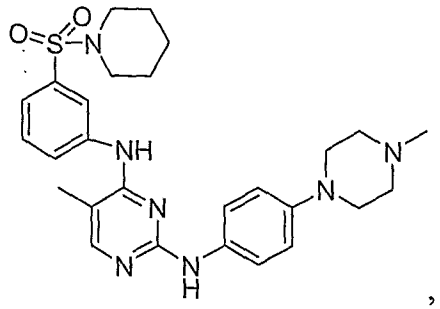

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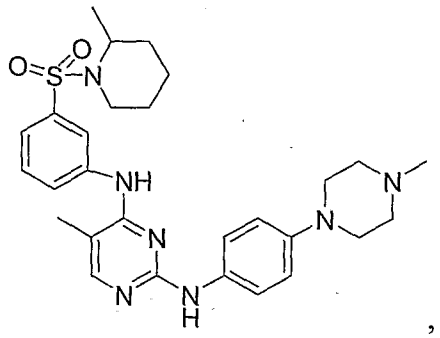

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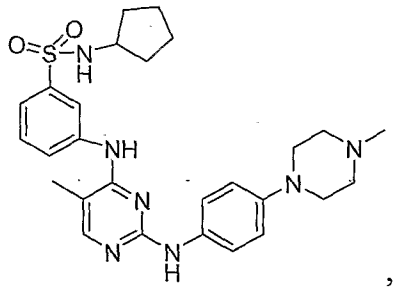

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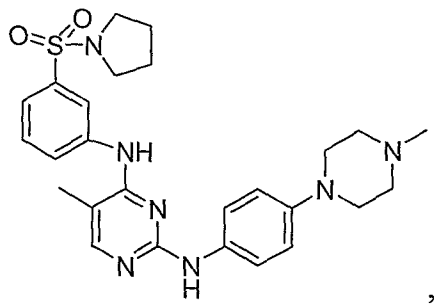

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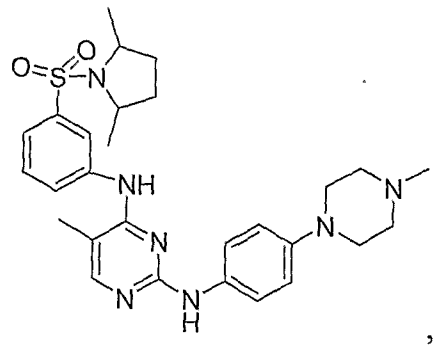

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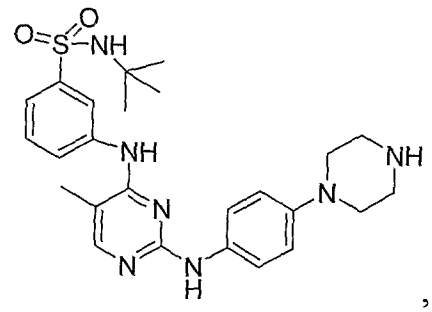

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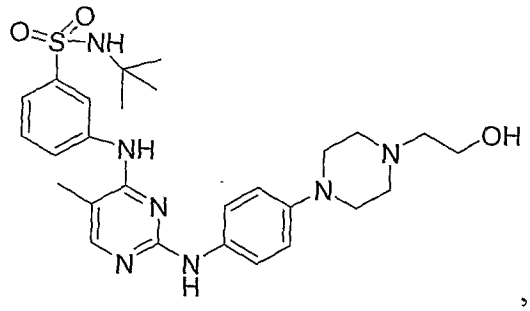

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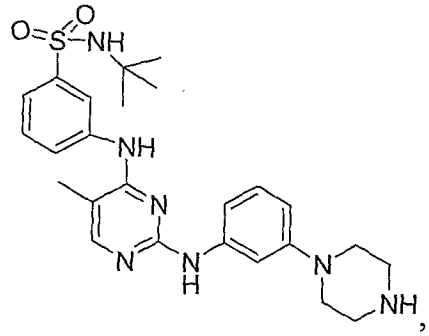

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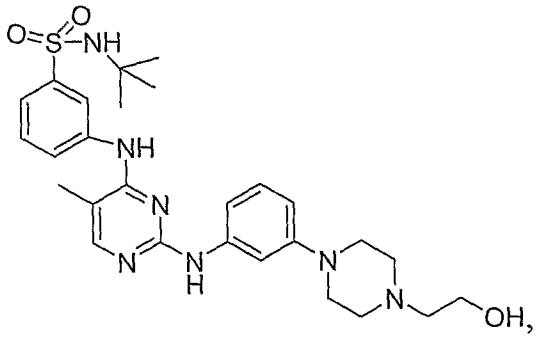

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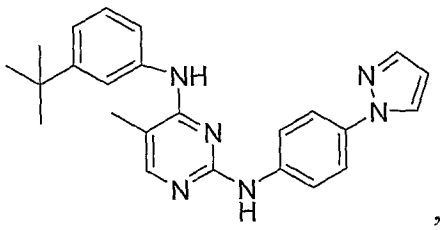

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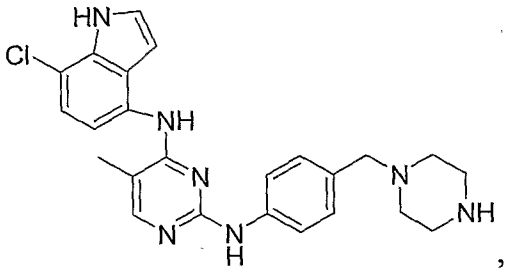

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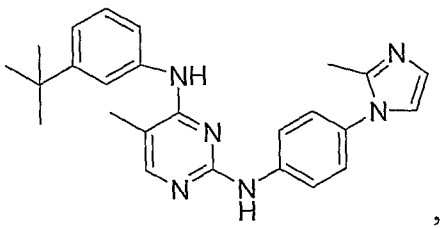

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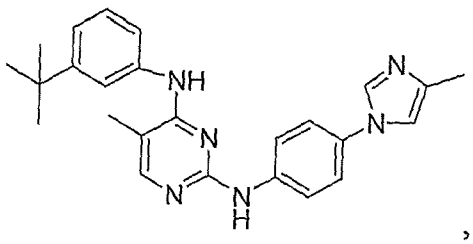

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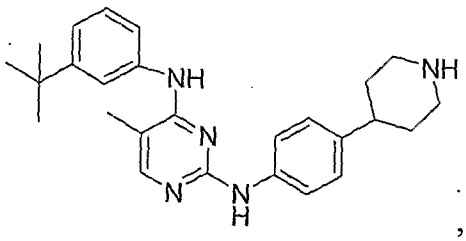

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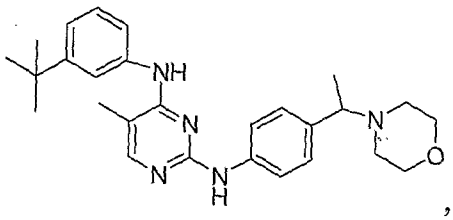

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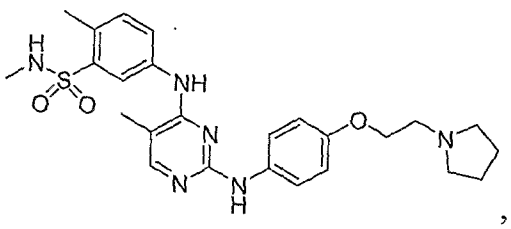

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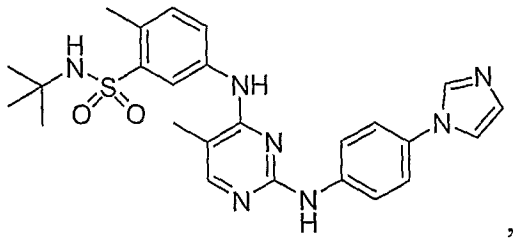

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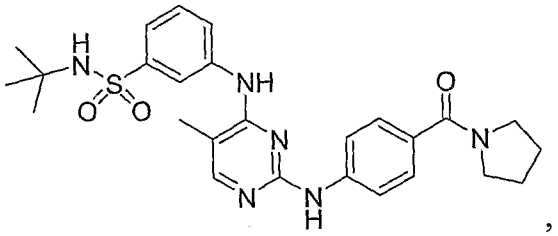

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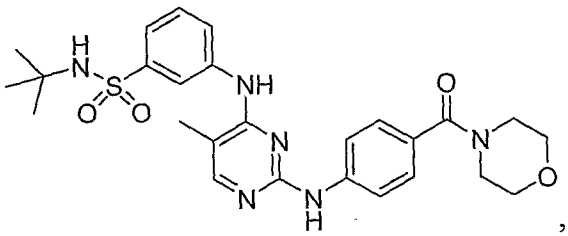

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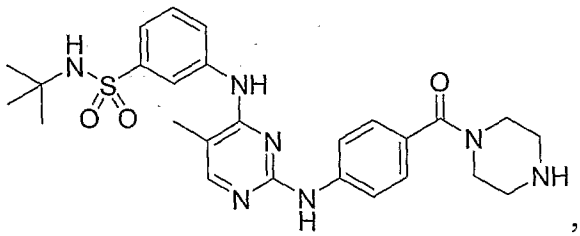

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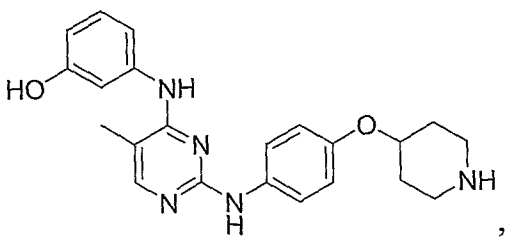

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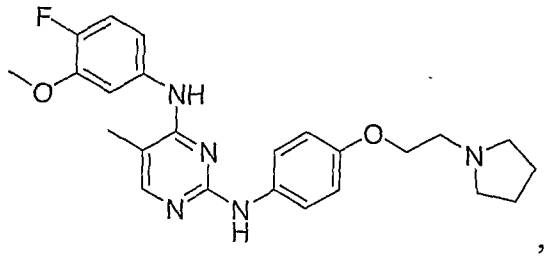

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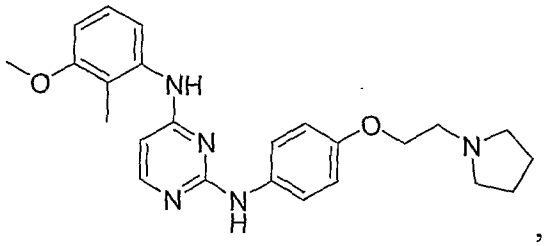

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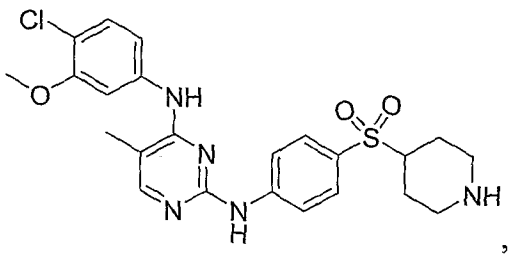

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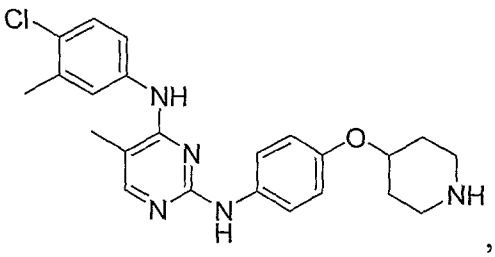

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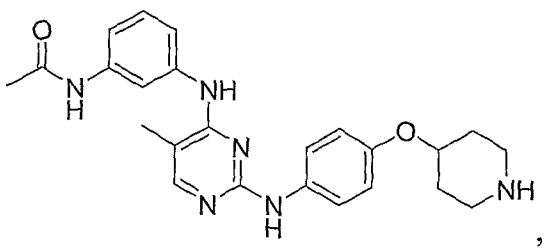

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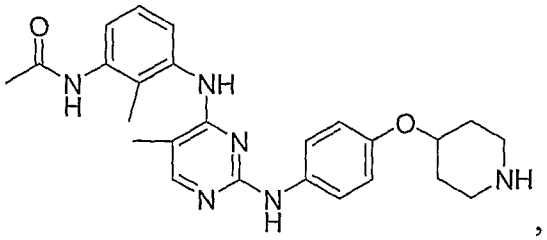

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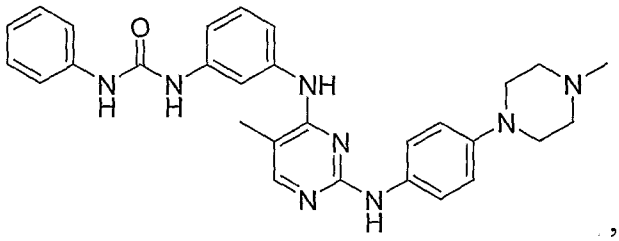

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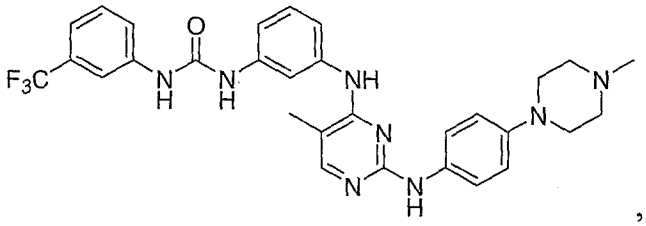

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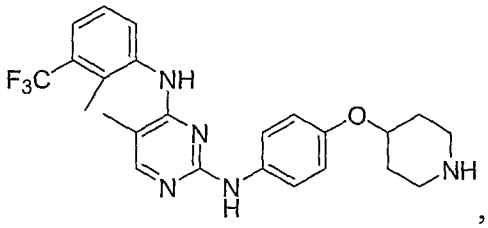

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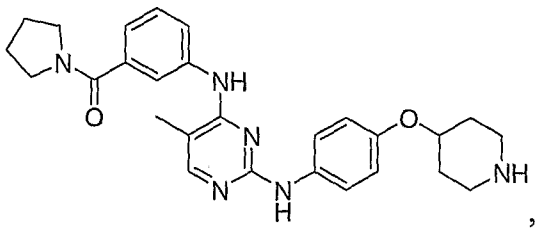

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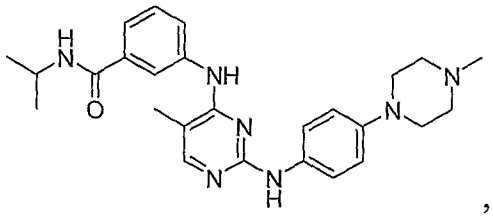

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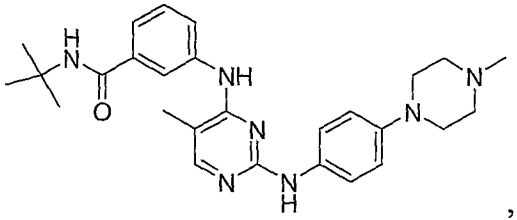

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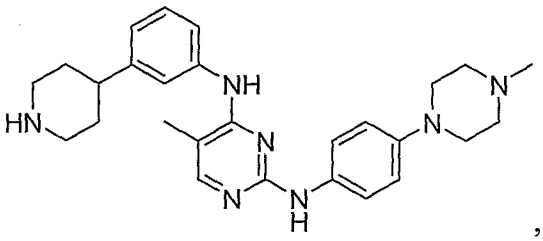

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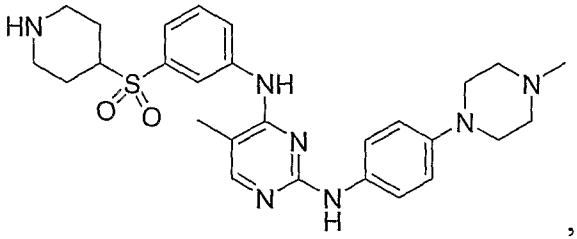

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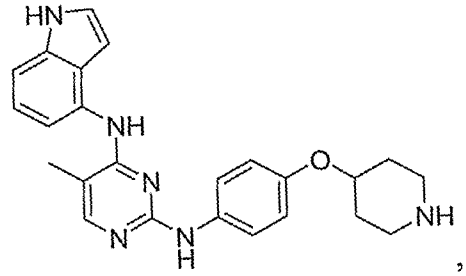
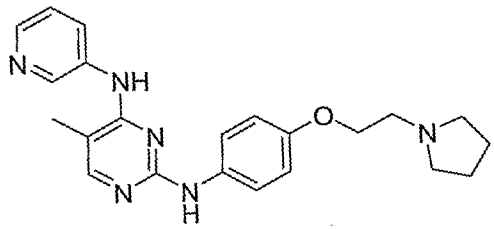
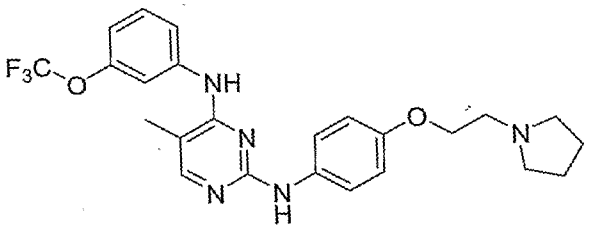


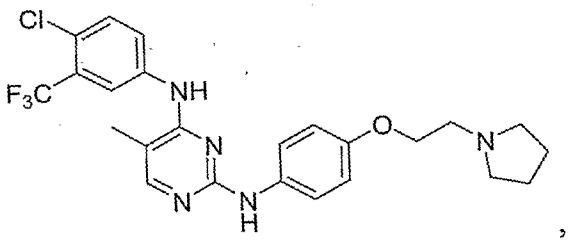
CLVI



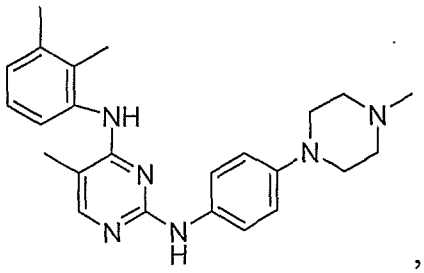
CLVII



CLVIII



CLIX



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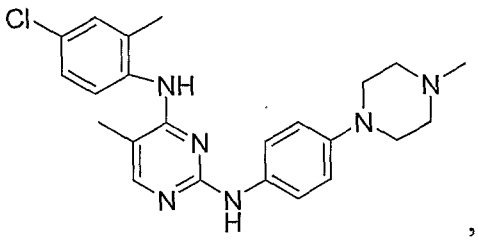
CLX



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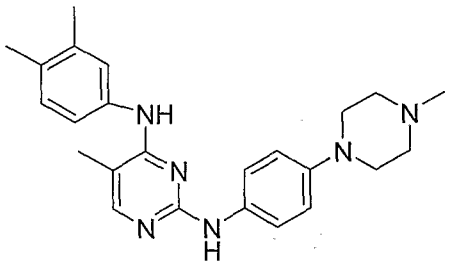
CLXI



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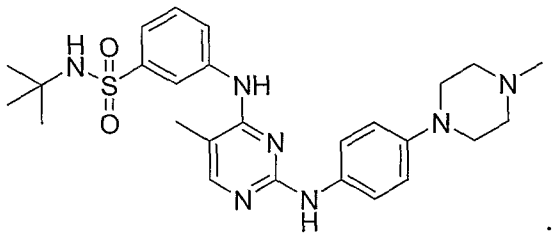
CLXII

4. The compound of claim 1, wherein the compound is



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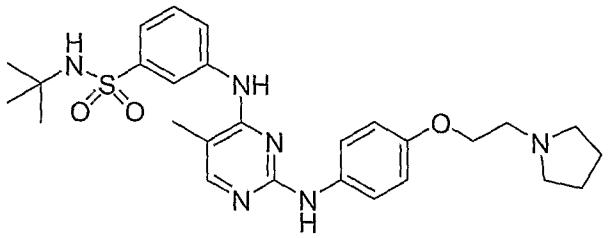
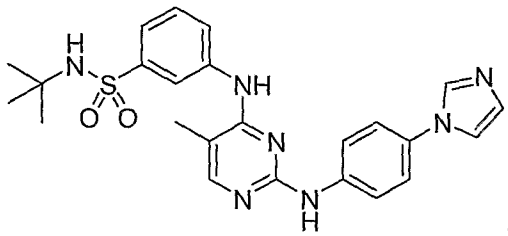
XLV

5. The compound of claim 1, wherein the compound is



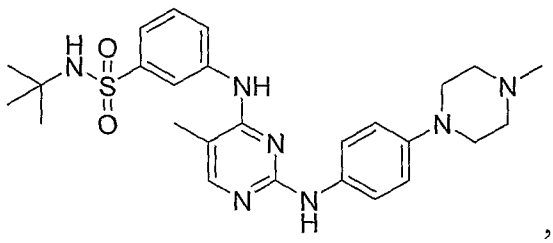
LVII

6. The compound of claim 1, wherein the compound is

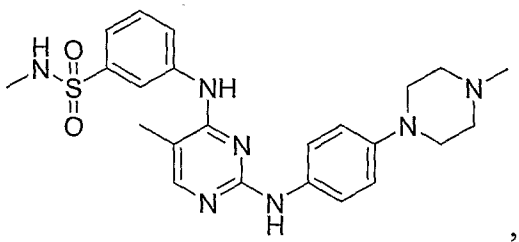


CI

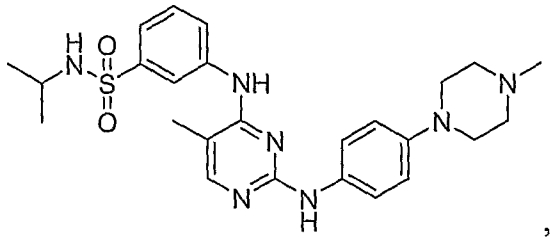
7. The compound of claim 1, wherein the compound is selected from the group consisting of:



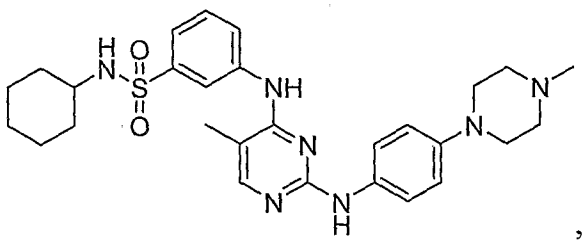
XLV



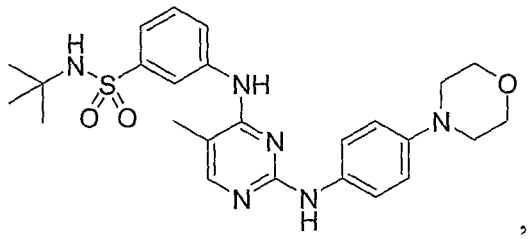
LIX



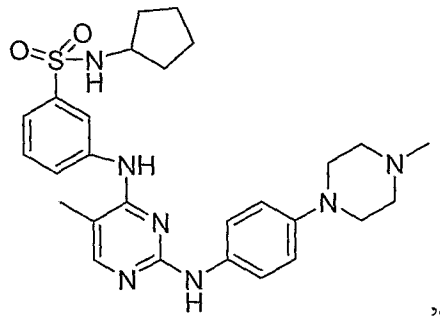
LXI



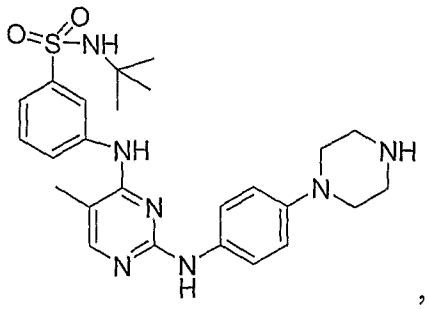
LXIII



CVIII

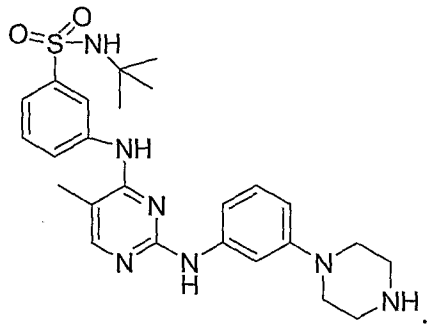


CXXIII



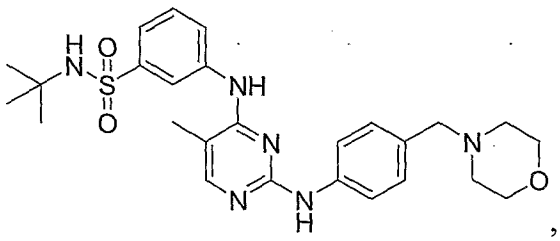
, and

CXXVI



CXXVIII

8. The compound of claim 1, wherein the compound is selected from the group consisting of:



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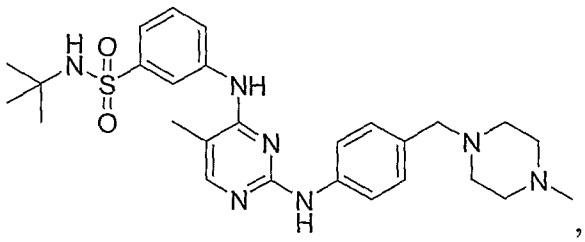
XLVI



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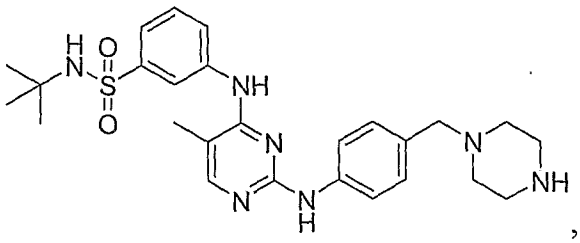
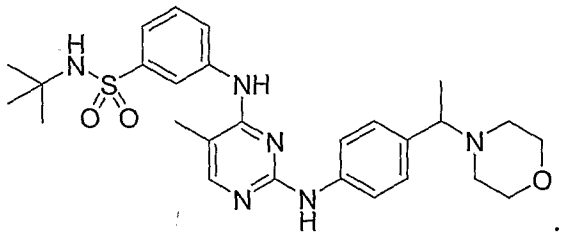
LII



, and

LVI



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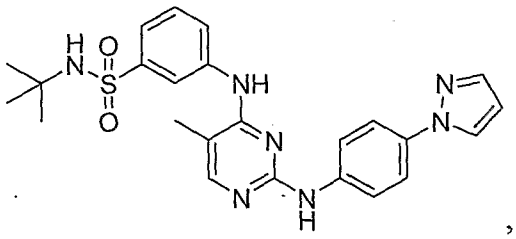
CXV

9. The compound of claim 1, wherein the compound is selected from the group consisting of:



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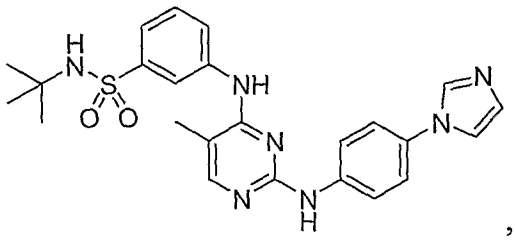
XLVIII



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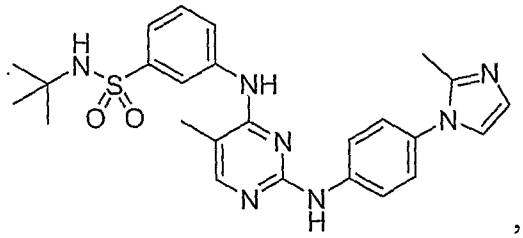
CI



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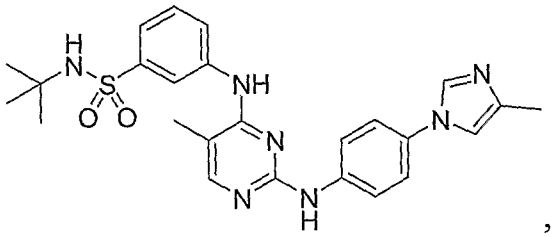
CV



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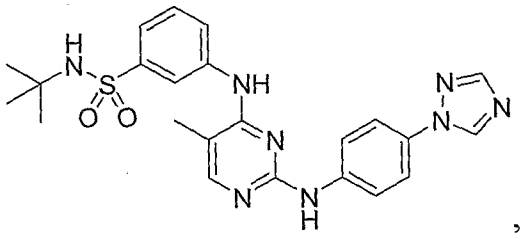
CX



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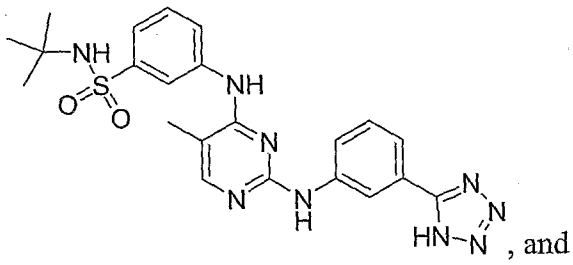
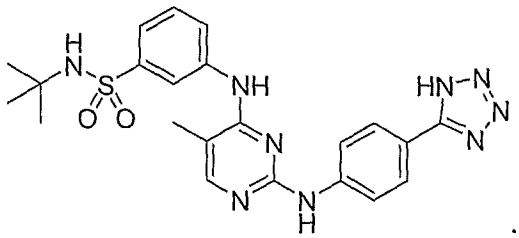
CXI



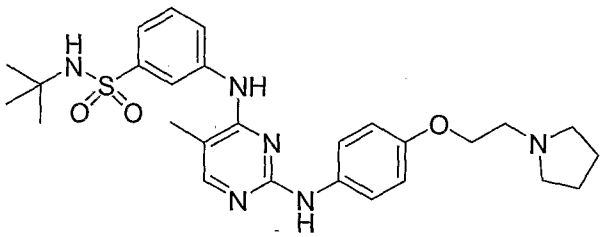
, and

CXII



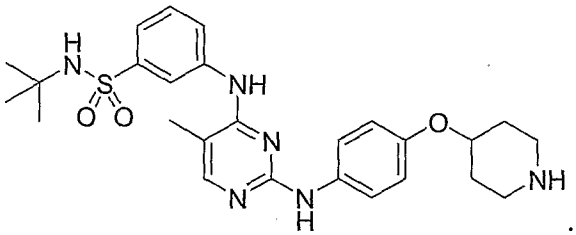
CXIII

10. The compound of claim 1, wherein the compound is selected from the group consisting of:



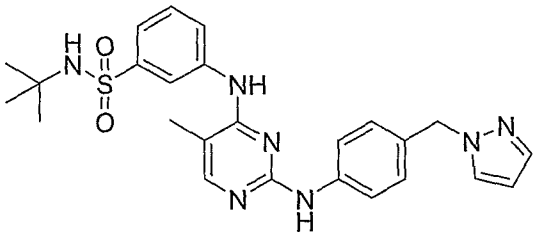
, and

LVII



XCVIII

11. The compound of claim 1, wherein the compound is selected from the group consisting of:



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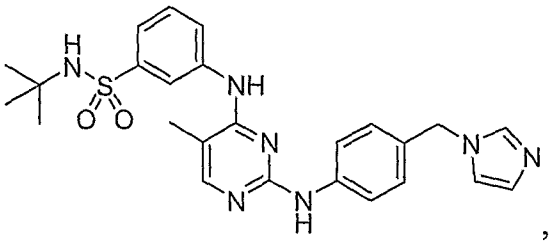

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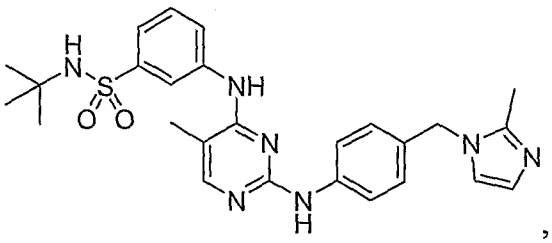
CII



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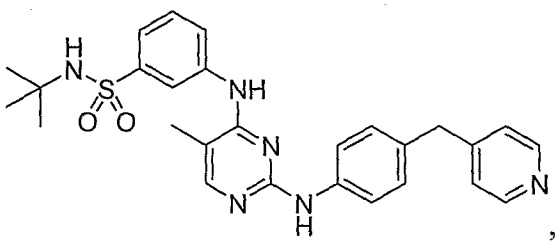
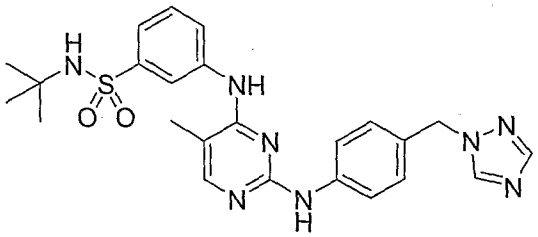
CVI



, and

CVII



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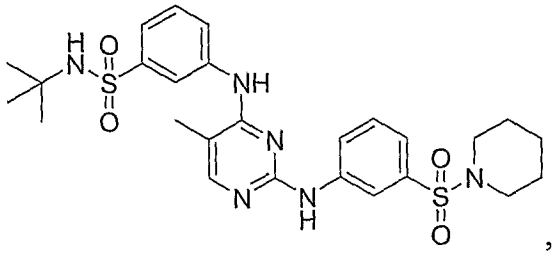
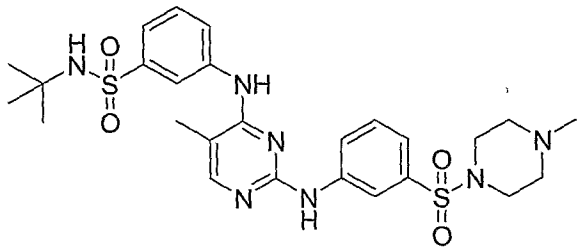
CIX

12. The compound of claim 1, wherein the compound is selected from the group consisting of:



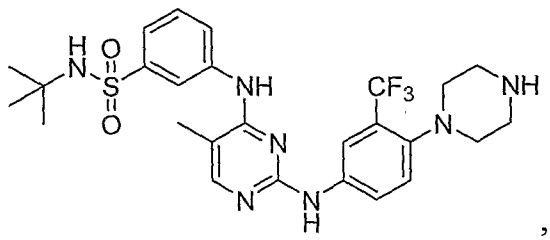
, and

LI



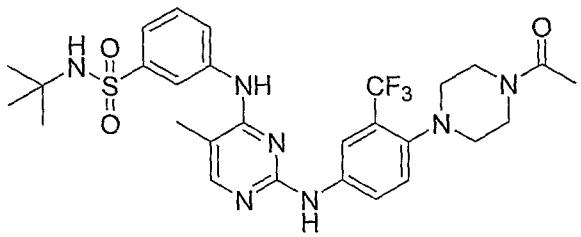
LV

13. The compound of claim 1, wherein the compound is selected from the group consisting of:



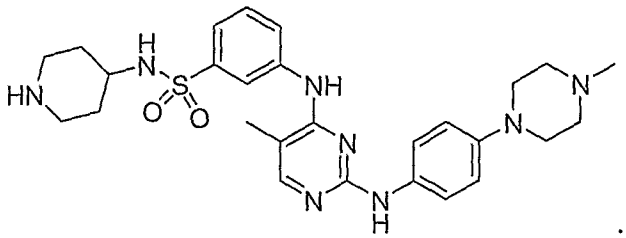
, and

LIII



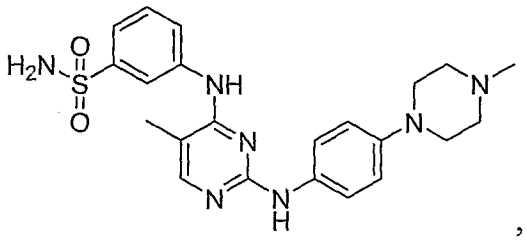
LIV

14. The compound of claim 1, wherein the compound is



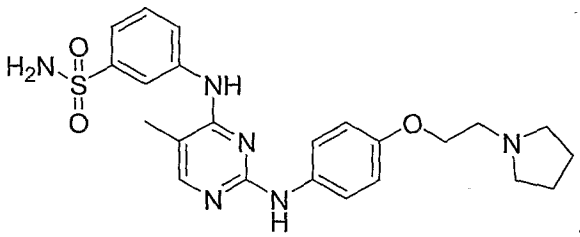
LXXXV

15. The compound of claim 1, wherein the compound is selected from the group consisting of:



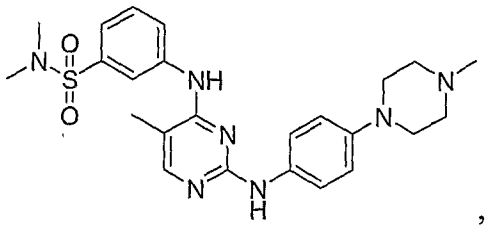
, and

LVIII



LXX

16. The compound of claim 1, wherein the compound is selected from the group consisting of:



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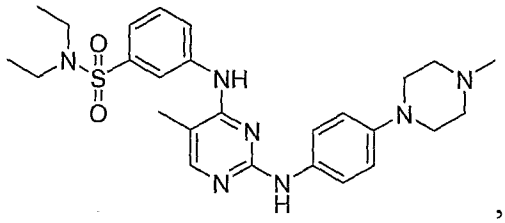
LX



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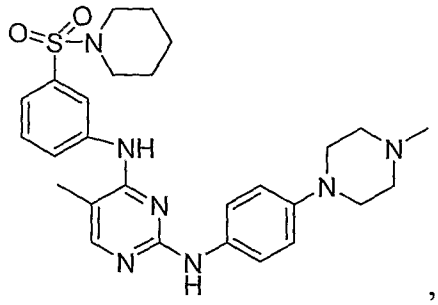
LXIV



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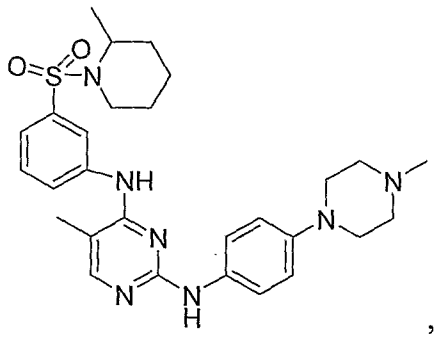
CXXI



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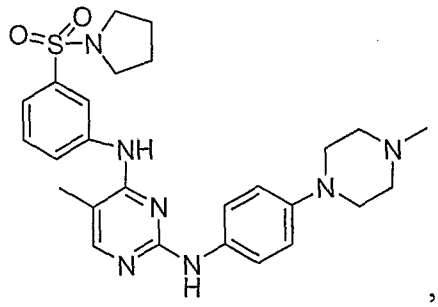
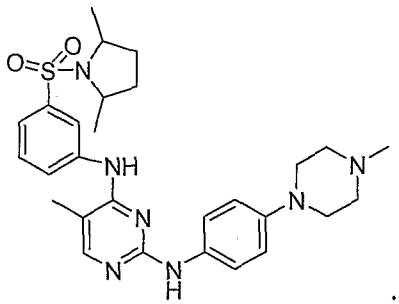
CXXII



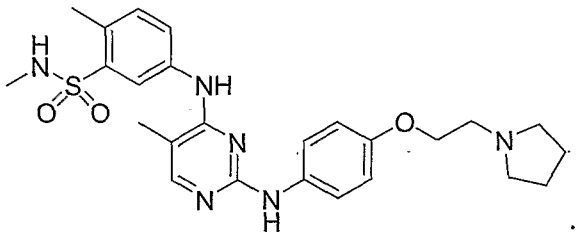
, and

CXXIV



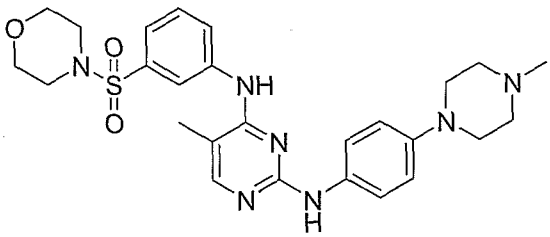
CXXV

17. The compound of claim 1, wherein the compound is



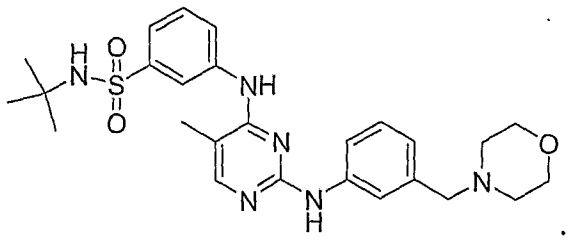
CXXXVI

18. The compound of claim 1, wherein the compound is



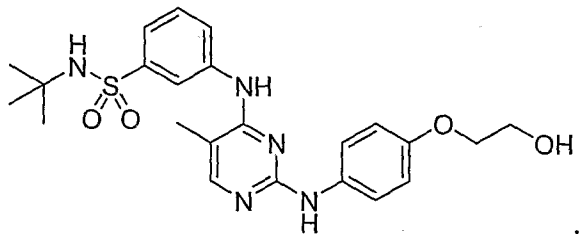
LXV

19. The compound of claim 1, wherein the compound is



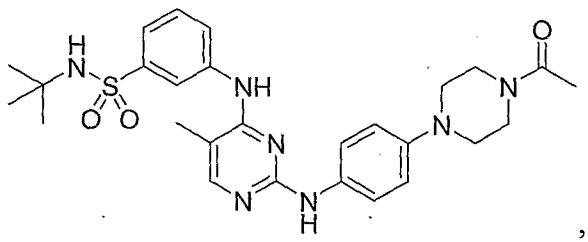
LXXXIX

20. The compound of claim 1, wherein the compound is

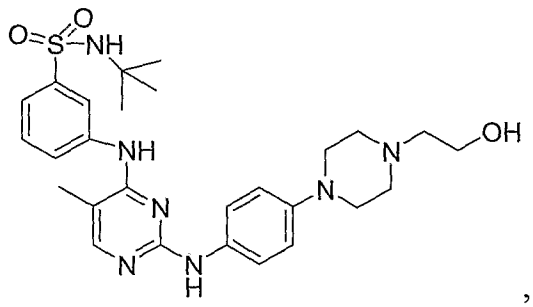


CIII

21. The compound of claim 1, wherein the compound is selected from the group consisting of:

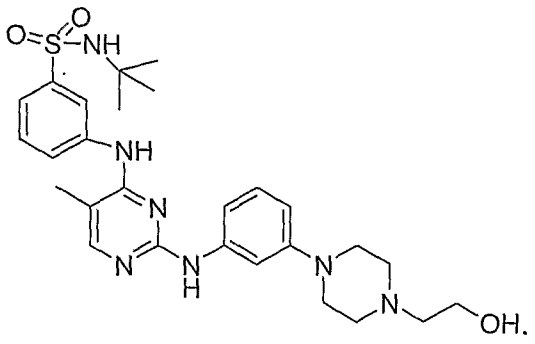


CXIV



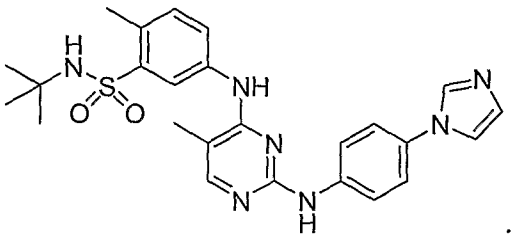
, and

CXXVII



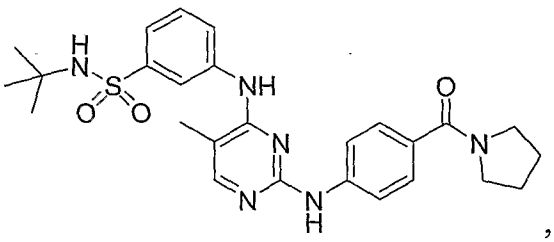
CXXIX

22. The compound of claim 1, wherein the compound is

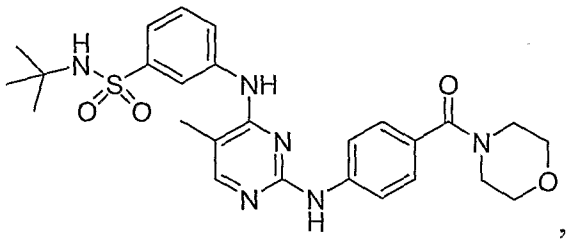


CXXXVII

23. The compound of claim 1, wherein the compound is selected from the group consisting of:

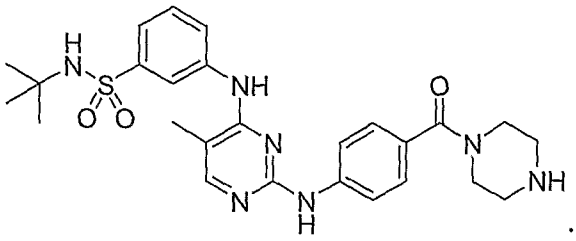


CXXXVIII



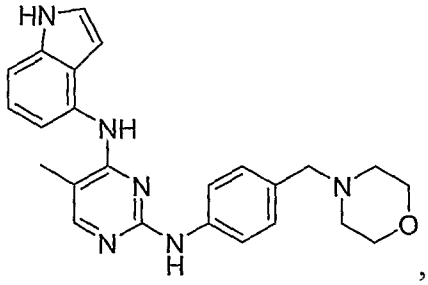
, and

CXXXIX



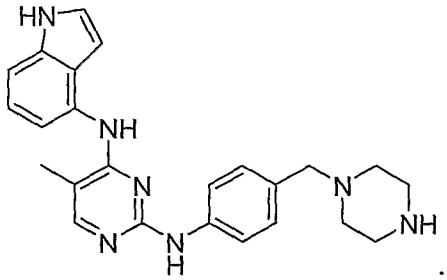
CXL

24. The compound of claim 1, wherein the compound is selected from the group consisting of:



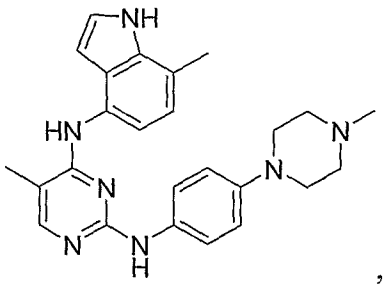
, and

LXXI



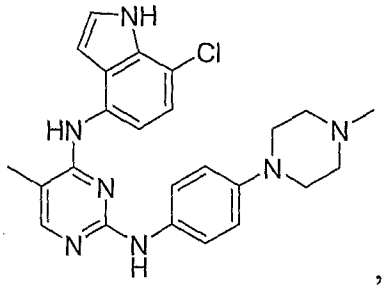
LXXII

25. The compound of claim 1, wherein the compound is selected from the group consisting of:



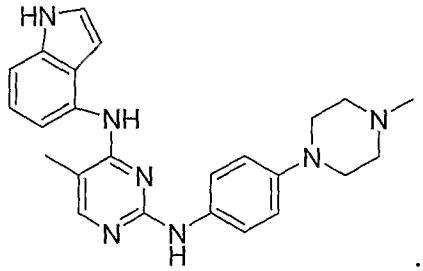
,

LXXIII



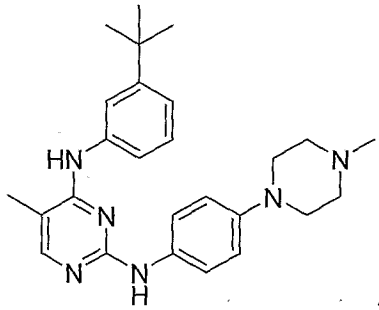
, and

LXXIV



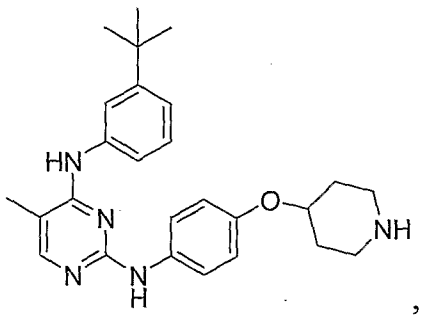
CXVI

26. The compound of claim 1, wherein the compound is



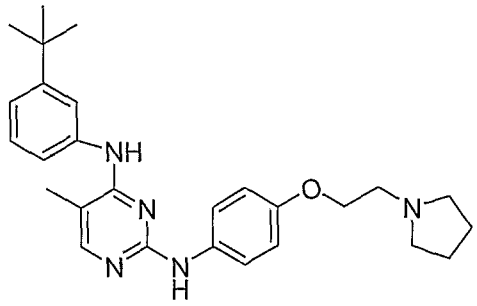
LXXVIII

27. The compound of claim 1, wherein the compound is selected from the group consisting of:



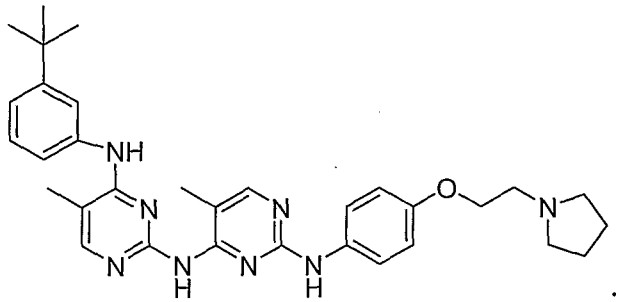
, and

LXXIX



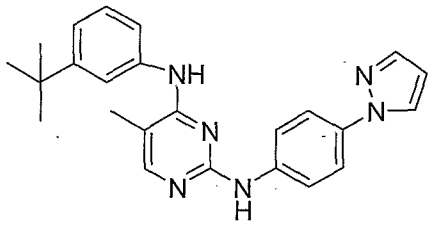
CXIX

28. The compound of claim 1, wherein the compound is

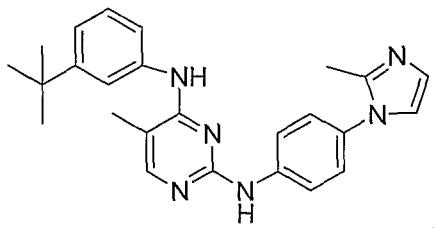


CXX

29. The compound of claim 1, wherein the compound is selected from the group consisting of:

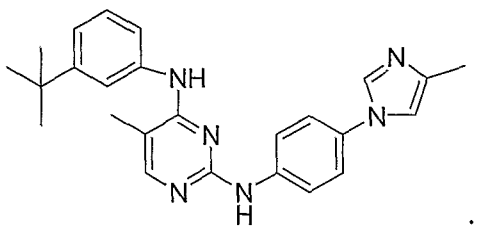


CXXX



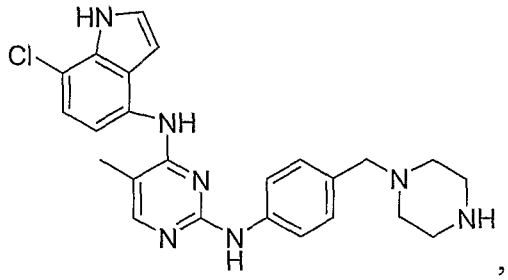
, and

CXXXII



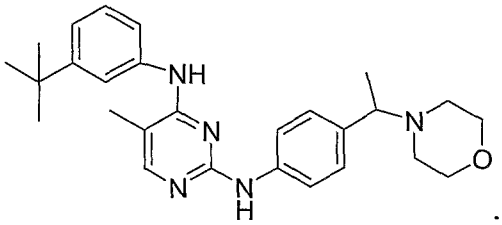
CXXXIII

30. The compound of claim 1, wherein the compound is selected from the group consisting of:



, and

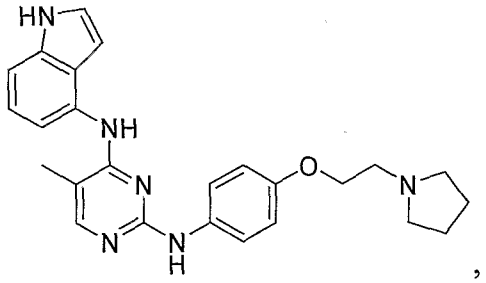
CXXXI



.

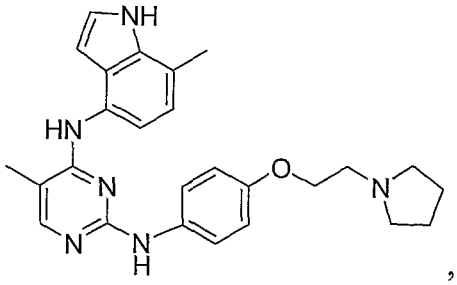
CXXXV

31. The compound of claim 1, wherein the compound is selected from the group consisting of:



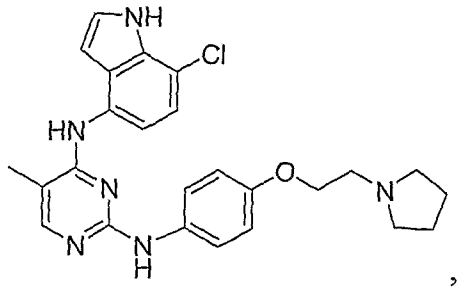
,

XXXI

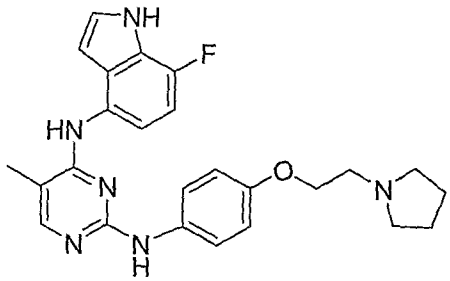


,

LXXV

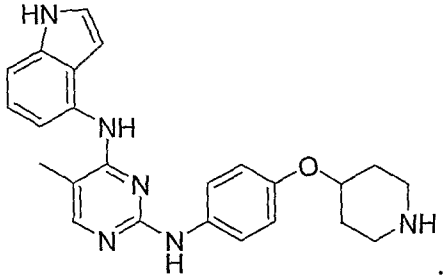


LXXVI



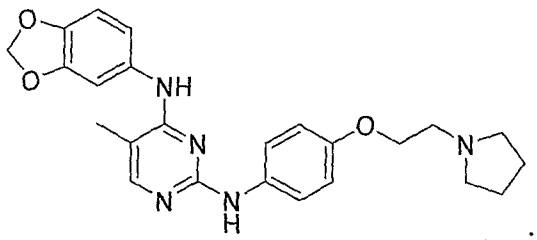
, and

LXXVII



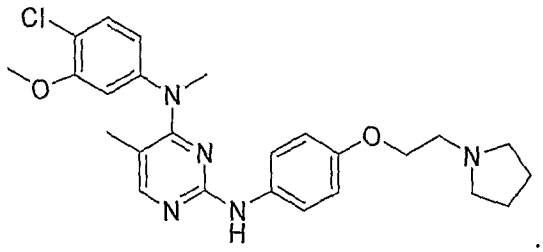
CLVI

32. The compound of claim 1, wherein the compound is



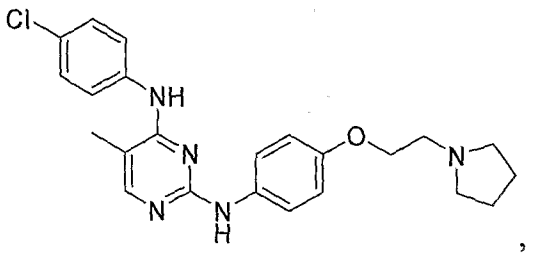
VI

33. The compound of claim 1, wherein the compound is

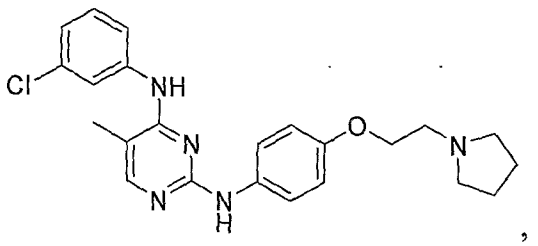


VII

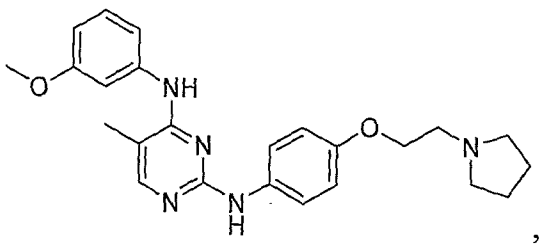
34. The compound of claim 1, wherein the compound is selected from the group consisting of:



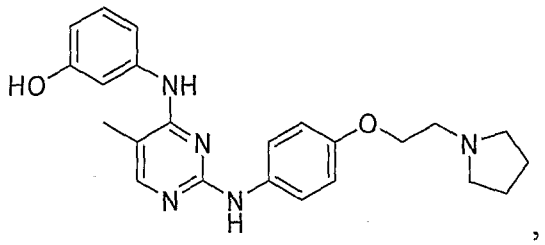
VII



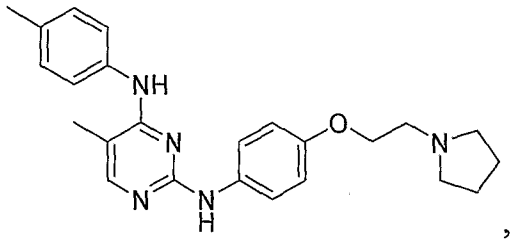
XV



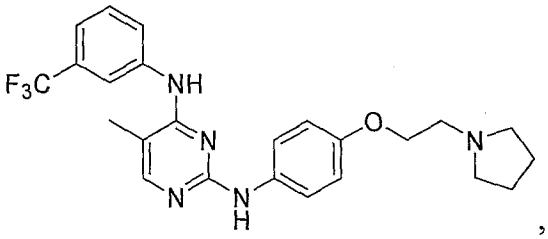
XXIV



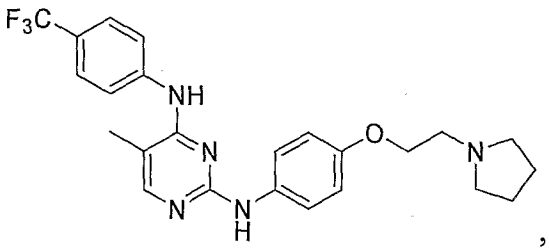
XXV



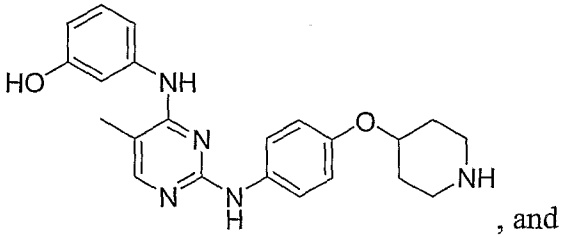
XXVIII



XXXIV

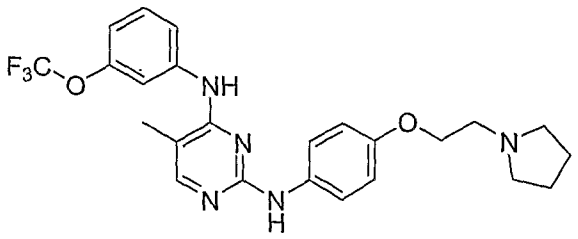


XXXV



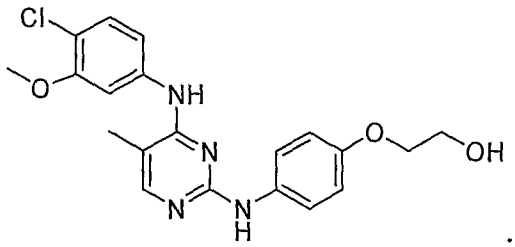
, and

CXLI



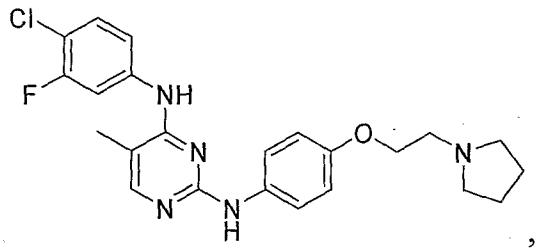
CLVIII

35. The compound of claim 1, wherein the compound is

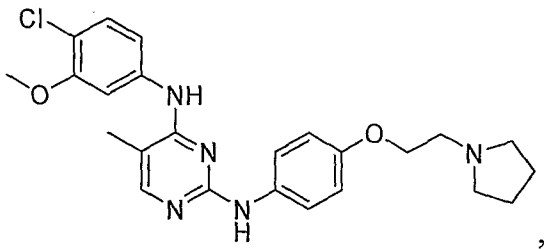


IX

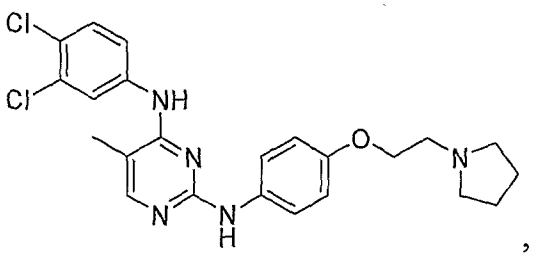
36. The compound of claim 1, wherein the compound is selected from the group consisting of:



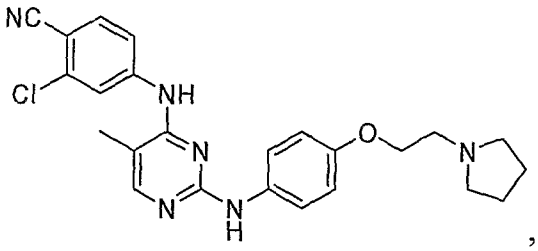
XI



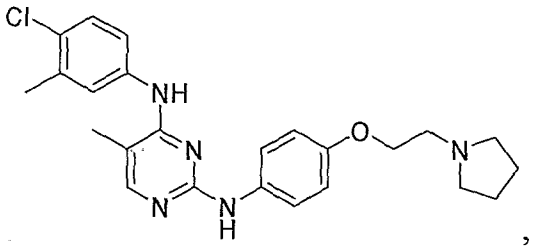
XVII



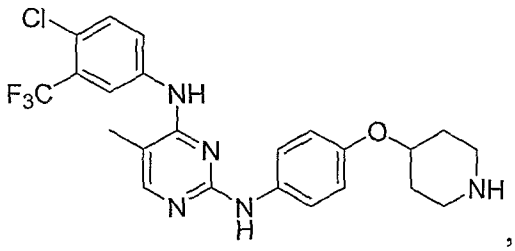
XIX



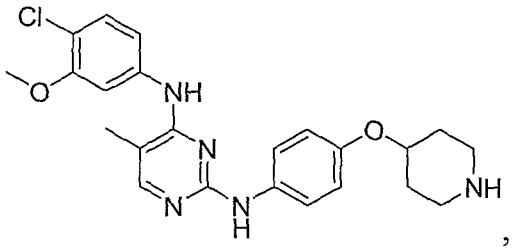
XXVII



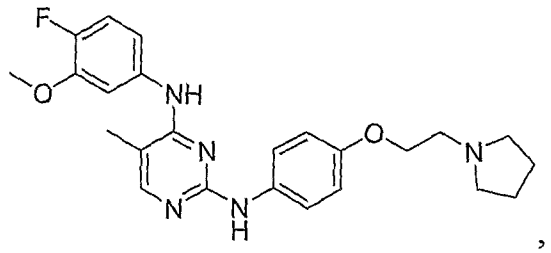
XXIX



LXIX



LXXXII



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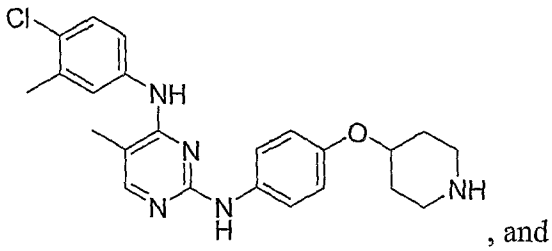
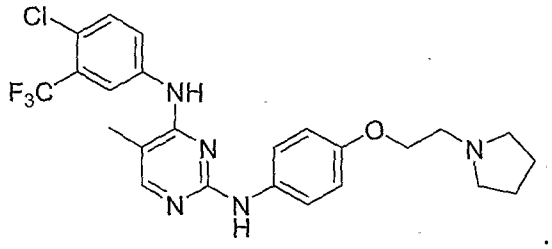
CXLII



, and

CXLV



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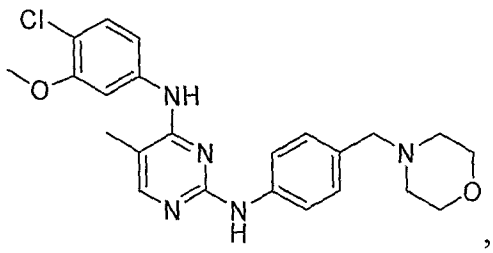
CLIX

37. The compound of claim 1, wherein the compound is selected from the group consisting of:



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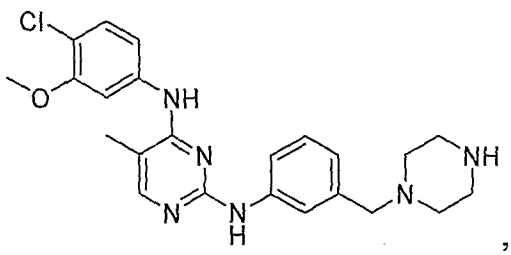
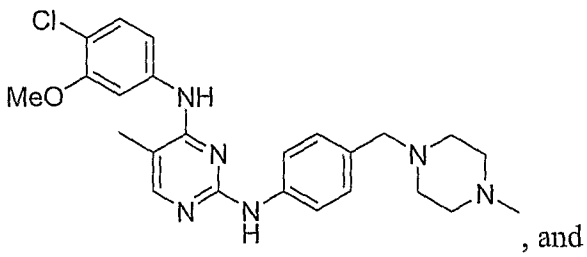
XII



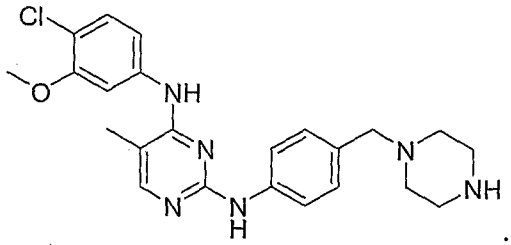
,

XX



, and

XLIII



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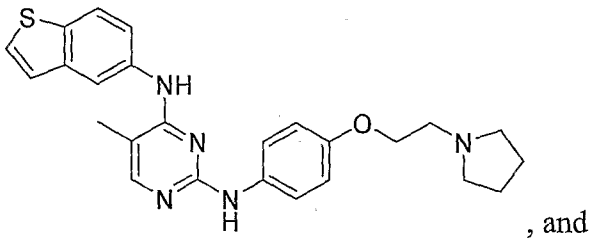
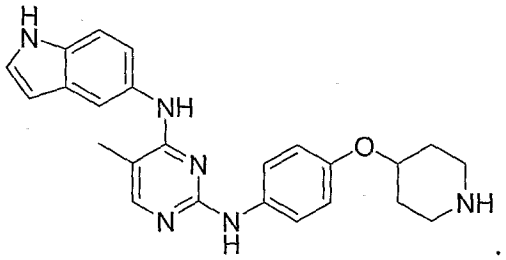
CIV

38. The compound of claim 1, wherein the compound is selected from the group consisting of:



, and

XIII



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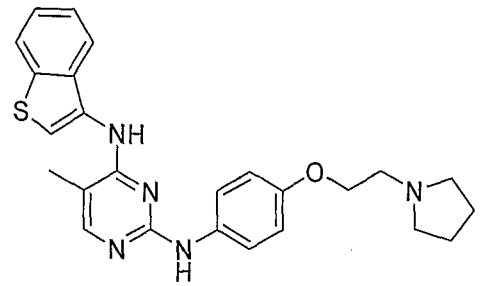
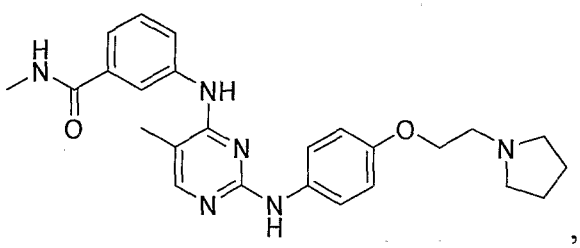
XCIV

39. The compound of claim 1, wherein the compound is

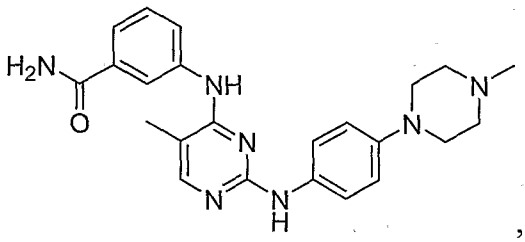


XIV

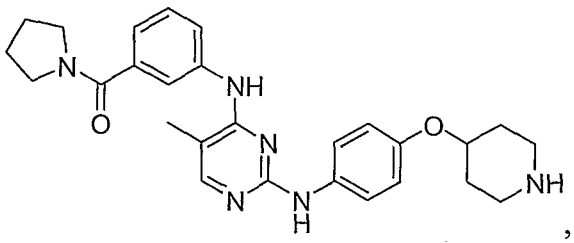
40. The compound of claim 1, wherein the compound is selected from the group consisting of:



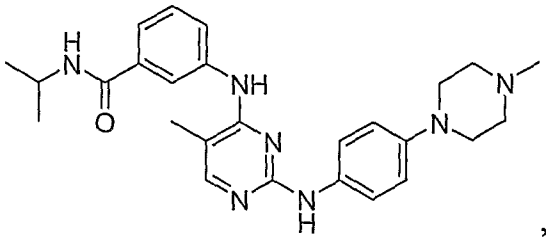
XVI



LXVI

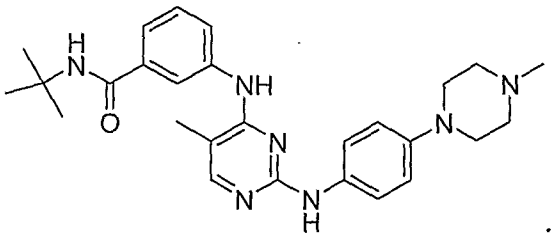


CLI



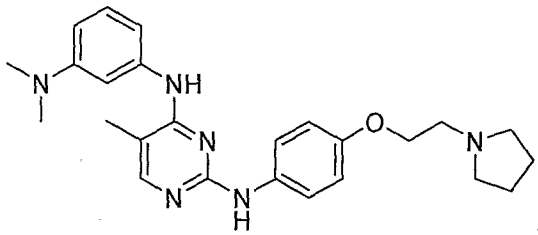
, and

CLII



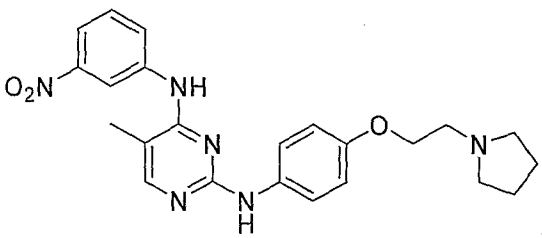
CLIII

41. The compound of claim 1, wherein the compound is selected from the group consisting of:



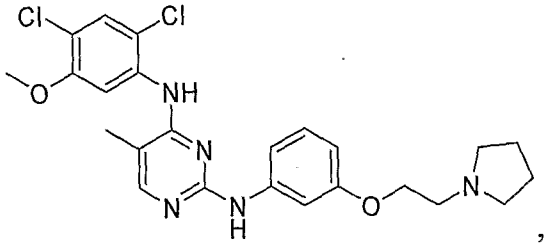
, and

XVIII



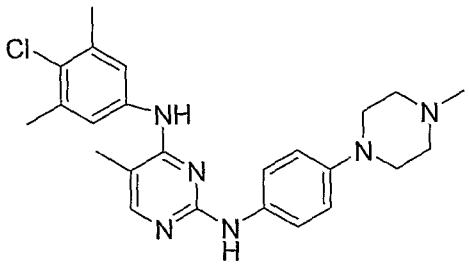
XXVI

42. The compound of claim 1, wherein the compound is selected from the group consisting of:



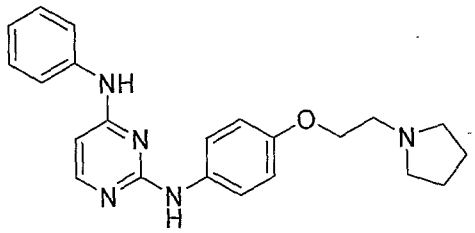
, and

XXIII



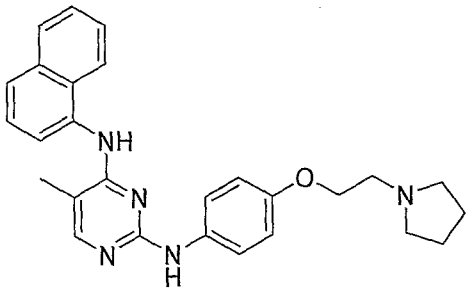
CXVIII

43. The compound of claim 1, wherein the compound is



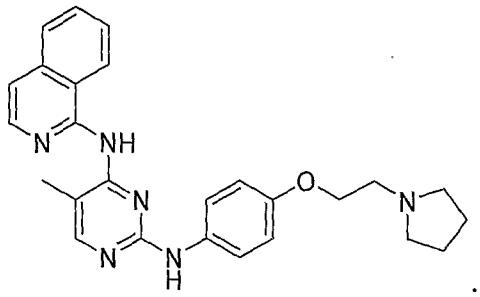
XXX

44. The compound of claim 1, wherein the compound is



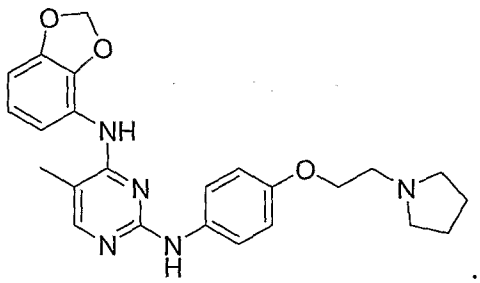
XXXII

45. The compound of claim 1, wherein the compound is



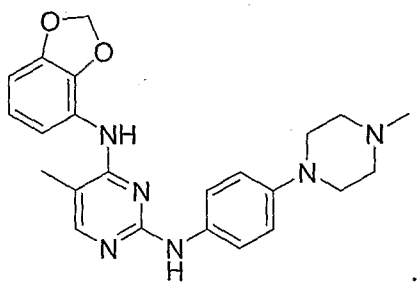
XXXIII

46. The compound of claim 1, wherein the compound is selected from the group consisting of:



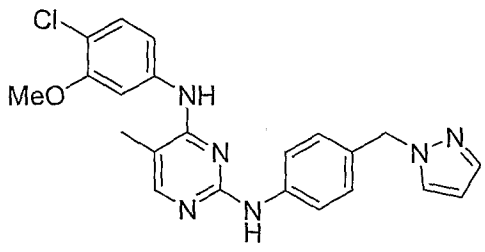
XXXVI

47. The compound of claim 1, wherein the compound is



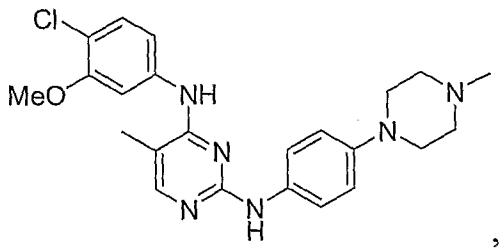
XXXVII

48. The compound of claim 1, wherein the compound is

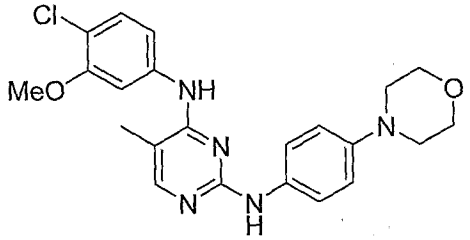


XXXVIII

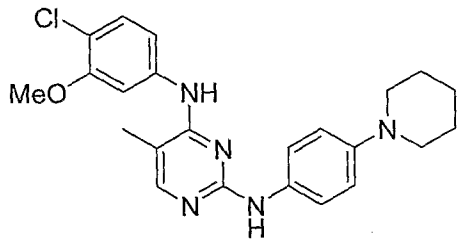
49. The compound of claim 1, wherein the compound is selected from the group consisting of:



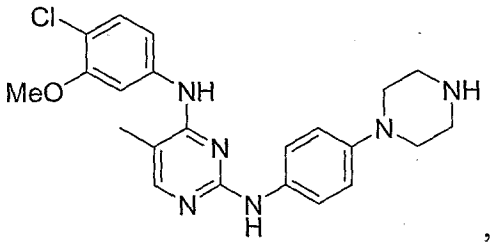
XXXIX



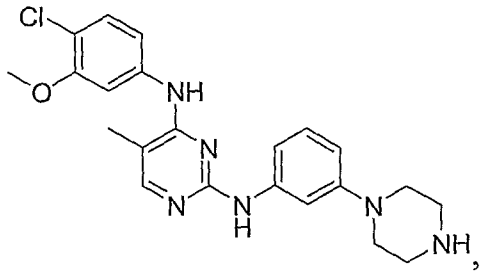
XL



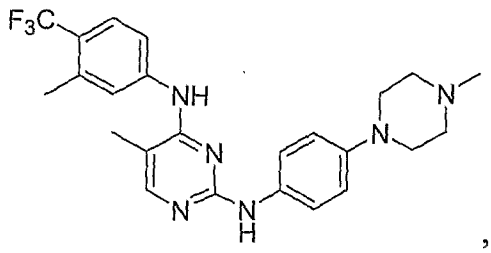
XLII



XLIV

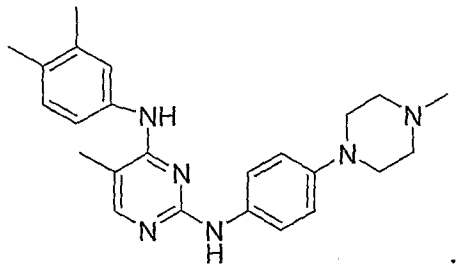


LXXXIII



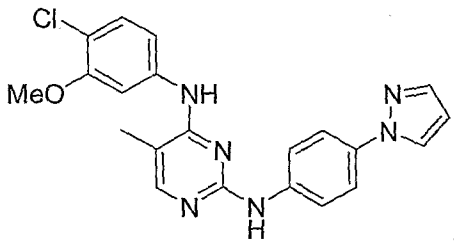
, and

LXXXVI



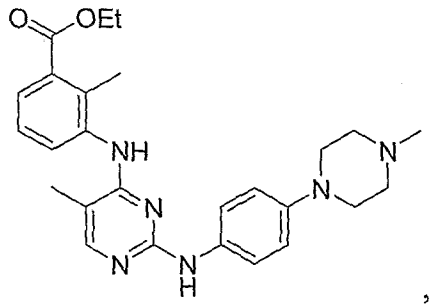
CLXII

50. The compound of claim 1, wherein the compound is



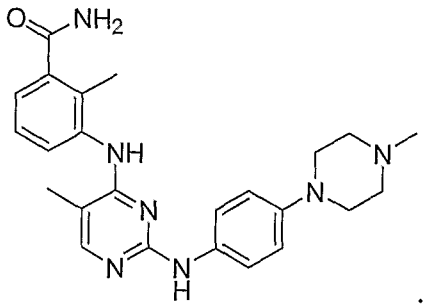
XLI

51. The compound of claim 1, wherein the compound is selected from the group consisting of:



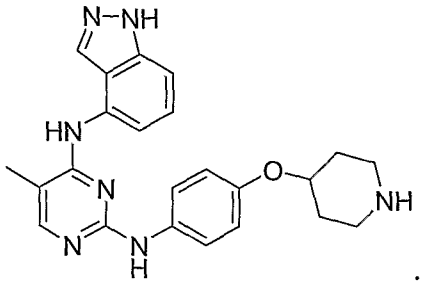
, and

LXVII



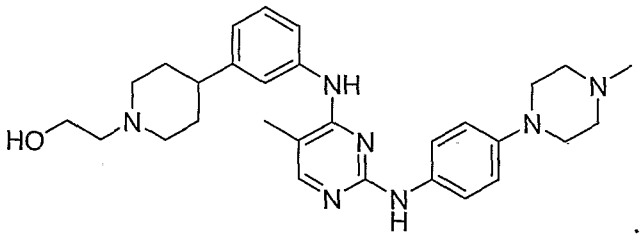
LXVIII

52. The compound of claim 1, wherein the compound is



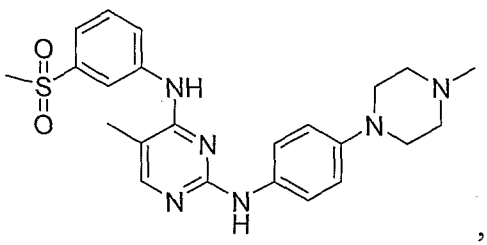
LXXX

53. The compound of claim 1, wherein the compound is



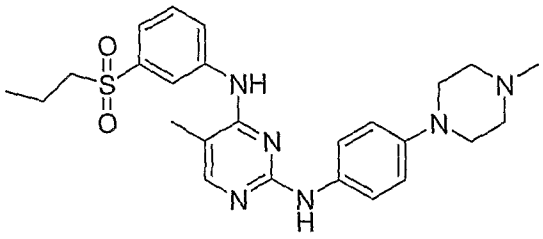
LXXXIV

54. The compound of claim 1, wherein the compound is selected from the group consisting of:



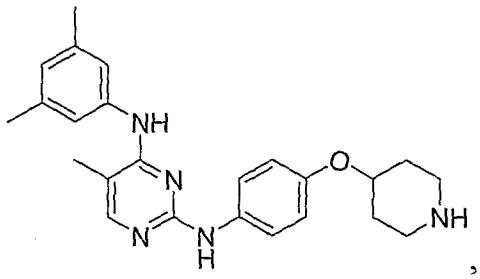
, and

LXXXVII



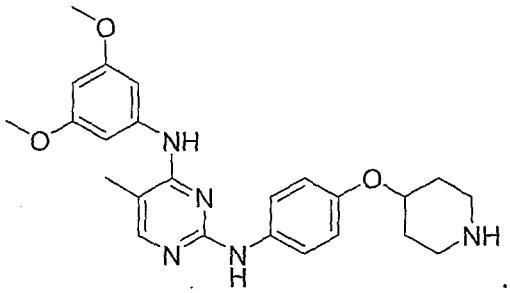
LXXXVIII

55. The compound of claim 1, wherein the compound is selected from the group consisting of:



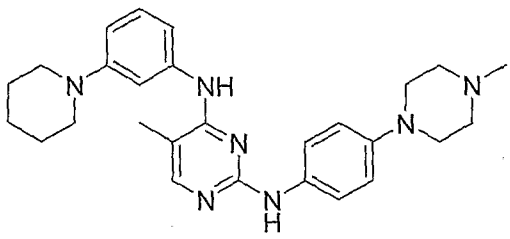
, and

XC



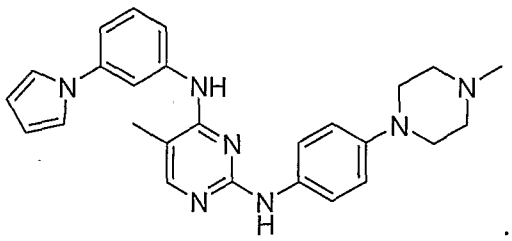
XCI

56. The compound of claim 1, wherein the compound is



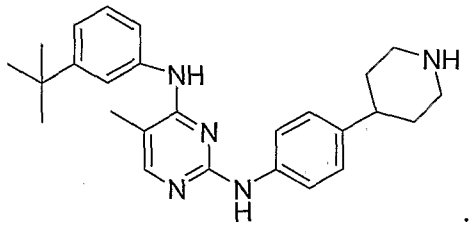
XCII

57. The compound of claim 1, wherein the compound is



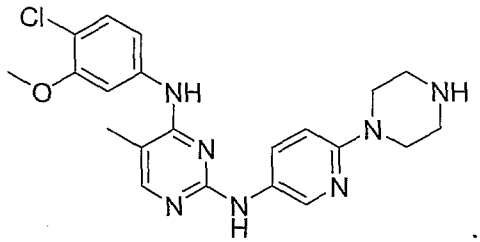
XCIII

58. The compound of claim 1, wherein the compound is



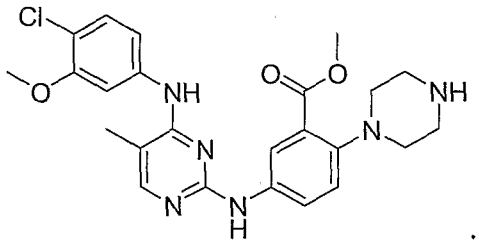
CXXXIV

59. The compound of claim 1, wherein the compound is



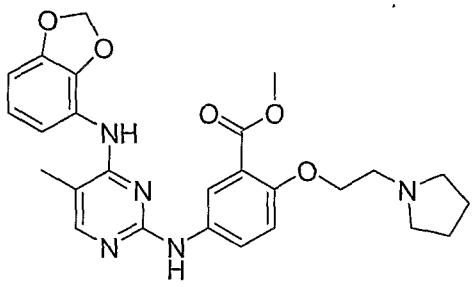
XCV

60. The compound of claim 1, wherein the compound is



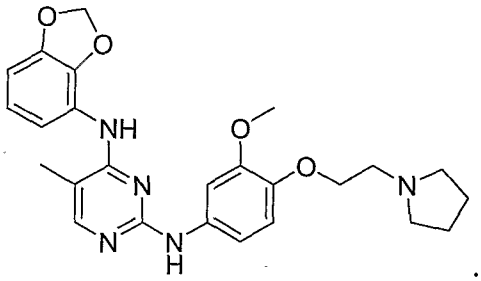
XCVI

61. The compound of claim 1, wherein the compound is selected from the group consisting of:



, and

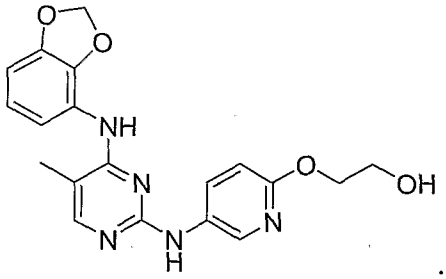
XCVII



.

C

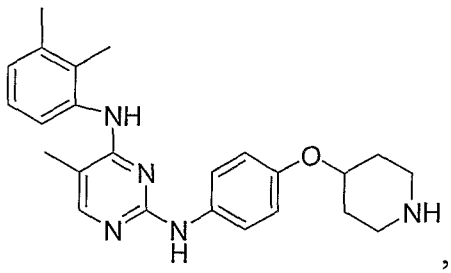
62. The compound of claim 1, wherein the compound is



.

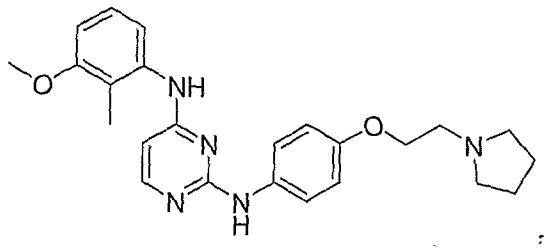
XCIX

63. The compound of claim 1, wherein the compound is selected from the group consisting of:

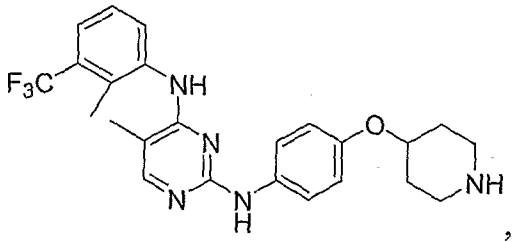


,

CXVII

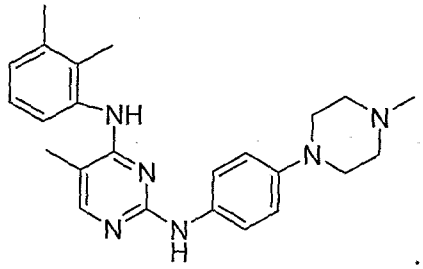


CXLIII



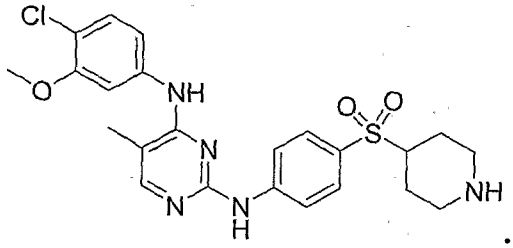
, and

CL



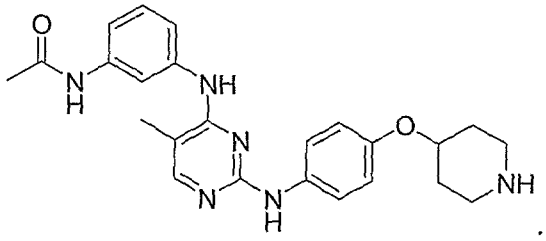
CLX

64. The compound of claim 1, wherein the compound is



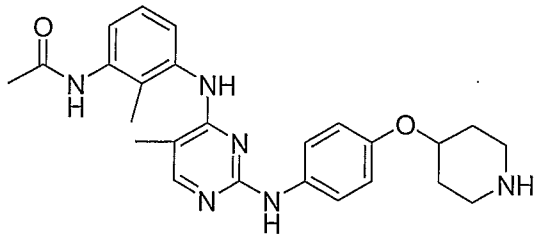
CXLIV

65. The compound of claim 1, wherein the compound is



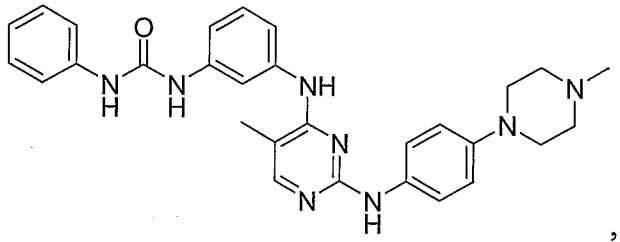
CXLVI

66. The compound of claim 1, wherein the compound is



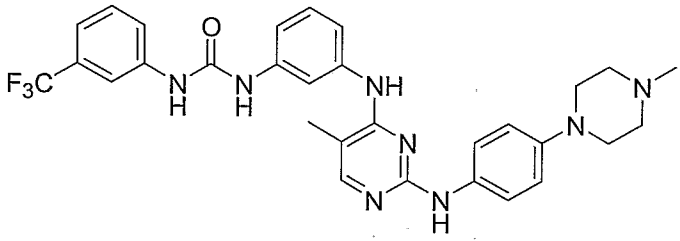
CXLVII

67. The compound of claim 1, wherein the compound is selected from the group consisting of:



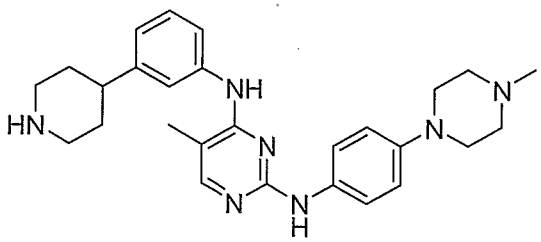
, and

CXLVIII



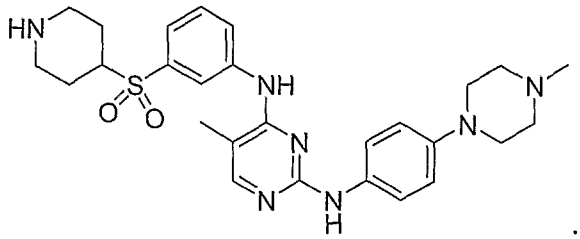
CXLIX

68. The compound of claim 1, wherein the compound is



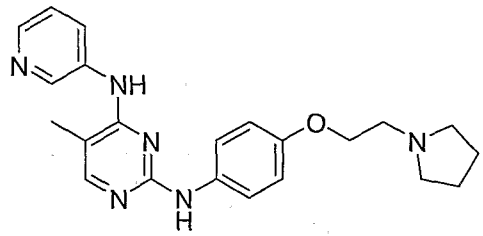
CLIV

69. The compound of claim 1, wherein the compound is



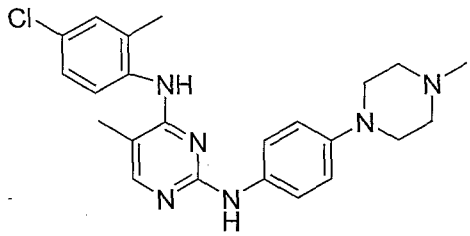
CLV

70. The compound of claim 1, wherein the compound is



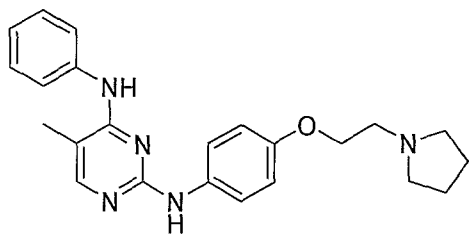
CLVII

71. The compound of claim 1, wherein the compound is



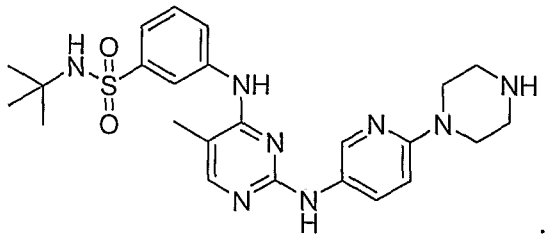
CLXI

72. The compound of claim 1, wherein the compound is



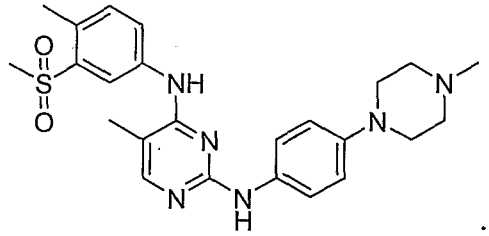
X

73. The compound of claim 1, wherein the compound is



XLIX

74. The compound of claim 1, wherein the compound is



LXII

75. A method for treating an angiogenic-associated disorder, comprising administering to a subject in need thereof a therapeutically effective amount of at least one compound of any one of claims 1-3, or pharmaceutically acceptable salts, hydrates, solvates, crystal forms, N-oxide(s), and individual diastereomers thereof, to a subject in need of such treatment.

76. The method of claim 75, wherein the disorder is a myeloproliferative disorder, polycythemia vera, essential thrombocythemia, myeloid fibrosis with myeloid metaplasia, any other myeloid-linked disorder, proliferative diabetic retinopathy, a cancer, eye disease, inflammation, psoriasis, any disease related to angiogenesis, or a viral infection.

77. The method of claim 75, wherein the disorder is polycythemia vera.

78. The method of claim 75, wherein the disorder is essential thrombocythemia.

79. The method of claim 75, wherein the disorder is myeloid fibrosis with myeloid metaplasia.

80. The method of claim 75, wherein the disorder is any myeloid-linked disorder.

81. The method of claim 76, wherein the cancer is selected from a group consisting of an alimentary/gastrointestinal tract cancer, colon cancer, liver cancer, skin cancer, breast cancer, ovarian cancer, prostate cancer, lymphoma, leukemia, kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer and brain cancer.

82. The method of claim 75, wherein the disorder is selected from a group consisting of ocular neovascularіaztion, infantile haemangiomas; organ hypoxia, vascular hyperplasia, organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type 1 diabetes, or Type II diabetes, and complications from diabetes, inflammatory disease, acute pancreatitis, chronic pancreatitis, asthma, allergies, adult respiratory distress syndrome, cardiovascular disease, liver disease, other blood disorders, asthma, rhinitis, atopic, dermatitits, autoimmune thryroid disorders, ulerative colitis, Crohn's disease, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, conditions associated with cytokines, and other autoimmune diseases including glomerulonephritis,, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, allergic asthma, atopic dermatitis, allergic rhinitis, chronic active hepatitis, myasthenia graivs, multiple scleroiss, inflammatory bowel disease, graft vs host disease, motor neuron disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral scelerosis, Huntington's disease, cerebral ischemia, or neurodegenerative disease caused by traumatic injury, strike, gluatamate neurtoxicity, hypoxia; ischemic/reperfusion injury in stroke, myocardial ischemica, renal ischemia, heart attacks, cardiac hypertrophy, atherosclerosis and arteriosclerosis, organ hyoxia, platelet aggregation, allergic contact dermatitis, hypersensitivity pneumonitis, systemic lupus erythematosus, juvenile arthritis, Sjogren's Syndrome, scleroderma, polymyositis, ankylosing spondylitis, psoriatic arthritis, Epstein Barr Virus, Hepatitis B, Hepatitis C, HIV, HTLV1, Vaicella-Zoster Virus, Human Papilloma Virus, food allergy, cutaneous inflammation, and immune suppression induced by solid tumors.

83. The method of claim 82, wherein the disorder is cardiovascular disease.

84. The method of claim 82, wherein the disorder is a hematological disorder.

85. The method of claim 75, wherein the disorder is chronic myelogenous leukemia (CML).

86. The method of claim 85, wherein said chronic myelogenous leukemia is resistant to current treatments.

87. The method of claim 75, wherein the disorder is a myeloproliferative disorder.

88. The method of claim 87, wherein the myeloproliferative disorder arises due to mutations in a kinase.

89. The method of claim 88, wherein the kinase is a JAK family kinase.

90. The method of claim 87, wherein the the myeloproliferative disorder arises due to gain-of-function of a JAK family kinase pathway.

91. The method of claim 87, wherein the myeloproliferative disorder arises as a result of gene or protein fusions due to gain-of-function of a JAK family kinase pathway.

92. The method of claim 75, wherein the disorder is associated with a kinase.

93. The method of claim 92, wherein the kinase is a JAK family kinase.

94. A pharmaceutical composition comprising at least one compound of any one of claims 1-3, or its N-oxides, or pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers thereof, and a pharmaceutically acceptable carrier therefore.

95. An article of manufacture comprising packaging material and a pharmaceutical composition contained within the packaging material, wherein the packaging material comprises a label which indicates that the pharmaceutical composition can be used for treatment of angiogenic-associated disorders, and wherein the pharmaceutical composition comprises at least one compound of any one of claims 1-3, or N-oxide(s), or pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers thereof.

96. An article of manufacture comprising packaging material and a pharmaceutical composition contained within the packaging material, wherein the packaging material comprises a label which indicates that the pharmaceutical composition can be used for treatment of myeloproliferative disorder, proliferative diabetic retinopathy, a cancer, eye disease, inflammation, psoriasis, or a viral infection, and wherein the pharmaceutical composition comprises at least one compound of any one of claims 1-3, or N-oxides, or pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers thereof.

97. The article of manufacture of claim 96, wherein the disorder is selected from a group consisting of an alimentary/gastrointestinal tract cancer, colon cancer, liver cancer, skin cancer, breast cancer, ovarian cancer, prostate cancer, lymphoma, leukemia, kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer and brain cancer.

98. A method of treating angiogenic-associated disorder, comprising the administration of a therapeutically effective amount of at least one compound of any one of claims 1-3, or N-oxide(s), or pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers thereof, in combination with an anti-inflammatory agent, chemotherapeutic agent, immunomodulatory agent, therapeutic antibody, or a protein kinase inhibitor, to a subject in need of such treatment.

99. A process for making a pharmaceutical composition comprising combining a combination of at least one compound of any one of claims 1-3, or its N-oxide(s), or its pharmaceutically acceptable salts, hydrates, solvates, crystal forms salts and individual diastereomers thereof, and a pharmaceutically acceptable carrier.

100. A method of treating angiogenic-associated disorder, comprising the topical administration of a therapeutically effective amount of at least one compound of any one of claims 1-3, or N-oxide(s), or pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers thereof, to a subject in need of such treatment.

101. The method of claim 100, wherein the administration is carried out in combination with administering an anti-inflammatory agent, chemotherapeutic agent, immunomodulatory agent, therapeutic antibody, or a protein kinase inhibitor.

102. The method of claim 100 or 101, wherein the disorder is an eye disease.

103. The method of claim 102, wherein the topical administration comprises administering eye drops.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/42044

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **C07D 239/48**(2006.01),**239/49**(2006.01);**A61K 31/505**(2006.01)
C07D 207/06(2006.01)

USPC: 544/122,323,324;514/235.8,275
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/122, 323, 324; 514/235.8, 275

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,838,464 B2 (PEASE et al) 04 January 2005 (04.01.2005), formula (I) in column 2 and the corresponding examples.	1-101

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search
13 March 2007 (13.03.2007)

Date of mailing of the international search report
28 MAR 2007

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer
Deepak Rao

Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/42044

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

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

3. ☒ Claims Nos.: 102-103
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

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

☐ No protest accompanied the payment of additional search fees.