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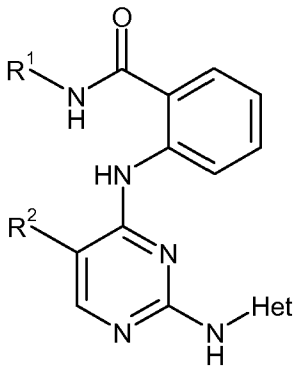

(I)

(57) Abstract: The present invention relates to a compound of Formula I: or a pharmaceutically acceptable salt thereof wherein R1, R2, and Het are as defined herein. Compounds of the present invention are useful as Aurora kinase inhibitors.

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ANTHRANILAMIDES

BACKGROUND OF THE INVENTION

The present invention relates to anthranilamide compounds, compositions, and medicaments thereof, as well as methods of treatments therefor. These anthranalimide compounds are useful in the treatment of diseases associated with Aurora kinase activity.

Protein kinases catalyze the phosphorylation of hydroxylic amino acid side chains in proteins by the transfer of the γ-phosphate of ATP-Mg^{2+} to form a mono-phosphate ester of serine, threonine or tyrosine. Studies have shown that protein kinases are key regulators of many cell functions, including signal transduction, transcriptional regulation, cell motility and cell division. Several oncogenes have also been shown to encode protein kinases, suggesting that kinases may play a role in oncogenesis.

The protein kinase family of enzymes is typically classified into two main subfamilies: protein tyrosine kinases and protein serine/threonine kinases, based on the amino acid residue they phosphorylate. Aberrant protein serine/threonine kinase activity has been implicated or is suspected in a number of pathologies such as rheumatoid arthritis, psoriasis, septic shock, bone loss, cancers and other proliferative diseases. Tyrosine kinases play an equally important role in cell regulation. These kinases include several receptors for molecules such as growth factors and hormones, including epidermal growth factor receptor, insulin receptor and platelet derived growth factor receptor. Studies have indicated that many tyrosine kinases are transmembrane proteins with their receptor domains located on the outside of the cell and their kinase domains on the inside. Accordingly, both kinase subfamilies and their signal transduction pathways are important targets for drug design.

Since its discovery in 1997, the mammalian Aurora family of serine/threonine kinases has been closely linked to tumorigenesis. The three known mammalian family members, Aurora-A ("2"), B ("1") and C ("3"), are highly homologous proteins responsible for chromosome segregation, mitotic spindle function and cytokinesis. Aurora expression is low or undetectable in resting cells, with expression and activity peaking during the G2 and mitotic phases in cycling cells. In mammalian cells proposed substrates for the Aurora A and B kinases include histone H3, CENP-A, myosin II regulatory light chain,

protein phosphatase 1, TPX2, INCENP, p53 and survivin, many of which are required for cell division.

The Aurora kinases have been reported to be over-expressed in a wide range of human tumors. Elevated expression of Aurora-A has been detected in colorectal, ovarian and pancreatic cancers and in invasive duct adenocarcinomas of the breast. High levels of Aurora-A have also been reported in renal, cervical, neuroblastoma, melanoma, lymphoma, pancreatic and prostate tumor cell lines. Amplification/over-expression of Aurora-A is observed in human bladder cancers and amplification of Aurora-A is associated with aneuploidy and aggressive clinical behavior. Moreover, amplification of the *Aurora-A* locus (20q13) correlates with poor prognosis for patients with node-negative breast cancer. In addition, an allelic variant, isoleucine at amino acid position 31, is reported to be a low-penetrance tumor-susceptibility gene and displays greater transforming potential than the phenylalanine-31 variant and is associated with increased risk for advanced and metastatic disease. Like Aurora A, Aurora-B is also highly expressed in multiple human tumor cell lines, including leukemic cells. Levels of Aurora-B increase as a function of Duke's stage in primary colorectal cancers. Aurora-C, which is normally only found in germ cells, is also over-expressed in a high percentage of primary colorectal cancers and in a variety of tumor cell lines including cervical adenocarinoma and breast carcinoma cells.

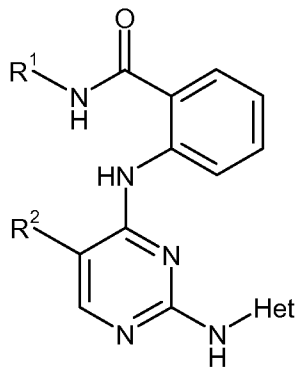
The literature supports the hypothesis that *in vitro* an inhibitor of Aurora kinase activity would disrupt mitosis causing cell cycle defects and eventual cell death. Therefore, *in vivo*, an Aurora kinase inhibitor should slow tumor growth and induce regression. For example, Hauf et al. describe an Aurora B inhibitor, Hesperadin, that causes defects in chromosomal segregation and a block in cytokinesis, thereby resulting in polyploidy [Hauf, S et al. JCB 161(2), 281-294 (2003)]. Ditchfield et al. have described an equipotent inhibitor of Aurora A and B (ZM447439) that causes defects in chromosome alignment, chromosome segregation and cytokinesis [Ditchfield, C. et al., JCB 161(2), 267-280 (2003)]. Furthermore, the authors show that proliferating cells, but not cell-cycle arrested cells, are sensitive to the inhibitor. Efficacy of a potent Aurora A and B inhibitor in mouse and rat xenograft models was recently reported [Harrington, E.A. et al., Nature Medicine 10(3), 262-267, (2004)]. These results demonstrate that inhibition

of Aurora kinases can provide a therapeutic window for the treatment of proliferative disorders such as cancer (see Nature, Cancer Reviews, Vol. 4, p927-936, Dec. 2004, for a review by N. Keen and S Taylor, which outlines the therapeutic potential of Aurora kinase inhibitors for the treatment of cancer).

In view of the teachings of the art, there is a need for the discovery of kinase activity inhibitors, in particular, compounds that inhibit the activity of Aurora kinases.

SUMMARY OF THE INVENTION

In a first aspect, the present invention relates to a compound represented by the following Formula I:



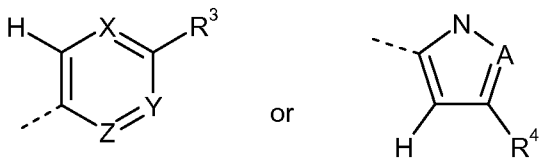
I

or a pharmaceutically acceptable salt thereof wherein:

R^1 is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl-CH_2-, or HO-C_1-C_6-alkyl;

R^2 is CH_3, F, or Cl;

Het is a nitrogen-containing heterocyclic group represented by:



where the dotted line represents the point of attachment; wherein

X is CR^5 or N;

Y is CR^5 or N; and

Z is CH or N; with the proviso that at least one of X, Y, and Z is N, and with the further proviso that at least one of X and Z is not N;

A is NR^6 or O;

R^3 is C_1-C_6-alkyl, OH, or $-N(R^7)_2$;

R^4 is H, CH_3, $-CH_2N(CH_3)_2$, $-CH_2$-piperazinyl, $-CH_2$-4-methylpiperazinyl, or 1-ethyl-2-pyrrolidinyl;

R^5 is H or C_1-C_6-alkyl;

R^6 is H, $-CH_3$, or $-CH_2CH_3$; and

each R^7 is independently H, C_1-C_6-alkyl, HO-C_1-C_6-alkyl, C_1-C_3-alkyl-OC(O)-CH_2-NH-CH_2CH_2-, C_1-C_3-alkyl-O-CH_2CH_2-, or, together with the nitrogen atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group or a 9- or 10-membered heterobicycloalkyl group.

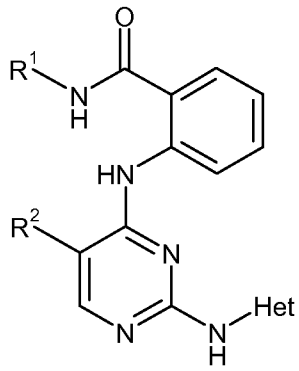
In a second aspect, the present invention is a method for treating a cancer comprising administering to a patient in need thereof the compound of Formula I, or a pharmaceutically acceptable salt thereof.

In a third aspect, the present invention is a method for treating cancer comprising the step of administering to a patient in need thereof an effective amount of a composition comprising the compound of Formula I, or a pharmaceutically acceptable salt thereof; and (b) at least one pharmaceutically acceptable excipient.

In a fourth aspect, the present invention is a composition comprising a) the compound of Formula or a pharmaceutically acceptable salt thereof; and b) at least one pharmaceutically acceptable excipient.

DETAILED DESCRIPTION OF THE INVENTION

In a first aspect, the present invention relates to a compound of Formula I:

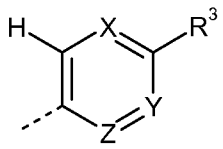


I

or a pharmaceutically acceptable salt thereof wherein R^1, R^2, and Het are defined hereinabove.

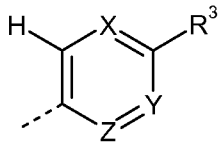
C_1-C_6-alkyl refers to a linear or branched alkyl group including methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, *n*-pentyl, and *n*-hexyl.

In one embodiment, Het is

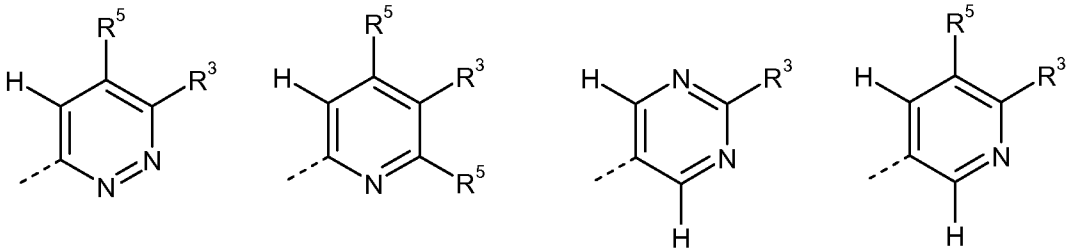


wherein R^3 is C_1-C_6-alkyl, OH, or $-N(R^7)_2$. In the case where R^3 is $-N(R^7)_2$, each R^7 together with the nitrogen atom to which they are attached may form a 5- or 6-membered heterocycloalkyl group or a 9- or 10-membered heterobicycloalkyl group. Examples of such 5- and 6-membered heterocycloalkyl groups include piperazinyl, 4-methylpiperazinyl, 2-oxo-piperazinyl, 4-hydroxyethylpiperazinyl, morpholino, thiomorpholino, pyrrolidinyl, and piperidinyl groups. Examples of 9- or 10-membered heterobicycloalkyl groups include fused ring groups such as a hexahydropyrrolopyrazinyl group.

Het groups of the form:

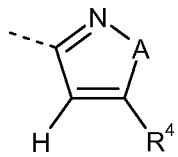


denote the following groups:

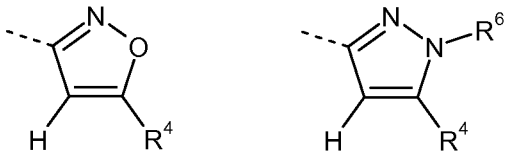


Thus, at least one of X and Z is not N, meaning that if X is N, Z must be C-H; if Z is N, X must be CR^5. It is also permissible for neither X nor Z to be N, in which case Y must be N.

Similarly, examples of Het groups of the form:



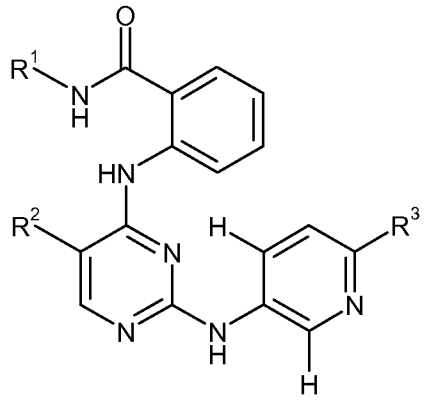
denote the following groups:



It is considered a critical aspect of the present invention that the atom on Het ortho to the NH group to which Het is attached be unsubstituted. It has been surprisingly discovered that ortho substituents tend to have an adverse affect on activity with respect to Aurora B as well as selectivity with respect to other targets.

In another aspect, R^1 is C_1-C_6-alkyl. In another aspect, R^2 is methyl or F.

In another aspect, the compound of the present invention is represented by the following formula:



Ia

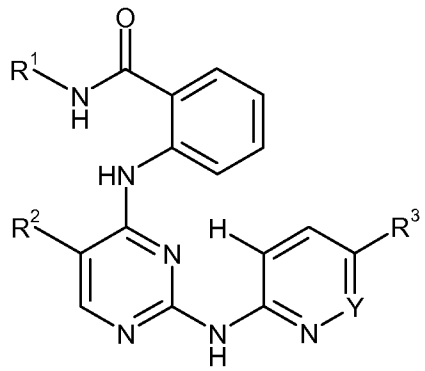
or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention is represented by Formula Ia or a pharmaceutically acceptable salt thereof, wherein R^3 is $-N(R^7)_2$, where each R^7, together with the nitrogen atom to which they are attached, form a pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-hydroxyethylpiperazinyl, morpholino, or 2-oxo-piperazinyl group.

In another aspect, the present invention is represented by a compound of Formula Ia or a pharmaceutically acceptable salt thereof, wherein each R^7, together with the nitrogen atom to which they are attached, form a 4-methylpiperazinyl group.

In another aspect, the present invention is represented by a compound of Formula Ia or a pharmaceutically acceptable salt thereof, wherein R^1 is isopropyl and R^2 is methyl.

In another aspect, the present invention is represented by a compound having the following formula:



wherein Y is N or CH, R^1 is C_1-C_6 alkyl; and R^3 is wherein R^3 is $-N(R^7)_2$.

As used herein, pharmaceutically acceptable refers to those compounds, materials, compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, or other problem or complication, commensurate with a reasonable benefit/risk ratio. The skilled artisan will appreciate that pharmaceutically acceptable salts of compounds of the present invention may be prepared. These pharmaceutically acceptable salts may be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free base form with a suitable acid.

Compounds of the present invention contain a basic functional group and are therefore capable of forming pharmaceutically acceptable acid addition salts by treatment with a suitable acid. Suitable acids include pharmaceutically acceptable inorganic acids and organic acids. Representative pharmaceutically acceptable acids include inorganic acids such as hydrogen chloride, hydrogen bromide, nitric acid, sulfuric acid, sulfonic acid, and phosphoric acid, as well as organic acids such as acetic acid, trifluoroacetic acid, hydroxyacetic acid, phenylacetic acid, propionic acid, butyric acid, valeric acid, maleic acid, acrylic acid, fumaric acid, malic acid, malonic acid, tartaric acid, citric acid, salicylic acid, benzoic acid, tannic acid, formic acid, stearic acid, lactic acid, ascorbic acid, *p*-toluenesulfonic acid, oleic acid, and lauric acid.

As used herein, the term "a compound" or "the compound" refers to one or more compounds.

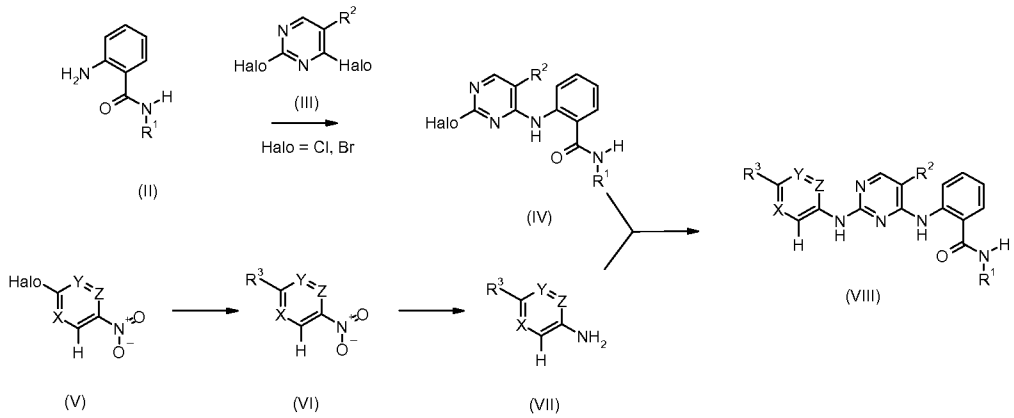
Compounds of the present invention may exist in a crystalline or noncrystalline form, or as a mixture thereof. The skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed for crystalline compounds wherein solvent molecules are incorporated into the crystalline lattice during crystallization. Solvates may involve non-aqueous solvents such as ethanol, isopropanol, DMSO, acetic acid, ethanolamine, and ethyl acetate, or they may involve water as the solvent that is incorporated into the crystalline lattice. Solvates wherein water is the solvent incorporated into the crystalline lattice are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. The invention includes all such solvates and forms.

Schemes

Aminobenzamide (II) and dichloro- or dibromopyrimidine (III) are commercially available or may be synthesized using techniques well known in the art. These intermediates may be advantageously reacted under reflux conditions using a polar, protic solvent such as *n*-butanol or isopropanol to produce Intermediate (IV).

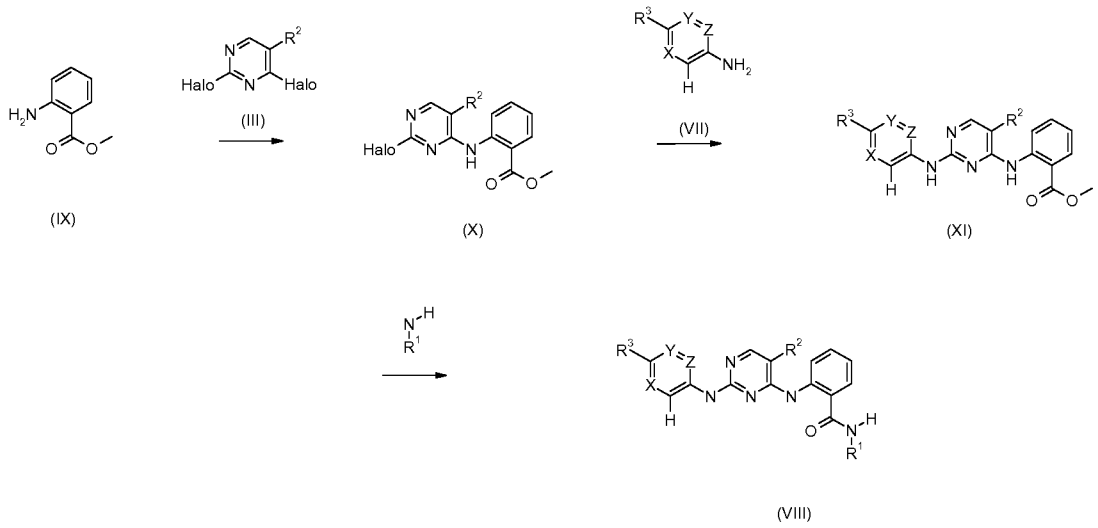
Compounds of formula (VII) are commercially available or may be synthesized using techniques well known in the art. For example, compounds of formula (V) may be reacted with nucleophiles to substitute the halogen and provide compounds of formula (VI), which can be reduced to provide a compound of formula (VII). Compounds of formula (IV) and (VII) may then be reacted to provide a compound of formula (VIII). The reaction is advantageously carried out under reflux in the presence of an acid such as hydrochloric acid or trifluoroacetic acid (TFA), and in a suitable solvent such as isopropanol, *n*-butanol, 1,4-dioxane, ethanol or N,N-dimethylformamide (DMF). Alternatively, compounds of formula (VIII) can be prepared from compounds of formula (IV) and (VII) by Buchwald coupling, using a palladium catalyst such as $Pd(OAc)_2$ or $Pd_2(dba)_3$, and a ligand such as XANTPHOS, in a suitable solvent such as dioxane or toluene. This coupling reaction is advantageously carried out at elevated temperatures (typically from about 40 to about 110 °C). If protecting groups are used, a final protecting group deprotection can be done using techniques well known in the art.

Scheme 1



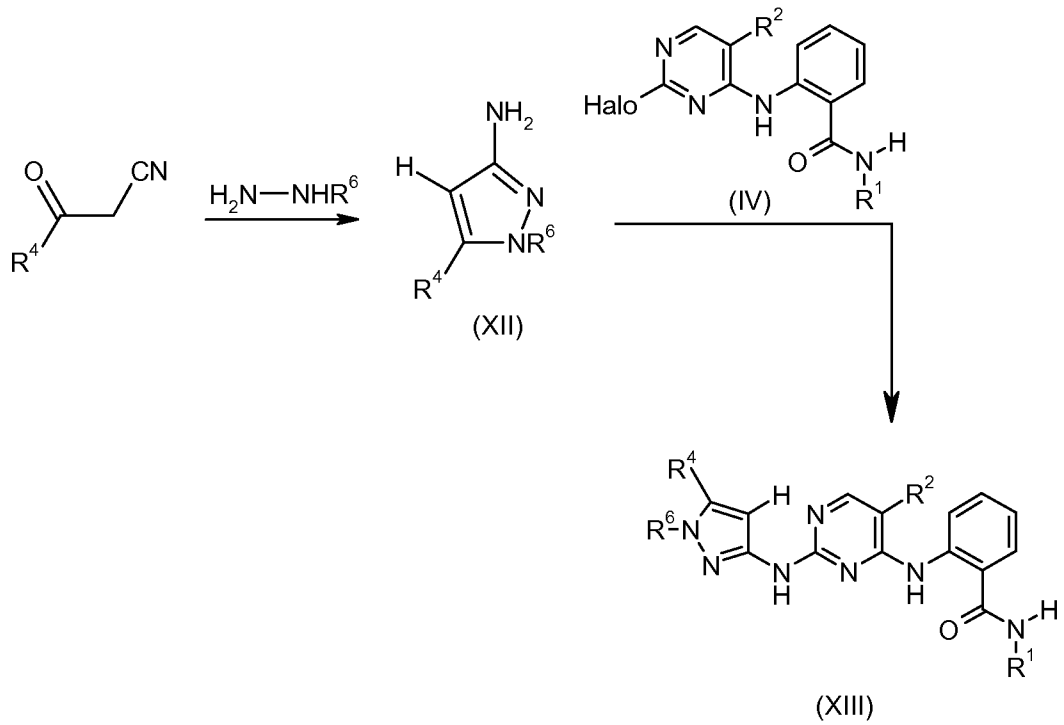
An alternative method for forming the amide is shown in Scheme 2. Reaction of aminobenzoate (IX) with pyrimidine (III) provides Intermediate (X). Heterocyclic aniline (VII) can then be reacted with Intermediate (X) to provide Intermediate (XI), which can be further reacted with an amine to form final product (VIII).

Scheme 2



Compounds of formula (XIII) can be prepared from Intermediates (IV) and (XII) using the methods describe for the synthesis of (VIII) and (XI) as shown in Scheme 3. Compounds of formula (XII) are commercially available or may be synthesized using techniques conventional in the art.

Scheme 3



BIOLOGICAL ASSAYS

Aurora A/TPX2 IMAP® Enzyme Activity Assay

Compounds of the present invention were tested for Aurora A/TPX2 protein kinase inhibitory activity in a substrate phosphorylation assay. This assay examines the ability of small molecule organic compounds to inhibit the serine phosphorylation of a peptide substrate, and was run in the IMAP® technology (Molecular Devices, Sunnyvale, California) fluorescent polarization assay format. The method measures the ability of the isolated enzyme to catalyze the transfer of the gamma-phosphate from ATP onto the serine residue of a fluorescein-labeled synthetic peptide (5FAM-GRTGRRNSI-NH_2). In a microwell assay format, the fluorescein-labeled peptide is phosphorylated in a kinase reaction. Addition of the IMAP® Binding System stops the kinase reaction and specifically binds the phosphorylated substrates. Phosphorylation and subsequent binding of the substrate to the beads (binding reagent) is detected by fluorescent polarization.

The substrate phosphorylation assays use recombinant human full-length Aurora A kinase expressed in baculovirus/Sf9 system. An N-terminal His-Thr-affinity tag was fused to the amino terminus of amino acids 2 through 403 of Aurora A. 5nM okadaic acid was added during the last 4 hours of expression (experimentally determined to enhance Aurora A's enzymatic activity). The enzyme was purified to approximately 70% purity by metal-chelate affinity chromatography.

Assays were performed in 384-well low volume black polystyrene plates (Greiner Bio-One, Longwood, FL). 5μLof a 4 nM Aurora A enzyme was added to the wells containing 0.1μl of test compound in 100% DMSO and incubated for 30 minutes followed by the addition of 5μL reaction mixture resulting in a final assay volume of 10 μL containing 1 mM magnesium chloride, 2 μM ATP, 1 μM peptide substrate, 40 nM microtubule associated protein TPX2 peptide (1-43), 1.5 mM DTT, 25 mM NaCl, 0.15 mg/mL BSA and 0.01% Tween-20 in 50mM HEPES, pH 7.2. The reaction was allowed to proceed for 120 minutes at room temperature and was terminated by the addition of 10μL of a 1:500 dilution of Progressive Binding Reagent (nanoparticles beads) in the Molecular Devices proprietary 90% buffer A and 10% buffer B. After a 120 minute incubation time the plates were read in a Analyst GT (Molecular Devices) in fluorescence polarization mode with excitation at 485 nM, emission at 530 nM and using the 505 nM dichroic lens.

Data is captured in parallel and perpendicular directions and converted to mp by the instrument. For dose response curves, data were normalized and expressed as percent inhibition using the formula 100*(1-(U-C2)/(C1-C2)) where U is the unknown value, C1 is the average of the high signal (0% inhibition) and C2 is the average of the low signal (100% inhibition) control wells. Curve fitting was performed with the following equation: y = A+((B-A)/ (1+(10^x/10^C)^D)), where A is the minimum response, B is the maximum response, C is the log10(XC50), and D is the slope. The results for each compound were recorded as pIC50 values (-C in the above equation).

Aurora B/INCENP IMAP® Enzyme Activity Assay

Compounds of the present invention were also tested for Aurora B/INCENP protein kinase inhibitory activity in a substrate phosphorylation assay. The substrate

phosphorylation assay use recombinant human full-length Aurora B kinase expressed in baculovirus/Sf9 system. Following expression the culture is incubated with 50 nM okadaic acid for 1 hour prior to purification. An N-terminal His-affinity tag was fused to the amino terminus of amino acids 1 through 344 of Aurora B. The expressed protein was purified by metal-chelate affinity chromatography. 5μM Aurora B was activated in 50mM Tris-HCl pH 7.5, 0.1mM EGTA, 0.1% 2-mercaptoethanol, 0.1mM sodium vanadate, 10mM magnesium acetate, 0.1mM ATP with 0.1mg/ml GST-INCENP [826 - 919] at 30°C for 30 minutes. Following activation the enzyme is then dialyzed into enzyme storage buffer and stored at –70°C.

Assays were performed in 384-well low volume black polystyrene plates (Greiner Bio-One, Longwood, FL). 5μL of a 4nM Aurora B/INCENP was added to the wells containing 0.1μl of test compound in 100% DMSO and incubated for 30 minutes followed by the addition of 5μL of a reaction mixture resulting in a final assay volume of 10μL containing 2mM magnesium chloride, 2.5 μM ATP, 1.25 μM peptide substrate (5FAM-GRTGRRNSI-NH_2), 2 mM DTT, 25 mM NaCl, 0.15mg/mL BSA, 0.01% Tween-20 in 50mM HEPES, pH 7.5. The reaction was allowed to proceed for 120 minutes at room temperature and was terminated by the addition of 10μL of a 1:500 dilution of Progressive Binding Reagent (nanoparticles beads) in the Molecular Devices proprietary 95% buffer A and 5% buffer B. After a 120-minute incubation time the plates were read in a Analyst GT in fluorescence polarization mode with excitation at 485 nM, emission at 530 nM and using the 505 nM dichroic lens.

Data was captured as described for the Aurora A assay.

EXPERIMENTAL

The following examples are for illustrative purposes only and are not intended to limit the scope of the present invention. The dotted lines in the examples represent the point of attachment. All exemplified compounds have pIC_{50} of greater than 7.5 for Aurora B.

The compounds were named using ACD Name software (Advanced Chemistry Development). A PE Sciex API 150 single quadrupole mass spectrometer (PE Sciex, Thornhill, Ontario, Canada) was operated using electrospray ionization in the positive ion detection mode. The nebulizing gas was generated from a zero air generator (Balston

Inc., Haverhill, MA) and delivered at 65 psi and the curtain gas was high purity nitrogen delivered from a Dewar liquid nitrogen vessel at 50 psi. The voltage applied to the electrospray needle was 4.8 kV. The orifice was set at 25 V and mass spectrometer was scanned at a rate of 0.5 scan/sec using a step mass of 0.2 amu and collecting profile data.

Samples are introduced into the mass spectrometer using a CTC PAL autosampler (LEAP Technologies, Carrboro, NC) equipped with a hamilton 10 uL syringe which performed the injection into a Valco 10-port injection valve. The HPLC pump was a Shimadzu LC-10ADvp (Shimadzu Scientific Instruments, Columbia, MD) operated at 0.3 mL/min and a linear gradient 4.5% A to 90% B in 3.2 min. with a 0.4 min. hold. The mobile phase was composed of 100% (H2O 0.02% TFA) in vessel A and 100% (CH3CN 0.018% TFA) in vessel B. The stationary phase is Aquasil (C18) and the column dimensions are 1 mm x 40 mm. Detection was by UV at 214 nm, evaporative light-scattering (ELSD) and MS.

Alternatively, an Agilent 1100 analytical HPLC system with an LC/MS was used and operated at 1 mL/min and a linear gradient 5% A to 100% B in 2.2 min with a 0.4 min hold. The mobile phase was composed of 100% (H_2O 0.02% TFA) in vessel A and 100% (CH_3CN 0.018% TFA) in vessel B. The stationary phase was Zobax (C8) with a 3.5 um partical size and the column dimensions were 2.1 mm x 50 mm. Detection was by UV at 214 nm, evaporative light-scattering (ELSD) and MS.

^{1}H-NMR (hereinafter "NMR") spectra were recorded at 400 MHz using a Bruker AVANCE 400 MHz instrument, with ACD Spect manager ver 10 using for reprocessing. Multiplicities indicated are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, dt=doublet of triplets etc. and br indicates a broad signal.

Analytical HPLC: Products were analyzed by Agilent 1100 Analytical Chromatography system, with 4.5 x 75 mm Zorbax XDB-C18 column (3.5 μm) at 2 mL/min with a 4 min gradient from 5% CH_3CN (0.1% formic acid) to 95% CH_3CN (0.1% formic acid) in H_2O (0.1% formic acid) and a 1 min hold.

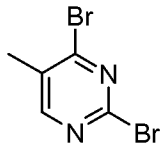
Preparative HPLC: Products were purified using a Gilson preparative chromatography system with a 75 x 30 mm I. D. YMC CombiPrep ODS-A column (5 μm) at 50 mL/min

with a 10 min gradient from 5% CH_3CN (0.1% formic acid) to 95% CH_3CN (0.1% formic acid) in H_2O (0.1% formic acid) and a 2 min hold; alternatively, products were purified using an Agilent 1100 Preparative Chromatography system, with 100 x 30 mm Gemini C18 column (5 μm) at 60 mL/min with a 10 min gradient from 5% CH_3CN (0.1% formic acid) to 95% CH_3CN (0.1% formic acid) in H_2O (0.1% formic acid) and a 2 min hold.

Preparative normal phase chromatography was carried out using an Analogix IntelliFlash 280 System with SuperFlash Sepra Si 50 columns.

Intermediate 1

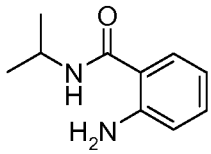
2,4-Dibromo-5-methylpyrimidine



To thymine (3.7 g, 29 mmol) and phosphorus(V) oxybromide (25.0 g, 87.2 mmol) in acetonitrile (CH_3CN) (150 mL) at 0 °C was added portion wise K_2CO_3 (12.1 g, 87.2 mmol). The mixture was allowed to warm to room temperature and then heated to 80 °C for 3 days. The reaction mixture was poured onto ice and the pH of the resulting slurry was adjusted to pH 7 by addition of $K_2CO_{3(S)}$. The aqueous layer was extracted with methylene chloride (CH_2Cl_2). The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (0 – 30 % ethyl acetate (EtOAc)/hexanes) afforded the desired product (7.1 g, 96%) as a white solid. LC-MS (ES) m/z = 251, 253 and 255 $[M+H]^+$.

Intermediate 2

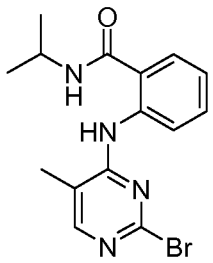
2-Amino-*N*-(1-methylethyl)benzamide



To a solution of isatoic anhydride (50.0 g, 0.3 mol,) in water (600 mL) was added isopropylamine (46.5 mL, 0.55 mol) slowly and the resulting mixture was stirred at room temperature for 30 minutes. A sandy-brown solid precipitated from the reaction mixture. The solid was collected via vacuum filtration and the filter cake was washed with water and hexanes. The resulting solid was dried overnight under reduced pressure to afford the title compound (49.2 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 6.6 Hz, 6H), 4.27 (m, 1H), 5.91 (bs, 1H), 6.77 (t, J = 7.1 Hz, 1H), 6.77 (d, J = 8.3 Hz, 1H), 7.22 (t, J = 8.5 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H). LC-MS (ES) m/z = 201 $(M+Na)^+$.

Intermediate 3

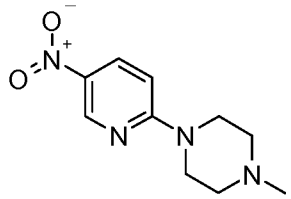
2-[(2-Bromo-5-methyl-4-pyrimidinyl)amino]-*N*-(1-methylethyl)benzamide



In a tube were combined Intermediate 1 (4.0 g, 15.9 mmol)), Intermediate 2 (2.8 g, 15.9 mmol), isopropanol (30 mL), and di-isopropyl-ethylamine (3.7 mL, 21.2 mmol). The vessel was sealed and the mixture was heated to 110 °C for 3 days. The reaction mixture was poured onto EtOAc and water. The layers were separated and the aqueous layer was further extracted with more EtOAc. The combined organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (0 – 30% EtOAc/hexanes) afforded the desired product (2.8 g, 50%) as a white solid. LC-MS (ES) m/z = 349, 351 $[M+H]^+$.

Intermediate 4

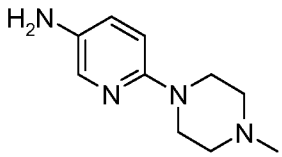
1-Methyl-4-(5-nitro-2-pyridinyl)piperazine



To a solution of 2-bromo-5-nitropyridine (22.3 g, 110 mmol) in CH_3CN (200 mL) was added *N*-methylpiperazine (30.5 mL, 275 mmol) and the resulting mixture was heated with stirring to reflux. After 90 min, the reaction was cooled to room temperature and concentrated to dryness. The solids were partitioned between water and EtOAc. The organic layer was separated and washed with brine, dried ($MgSO_4$), filtered and concentrated to dryness affording the title compound as a yellow solid (24.2 g, 99%). LC-MS (ES) m/z = 223 $[M+H]^+$.

Intermediate 5

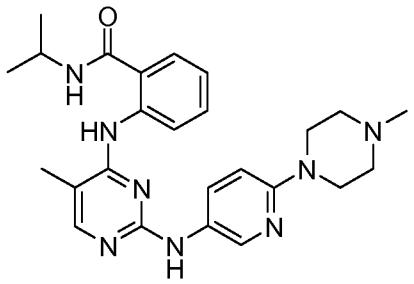
6-(4-Methyl-1-piperazinyl)-3-pyridinamine



To a solution of Intermediate 4 (2.84 g, 12.8 mmol) in ethanol (150 mL) in a 1000-mL flask under argon was added 10% Pd/C (0.28 g). The argon was evacuated and replaced with H_2. The reaction was stirred at room temperature for 3 h, after which time the H_2 was evacuated and replaced with argon. 4M HCl in dioxane (6.75 mL, 26.9 mmol) was syringed into the reaction mixture causing the formation of an off-white precipitate. After stirring for 5 min, hexane (500 mL) was added and the solid was filtered, washed with hexanes, and dried under vacuum at 40 °C overnight affording an HCl salt of the title compound as an off-white solid (3.41 g, 92%) (product contains impurity of 10% Pd/C). LC-MS (ES) m/z = 193 $[M+H]^+$.

Example 1

N-(1-Methylethyl)-2-[(5-methyl-2-{[6-(4-methyl-1-piperazinyl)-3-pyridinyl]amino}-4-pyrimidinyl)amino]benzamide

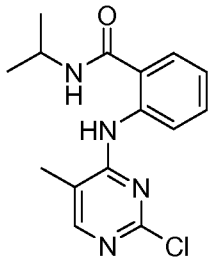


In a 150 mL tube were combined Intermediate 3 (2.36 g, 6.76 mmol), Intermediate 5 (1.97 g, 7.43 mmol), XANTPHOS (0.59 g, 1.01 mmol), and cesium carbonate (Cs_2CO_3) (11.0 g, 33.8 mmol) in dioxane (70 mL). After argon was bubbled through the mixture for 15 min, palladium(II) acetate (0.30 g, 1.35 mmol) was added, the vessel sealed, and the reaction was heated with stirring at 70 °C for 16 h. After cooling to room temperature, the reaction was diluted with chloroform ($CHCl_3$) (300 mL), filtered through Celite 503, and concentrated to dryness yielding a black solid that was partitioned between $CHCl_3$ (200 mL) and 0.5M $HCl_{(aq)}$ (250 mL). The organics were drawn off and discarded. The aqueous layer was adjusted to pH = 12 with 6M $NaOH_{(aq)}$ and extracted with $CHCl_3$ (2 x 150 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated to dryness. The solids were purified by reverse-phase HPLC (C18, CH_3CN/H_2O w/ 0.1% trifluoroacetic acid (TFA)). Clean fractions were combined and concentrated to remove CH_3CN. The aqueous solution was adjusted to pH = 12 with 6M $NaOH_{(aq)}$ and the free-base of the product was extracted with $CHCl_3$ (2 x 250 mL). The organics were dried ($MgSO_4$), filtered, and concentrated to dryness. The resulting light purple solid was dissolved in MeOH (50 mL) and treated with 4M HCl in dioxane (1.60 mL, 2.05eq). Concentration to dryness followed by co-evaporation with diethyl ether (Et_2O) afforded an HCl salt of the title compound as a light purple solid (1.43 g, 46%). LC-MS (ES) m/z = 461 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 11.41 (bs, 1H), 10.52 (s, 1H), 8.73 (d, J = 7.8 Hz, 1H), 8.32 (bs, 1H), 8.22 (d, J = 2.5 Hz, 1H), 7.95 (bs, 1H), 7.8 (m, 1H), 7.86 (dd, J = 8.0, 1.4 Hz, 1H), 7.43 (m, 1H), 7.27 (m, 1H),

7.10 (d, J = 9.4 Hz, 1H), 4.41 (m, 2H), 4.11 (m, 1H), 3.50 (m, 2H), 3.37 (m, 2H), 3.10 (m, 2H), 2.80 (d, J = 4.3 Hz, 3H), 2.17 (s, 3H), 1.18 (d, J = 6.6 Hz, 6H).

Intermediate 6

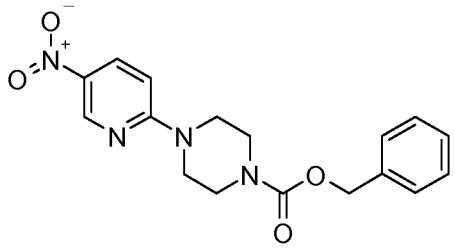
2-[(2-Chloro-5-methyl-4-pyrimidinyl)amino]-N-(1-methylethyl)benzamide



To solution of Intermediate 2 (39.0 g, 0.2 mol) in isopropanol (100 mL) were added di-isopropyl-ethylamine (37.8 mL, 0.22 mol) and 2,4-dichloro-5-methylpyrimidine (32.4 g, 0.2 mol). The reaction vessel was sealed and heated to 110 °C for three days. The reaction vessel was cooled to room temperature and the reaction mixture was concentrated to a solid. Flash chromatography over silica gel eluting with a gradient from $CHCl_3$ to 5% MeOH:$CHCl_3$ afforded impure product. The yellow solid was triturated with Et_2O. The resulting white solid was collected via vacuum filtration. ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 6.6 Hz, 6H), 2.29 (s, 3H), 4.29 (m, 1H), 6.18 (bs, 1H), 7.14 (t, J = 7.1 Hz, 1H), 7.55 (m, 2H), 8.05 (s, 1H), 8.76 (d, J = 7.6 Hz, 1H), 11.44 (bs, 1H). LC-MS (ES) m/z = 305, 307 $[M+H]^+$.

Intermediate 7

Phenylmethyl 4-(5-nitro-2-pyridinyl)-1-piperazinecarboxylate

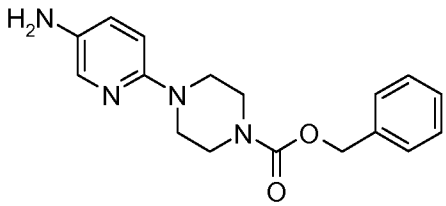


To a solution of 2-bromo-5-nitropyridine (15.6 g, 70 mmol) in CH_3CN were added benzyl-piperazine-carboxylate (11.8 mL, 60 mmol) and triethylamine (10.68 mL, 70

mmol). The resulting solution was heated to reflux. When the reaction was judged complete via LC/MS the reaction mixture was allowed to cool to room temperature overnight. Upon cooling a yellow precipitate formed and solvent was removed *in vacuo*. The filtrate was concentrated to a yellow solid under reduced pressure. The resulting solid was dissolved in methylene chloride (CH_2Cl_2) and washed with water. The organic phase was concentrated. Flash chromatography over silica gel eluting with a gradient from $CHCl_3$ to 5% acetone:$CHCl_3$ afforded the title compound (15.2 g, 58%) as a yellow solid. LC-MS (ES) m/z = 343 $[M+H]^+$.

Intermediate 8

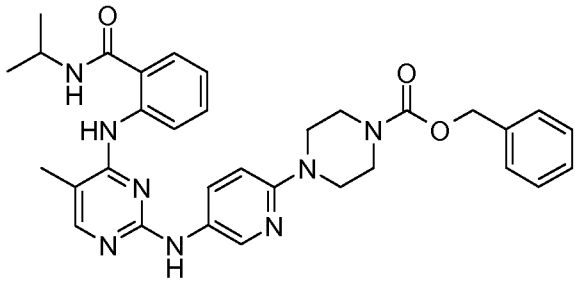
Phenylmethyl 4-(5-amino-2-pyridinyl)-1-piperazinecarboxylate:



To a solution of Intermediate 7 (8.74 g, 25 mmol) in MeOH were added iron (4.27 g, 76 mmol) and ammonium chloride (NH_4Cl) (12.3 g, 230 mmol). The resulting solution was refluxed for 2.5 h. The reaction mixture was diluted with MeOH and filtered through 2 pads of Celite. The filtrate was concentrated to a black solid. The solid was dissolved in EtOAc and washed with water. The aqueous layer was then made basic with 1.0 M NaOH and extract with EtOAc. The combined organics were concentrated under reduced pressure. Flash chromatography with 5% MeOH:$CHCl_3$ over silica gel afforded the free base. To the free base in MeOH was added excess 4.0 M HCl in dioxanes. The solution was concentrated to a black solid (4.7 g). LC-MS (ES) m/z = 313 $[M+H]^+$.

Intermediate 9

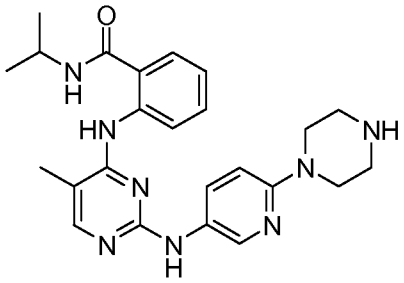
Phenylmethyl 4-[5-({5-methyl-4-[(2-{[(1-methylethyl)amino]carbonyl}phenyl)amino]-2-pyrimidinyl}amino)-2-pyridinyl]-1-piperazinecarboxylate



To a pressure vessel charged with Intermediate 6 (1.18 g, 3.9 mmol) and Intermediate 8 (1.35 g, 3.9 mmol) was added isopropanol (25 mL). The vessel was sealed and heated to 100 °C. The reaction was monitored via LC/MS. After heating for 2 days the reaction vessel was cooled to room temperature and filtered. The reaction mixture was split into 2 batches. One batch was subjected to flash chromatography over silica gel eluting with a gradient of $CHCl_3$ to 5% MeOH:$CHCl_3$. The second batch was dissolved in $CHCl_3$ and washed with 10% NaOH aq. The organic layer was concentrated and run through a plug of silica with 80:20:2 $CHCl_3$:MeOH:NH_4OH. The filtrate was concentrated and subjected to flash chromatography eluting with a gradient of $CHCl_3$ to 5% MeOH:$CHCl_3$. The combined title compound batches (1.63 g) were carried onto the next step (Example 2) without further purification. LC-MS (ES) m/z = 581 $[M+H]^+$.

Example 2

N-(1-methylethyl)-2-[(5-methyl-2-{[6-(1-piperazinyl)-3-pyridinyl]amino}-4-pyrimidinyl)amino]benzamide

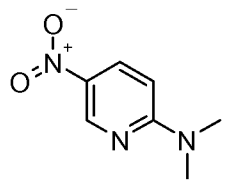


To a solution of Intermediate 9 (1.63 g) in MeOH was added a catalytic amount of Pd/C 10 wt% and a catalytic amount of concentrated HCl. The flask was fitted with a balloon of H_2 and the reaction mixture was stirred vigorously. The reaction mixture was monitored via LC/MS. After stirring for five days the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated to a solid. An impurity was

removed via recrystallization from CH_3CN. The filtrated was concentrated to a tan solid. The solid was dissolved in ~ 10 mL of water with a minimum amount of CH_3CN. The resulting solution was injected onto the Varian reverse phase HPLC (C18), 40 min prep. run 5 to 95% CH_3CN (0.1% TFA) / H_2O (0.1% TFA). The clean fractions were concentrated to a brown residue. Recrystallization from CH_3CN and Et_2O afforded a TFA salt of the title compound as a light tan solid (0.2 g for 2 steps). LC-MS (ES) m/z = 447 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 1.24 (d, *J* = 6.6 Hz, 6H), 2.18 (s, 3H), 3.38 (m, 4H), 3.88 (m, 4H), 4.23 (m, 1H), 7.07 (d, *J* = 9.1 Hz, 1H), 7.25 (m, 1H), 7.40 (t, *J* = 7.4Hz, 1H), 7.70 (s, 1H), 7.75 (dd, J = 8.0, 1.4 Hz, 1H), 7.83 (dd, J = 9.1, 2.5 Hz, 1H), 8.25 (d, *J* = 2.5 Hz, 1H), 8.35 (m, 1H).

Intermediate 10

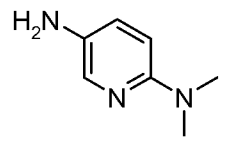
N,*N*-Dimethyl-5-nitro-2-pyridinamine



To a solution of dimethylamine (49 mL, 98.6 mmol, 2M in THF) was added 2-bromo-5-nitropyridine (1.0g, 4.9 mmol) in a 100-mL flask under N_2. The mixture was heated to reflux with stirring for 2 h. Upon cooling, the mixture was concentrated to dryness and the resulting solids were sonicated in EtOAc (100 mL). After filtration, the filtrate was concentrated to dryness, and the solids were sonicated once again in 90/10 Hexanes/EtOAc. The resulting solids were collected, washed with hexanes, and dried yielding the title compound as a yellow solid (0.62 g, 75%). LC-MS (ES) m/z = 168 $[M+H]^+$.

Intermediate 11

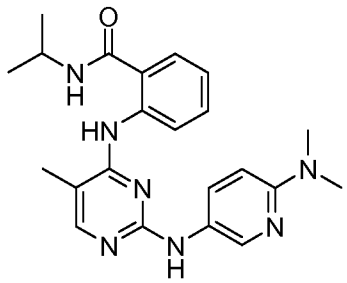
N^2,N^2-Dimethyl-2,5-pyridinediamine



To a slurry of Intermediate 10 (0.62 g, 3.7 mmol) in MeOH (20 mL) was added 10% Pd/C (cat.). The mixture was stirred at room temperature under atmospheric H_2. After 16 h, the H_2 was evacuated and replaced with argon. 4M HCl in dioxane (2.78 mL, 11.1 mmol) was added, the reaction filtered through a pad of Celite 503, and the filtrate concentrated to dryness. The resulting solids were dissolved in H_2O (15 mL), eluted through a 300mg plug of C18 (H_2O), and the aqueous was extracted with EtOAc which was then discarded. The aqueous phase was concentrated to dryness. The resulting solids were sonicated in 90/10 Hexanes/ethanol and then filtered followed by a hexane rinse. Drying yielded an HCl salt of the title compound as a light green solid (0.56 g, 72%). LC-MS (ES) m/z = 138 $[M+H]^+$.

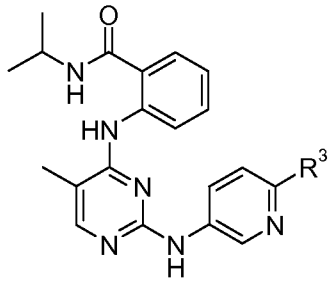
Example 3

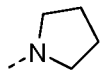
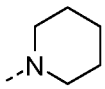
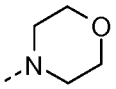
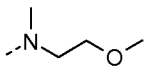
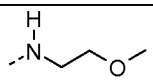
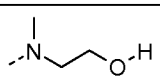
2-[(2-{[6-(Dimethylamino)-3-pyridinyl]amino}-5-methyl-4-pyrimidinyl)amino]-*N*-(1-methylethyl)benzamide



To a mixture of Intermediate 6 (0.18 g, 0.58 mmol) and Intermediate 11 (0.10 g, 0.58 mmol) was added isopropanol (5 mL) and the reaction heated with stirring in a 15 mL sealed tube at 95 °C for 16 h. The reaction was cooled to room temperature, concentrated to dryness, and the resulting solids were purified by reverse-phase HPLC (Varian Polaris C18, CH_3CN/H_2O w/ 0.1% TFA) yielding a purple solid that was sonicated in 1ml CH_3CN, filtered, and washed with hexanes to afford a TFA salt of the title compound as a light purple solid (0.022 g). LC-MS (ES) m/z = 406 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.79 (bs, 1H), 9.86 (bs, 1H), 8.63 (d, J = 7.6 Hz, 2H), 8.27 (bs, 1H), 7.91 (bs, 1H) 7.82 (d, J = 7.1 Hz, 2H), 7.45 (bs, 1H), 7.21 (t, J = 7.7 Hz, 1H), 6.97 (bs, 1H), 4.13 (m, 1H), 3.13 (s, 6H) 2.15 (s, 3H), 1.18 (d, J = 6.6 Hz, 6H).

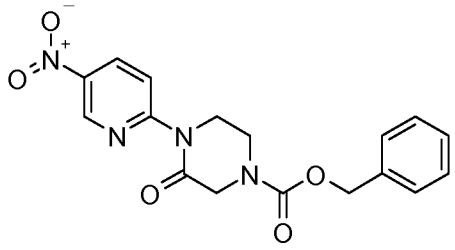
The following *N*-(1-methylethyl)-2-[(5-methyl-2-{[6-(substituted)-3-pyridinyl]amino}-4-pyrimidinyl)amino]benzamide compounds were prepared from the corresponding 2-[(2-chloro-5-methyl-4-pyrimidinyl)amino]-N-(1-methylethyl)benzamide Intermediate 6 and the corresponding pyridinamine (prepared substantially as shown for Intermediates 5 or 11) using a procedure similar to Example 3. The dashed bond for the groups in the table represents the point of attachment to the pyridine ring.



Ex. No.	R^3	Mass (M+H)+
4		432
5		446
6		448
7		379
8		450
9		436
10		436

Intermediate 12

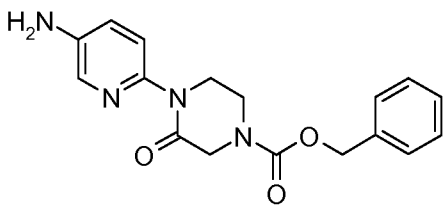
Phenylmethyl 4-(5-nitro-2-pyridinyl)-3-oxo-1-piperazinecarboxylate



To a mixture of phenylmethyl 3-oxo-1-piperazinecarboxylate (4.3 g, 18.5 mmol), 2-bromo-5-nitropyridine (3.75 g, 18.5 mmol), $Pd_2(dba)_3$ (0.46 g, 0.50 mmol), dppf (0.83 g, 1.5 mmol), and Cs_2CO_3 (6.5 g, 20 mmol) in a sealed tube under nitrogen was added degassed toluene and the mixture was vigorously stirred for 18 h at 100 °C. The reaction mixture was passed through a pad of silica gel eluting with EtOAc and the resulting solution was evaporated. Purification by flash chromatography on silica gel ($CHCl_3$/EtOAc) afforded a yellow residue. Recrystallization from Et_2O/Hexane afforded the title compound (1.5 g, 19%) as a light yellow solid. LC-MS (ES) m/z = 357 $[M+H]^+$.

Intermediate 13

Phenylmethyl 4-(5-amino-2-pyridinyl)-3-oxo-1-piperazinecarboxylate

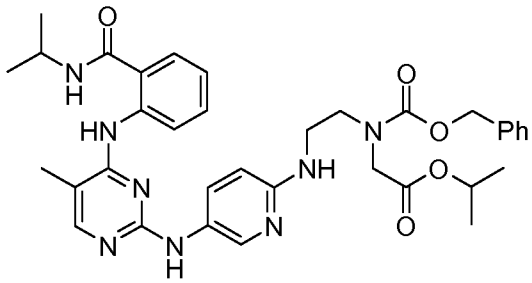


To a slurry of Intermediate 12 (1.46 g, 4.10 mmol) in MeOH (100 mL) and H_2O (50 mL) was added iron powder (1.14 g, 20.5 mmol) and ammonium chloride (1.97 g, 36.9 mmol). The mixture was heated in a 250-mL flask at 70 °C for 4 h. The reaction was cooled to room temperature, filtered through Celite 503 with MeOH, and concentrated to dryness. The resulting solid was diluted with EtOAc (100 mL) and sonicated. After filtering away the solids, the filtrate was concentrated to a red oil which was purified on

silica gel (CH_2Cl_2/MeOH) affording the title compound (1.20 g, 90%) as a tan oil. LC-MS (ES) m/z = 327 $[M+H]^+$.

Intermediate 14

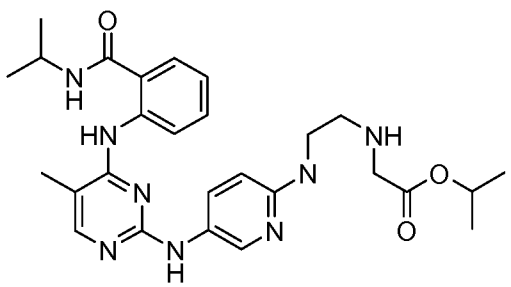
1-Methylethyl *N*-(2-{[5-({5-methyl-4-[(2-{[(1-methylethyl)amino]carbonyl}phenyl)amino]-2-pyrimidinyl}amino)-2-pyridinyl]amino}ethyl)-*N*-{[(phenylmethyl)oxy]carbonyl}glycinate



To a mixture of Intermediate 6 (0.16 g, 0.52 mmol) and Intermediate 13 (0.17 g, 0.52 mmol) was added isopropanol (10 mL) and 4M HCl in dioxane (0.39 mL, 1.56 mmol). The reaction was heated with stirring in a 15 mL sealed tube at 95 °C for 16 h. After cooling to room temperature, the mixture was diluted with Et_2O (3 mL) and the resulting solids were filtered and washed with Et_2O. This material was purified by reverse-phase HPLC (Varian Polaris C18, CH_3CN/H_2O w/ 0.1% TFA) affording a TFA salt of the title compound (0.12 g) as a tan solid. LC-MS (ES) m/z = 655 $[M+H]^+$.

Example 10

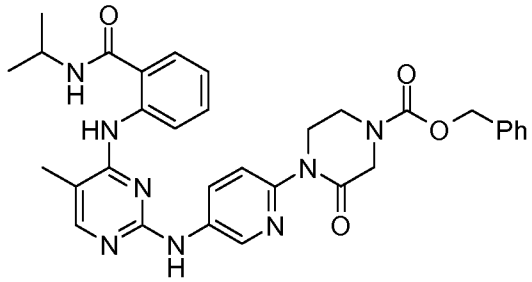
1-Methylethyl *N*-(2-{[5-({5-methyl-4-[(2-{[(1-methylethyl)amino]carbonyl}phenyl)amino]-2-pyrimidinyl}amino)-2-pyridinyl]amino}ethyl)glycinate



To a solution of Intermediate 14 (0.12 g, 0.18 mmol) in MeOH (10 mL) was added 10% Pd/C (cat.) and the reaction stirred at room temperature for 16 h under H_2 atmosphere. The reaction was filtered through Celite 503 and the filtrate concentrated to dryness affording a TFA salt of the title compound (0.054 g, 57%) as a tan solid. LC-MS (ES) m/z = 521 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.73 (bs, 1H), 9.77 (bs, 1H), 9.30 (bs , 2H), 8.61 (bs , 2H), 8.13 (bs , 1H), 7.82 (d, J = 7.3 Hz, 2H), 7.68 (bs , 1H), 7.42 (bs , 1H), 7.19 (bs , 1H), 6.70 (d, J = 3.5 Hz, 1H), 5.03 (m, 1H), 4.13 (m, 1H), 4.04 (s, 2H), 3.58 (m , 2H), 3.17 (m, 2H), 2.14 (s, 3H), 1.24 - 1.25 (d, J = 6.3 Hz, 6H), 1.17 – 1.19 (d, J = 6.2 Hz, 6H).

Intermediate 15

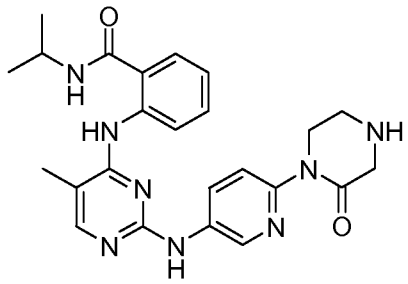
Phenylmethyl 4-[5-({5-methyl-4-[(2-{[(1-methylethyl)amino]carbonyl}phenyl)amino]-2-pyrimidinyl}amino)-2-pyridinyl]-3-oxo-1-piperazinecarboxylate



In a 25 mL sealed tube under argon were combined Intermediate 6 (0.19 g, 0.61 mmol), Intermediate 13, XANTPHOS (0.005 g, 0.092 mmol), and Cs_2CO_3 (0.80 g, 2.45 mmol) in 1,4-dioxane (5 mL). After purging the system with argon for 10 min, palladium(II) acetate (0.041g, 0.18 mmol) was added, the vessel sealed, and the reaction was heated with stirring at 70 °C for 16 h. After cooling to room temperature, the reaction was diluted with 10 mL 10/1 CH_2Cl_2/MeOH and filtered through Celite 503. The filtrate was concentrated to dryness, neutralized with TFA/MeCN, and purified by reverse-phase HPLC (C18, MeCN/H_2O w/ 0.1% TFA) affording a TFA salt of the title compound as a yellow solid (0.076 g, 21%). LC-MS (ES) m/z = 595 $[M+H]^+$.

Example 11

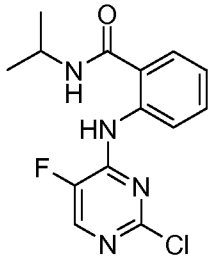
N-(1-Methylethyl)-2-[(5-methyl-2-{[6-(2-oxo-1-piperazinyl)-3-pyridinyl]amino}-4-pyrimidinyl)amino]benzamide



To a solution of Intermediate 15 (0.076g, 0.13 mmol) in MeOH (10 mL) was added 10% Pd/C (cat.) and the reaction stirred at room temperature for 16 h under H_2 atmosphere. The reaction was filtered through Celite 503 and the filtrate concentrated to dryness affording a TFA salt of the title compound as a tan solid (0.047g, 80%). LC-MS (ES) m/z = 461 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.15 (bs, 1H), 9.53 (bs, 1H), 9.29 (bs, 1H), 8.73 (d, *J* = 2.5 Hz, 1H), 8.54 (d, *J* = 7.8 Hz, 1H), 8.22 (dd, *J* = 9.0, 2.7 Hz, 1H), 8.02 (s, 1H), 7.78 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.67 (d, *J* = 9.1 Hz, 1H), 7.48 (dd, *J* = 15.7, 1.3 Hz, 1H), 7.12 (t, *J* = 7.07 Hz, 1H), 4.03 - 4.20 (m, 3H), 3.97 (s, 2H), 3.56 (t, *J* = 5.68 Hz, 2H), 2.13 (s, 3H), 1.18 (d, *J* = 6.6 Hz, 6H).

Intermediate 16

2-[(2-Chloro-5-fluoro-4-pyrimidinyl)amino]-*N*-(1-methylethyl)benzamide

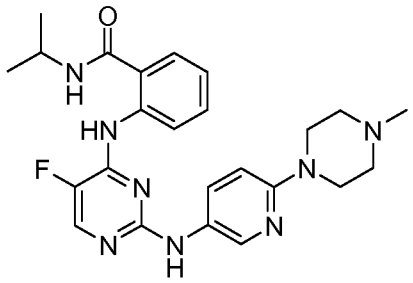


To solution of Intermediate 2 (10.7 g, 60 mmol) in isopropanol (550 mL) were added di-isopropyl-ethylamine (10.5 mL, 60 mmol) and 2,4-dichloro-5-fluoropyrimidine (9.2 g, 55 mmol). The reaction mixture was heated overnight at 88 °C. The mixture was filtered hot through a path of Celite 503. The solvent was partially removed (~2/3

volume) and a white solid precipitated from the solution. Hexane (100 mL) was added and the mixture was sonicated for 0.5 h. The resulting white solid (6.42 g) was collected via vacuum filtration. The filtrate was evaporated (~3/4 volume) until another precipitate was formed. Hexane (300 mL) was added and the mixture was sonicated for 0.5 h. The resulting white solid (3.51 g) was collected via vacuum filtration. The total yield of product was 9.93 g. (58% yield). LC-MS (ES) m/z = 309 $[M+H]^+$.

Example 12

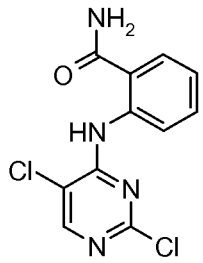
2-[(5-Fluoro-2-{[6-(4-methyl-1-piperazinyl)-3-pyridinyl]amino}-4-pyrimidinyl)amino]-*N*-(1-methylethyl)benzamide



Intermediate 5 (0.16 g, 0.70 mmol) and Intermediate 16 (0.22 g, 0.72 mmol) were combined in isopropanol. The pressure vessel was sealed and heated to 100 °C. The reaction was stirred for 5 days. The reaction vessel was cooled to room temperature and concentrated to a purple tar. The purple residue was dissolved in ~ 4 mL of water and washed with $CHCl_3$. The aqueous layer was then made basic with 6.0 M NaOH (pH 13). The basic aqueous layer was then extracted with $CHCl_3$. The organic layer was acidified with 6.0 M HCl and concentrated to a purple black solid. The solid was dissolved in CH_3CN and precipitated with Et_2O. An HCl salt of the title compound was isolated as a purple solid (0.1 g, 30%). ^1H NMR (400 M Hz, CD_3OD) δ 1.26 (d, J = 6.8 Hz, 6H), 3.03 (s, 3H), 3.40 (m, 2H), 3.63 (m, 2H), 3.74 (m, 2H), 4.22 (m, 1H), 4.51 (m, 2H), 7.38 (m, 2H), 7.57 (t, J = 7.7Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 8.11 (d, J = 9.1 Hz, 1H), 8.17 (d, J = 5.1 Hz, 1H), 8.31 (m, 2H). LC-MS (ES) m/z = 465 $[M+H]^+$.

Intermediate 17

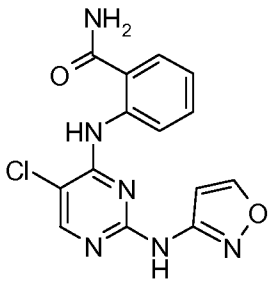
2-[(2,5-Dichloro-4-pyrimidinyl)amino]benzamide



A round-bottom flask was charged with 2,4,5-trichloropyrimidine (7 g, 38 mmol), ortho-anthranilamide (6.2 g, 45.8 mmol), di-isopropyl-ethylamine (8.0 mL, 45.8 mmol) and isopropanol (100 mL). The flask was fitted with a reflux condenser and the reaction was heated to reflux and stirred for 18 h. A white solid appeared in the reaction mixture. The reaction was cooled to room temperature, 1/3 of the volume was removed under vacuum and the solid was filtered off and washed with isopropanol. After drying, the white solid (9 g, 83%) was identified as 2-[(2,5-dichloro-4-pyrimidinyl)amino]benzamide. LC-MS (ES) m/z = 284, 286 $(M+H)^+$. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.68 - 8.78 (m, 1H) 7.85 (dd, *J* = 8.1, 1.5 Hz, 1H,) 7.52 - 7.67 (m,1H).

Example 13

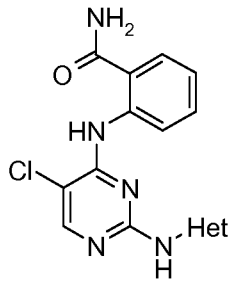
2-{[5-Chloro-2-(3-isoxazolylamino)-4-pyrimidinyl]amino}benzamide

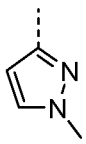
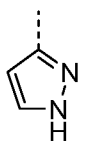
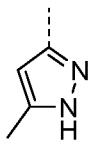
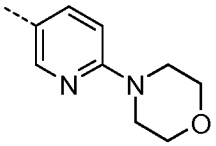
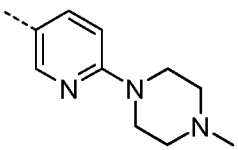
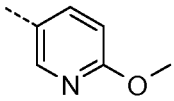


Intermediate 17 (0.1 g, 0.35 mmol) and 3-aminoisoxazole (0.27 g, 0.42 mmol) were combined in a tube with isopropanol (3 mL) and 1 drop of 12N HCl. The vessel was sealed and heated with stirring at 90 °C for 24 h. The reaction was cooled to room temperature and concentrated. The reaction mixture was purified via reverse-phase HPLC to give the title compound (18 mg) as a light brown solid. LC-MS (ES) m/z = 331, 333 $(M+H)^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 8.86 (d, *J* = 8.4 Hz, 1H) 8.42 (d, *J* =

1.7 Hz, 1H), 8.19 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.58 (dd, J = 8.0, 1.4 Hz, 1H) 7.18 (dd, J = 8.0, 1.7 Hz, 1H), 6.98 (d, J = 1.7 Hz, 1H).

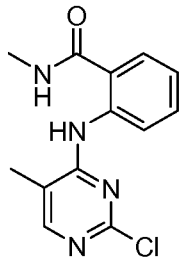
The following 2-{[5-chloro-2-(amino heterocyclic)-4-pyrimidinyl]amino}-benzamide compounds were prepared from the corresponding 2-[(2,5-dichloro-4-pyrimidinyl)amino]-benzamide Intermediate 17 and the corresponding amino-heterocycle using a procedure similar to Example 13.



Ex. No.	Het	Mass (m/z)
14		344, 346
15		330, 332
16		344, 346
17		426, 428
18		440, 442
19		371, 373

Intermediate 18

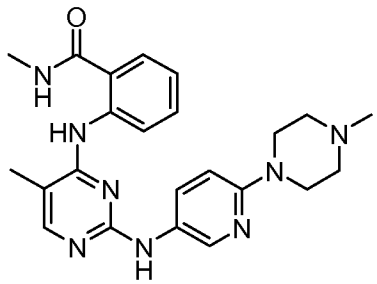
2-[(2-Chloro-5-methyl-4-pyrimidinyl)amino]-*N*-methylbenzamide



A sealed tube was charged with 2,4-dichloro-5-methylpyrimidine (10 g, 61.3 mmol), 2-amino-*N*-methylbenzamide (9.2 g, 61.3 mmol), di-isopropyl-ethylamine (21 mL, 122 mmol) and *n*-butanol (50 mL). The reaction vessel was sealed and heated with stirring at 95° C for 18 h. The reaction was cooled to room temperature, whereupon a white solid precipitated in the reaction mixture. The solid was filtered, washed with cold isopropanol, and collected. About 1/3 of the mother liquid was removed *in vacuo* and the concentrated mother liquid was heated and cooled as before, upon which further precipitation occurred. This precipiate was collected and dried and combined with the initial precipiate. (9.04 g, 32.8 mmol, 53% yield) was identified as 2-[(2-chloro-5-methyl-4-pyrimidinyl)amino]-*N*-methylbenzamide. LC-MS (ES) m/z = 277, 278 $(M+H)^+$.

Example 20

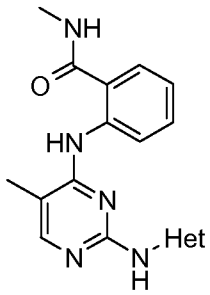
N-Methyl-2-[(5-methyl-2-{[6-(4-methyl-1-piperazinyl)-3-pyridinyl]amino}-4-pyrimidinyl)amino]benzamide

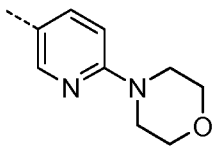
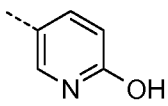
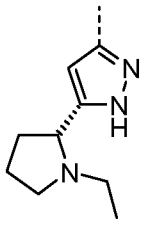


To a mixture of Intermediate 18 (1.92 g, 6.94 mmol) and Intermediate 5 (1.84 g, 6.94 mmol) was added isopropanol (75 mL); the reaction mixture was heated with stirring in a 150-mL sealed tube at 100 °C for 3 days. The reactor was cooled to room temperature and diluted with Et_2O (50 mL); the resulting purple solids were filtered and washed with

Et_2O, yielding 3.08 g. Part of this material (1.0 g) was purified in 2 batches on 2 x 40 g SiO_2 (90/10/1 CH_2Cl_2/MeOH/NH_4OH). The purified material was combined, dissolved in MeOH, and treated with excess 4M HCl in dioxanes. Concentration to dryness afforded an HCl salt of the title compound as a tan solid (0.42 g, 42%). LC-MS (ES) m/z = 433 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.23 (bs, 1H), 11.06 (bs, 1H), 10.37 (bs, 1H), 8.98 (t, J = 4.3 Hz, 1H), 8.46 (bs, 1H), 8.23 (d, J = 2.3 Hz, 1H), 7.85 (dd, J = 8.0, 1.1 Hz, 1H), 7.76 (bs, 1H), 7.42 (bs, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 9.1 Hz, 1H), 4.40 (d, J = 14.2 Hz, 2H), 3.51 (d, J = 11.4 Hz, 2H), 3.23 - 3.39 (m, 2 H), 3.09 (m, 2H), 2.82 (s, 3H), 2.81 (s, 3H), 2.18 (s, 3H).

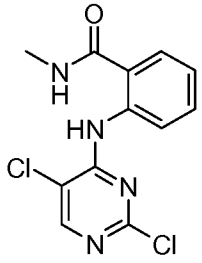
The following *N*-methyl-2-{[5-methyl-2-(amino heterocyclic)-4-pyrimidinyl]amino}-benzamide compounds were prepared from the corresponding 2-[(2-Chloro-5-methyl-4-pyrimidinyl)amino]-*N*-methylbenzamide Intermediate 18 and the corresponding amino-heterocycle using a procedure similar to Example 20.



Ex. No.	Het	Mass (m/z)
21		420
22		351
23		421

Intermediate 19

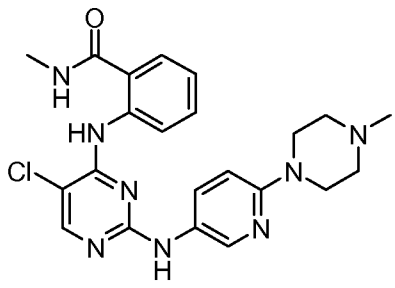
2-[(2,5-Dichloro-4-pyrimidinyl)amino]-*N*-methylbenzamide



A round-bottom flask was charged with 2,4,5-trichloropyrimidine (2 g, 11.1 mmol), 2-amino-*N*-methylbenzamide (2 g, 13.3 mmol), di-isopropyl-ethylamine (2.3 mL, 13.3 mmol) and isopropanol (40 mL). The flask was fitted with a reflux condenser and the reaction was heated to reflux and stirred for 18 h. A white solid appeared in the reaction mixture. The reaction was cooled to room temperature, and the solid was filtered off and washed with isopropanol. After drying, the white solid (3.16 g, 10.5 mmol, 95% yield) was identified as 2-[(2,5-dichloro-4-pyrimidinyl)amino]-*N*-methylbenzamide. LC-MS (ES) m/z = 297, 299 $(M+H)^+$.

Example 24

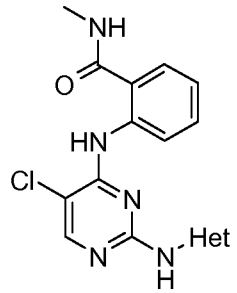
2-[(5-Chloro-2-{[6-(4-methyl-1-piperazinyl)-3-pyridinyl]amino}-4-pyrimidinyl)amino]-*N*-methylbenzamide

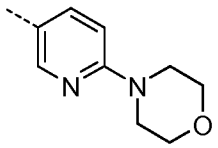
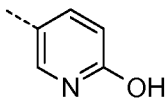
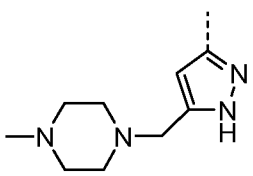
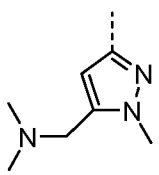


To a mixture of Intermediate 19 (0.25 g, 0.84 mmol) and Intermediate 5 (0.19 g, 0.73 mmol) was added isopropanol (10 mL). The mixture was heated with stirring in a 15 mL sealed tube at 100 °C overnight. Upon cooling, the reaction was stirred at room temperature for 2 days. The mixture was then concentrated to dryness and the resulting solids were purified on 40 g SiO_2 (94/5/1 $CHCl_3$/MeOH/triethylamine) yielding the title

compound as a tan solid (0.10 g, 26%). LC-MS (ES) m/z 453 = $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.63 (s, 1H), 9.20 (s, 1H), 8.75 (d, J = 4.6 Hz, 2H), 8.28 (d, J = 2.0 Hz, 1H), 8.16 (s, 1H), 7.67 - 7.90 (m, 2H), 7.43 (bs, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 9.1 Hz, 1H), 3.42 (m, 4H), 2.81 (d, J = 4.29 Hz, 3H), 2.42 (m, 4H), 2.22 (s, 3H).

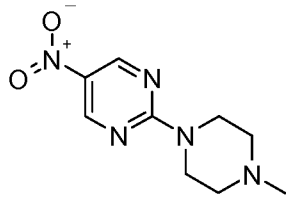
The following *N*-methyl-2-{[5-chloro-2-(amino heterocyclic)-4-pyrimidinyl]amino}-benzamide compounds were prepared from the corresponding 2-[(2,5-dichloro-4-pyrimidinyl)amino]-*N*-methylbenzamide Intermediate 19 and the corresponding amino-heterocycle using a procedure similar to Example 24.



Ex. No.	Het	Mass (m/z)
25		440
26		371
27		455, 457
28		415

Intermediate 20

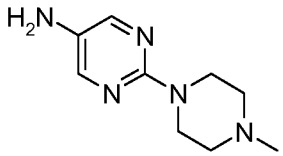
2-(4-Methyl-1-piperazinyl)-5-nitropyrimidine



2-Chloro-5-nitropyrimidine (2.0 g, 12.5 mmol) was added to a solution of *N*-methylpiperazine (1.4 mL, 12.5 mmol) in tetrahydrofuran (50 mL) and triethylamine (3.5 mL, 25 mmol) and the reaction mixture was stirred overnight at room temperature. The mixture was poured onto EtOAc and a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous layer was further extracted with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated to afford the title compound (2.55 g, 91%) as a solid. LC-MS (ES) m/z = 224 $[M+H]^+$.

Intermediate 21

2-(4-Methyl-1-piperazinyl)-5-pyrimidinamine

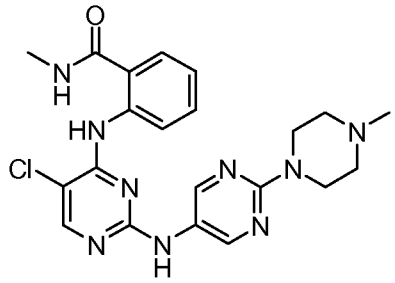


To Intermediate 20 (2.55 g, 11.4 mmol) was added MeOH (40 mL) and water (20 mL). Ammonium chloride (5.3 g, 100 mmol) and iron (1.91 g, 34.2 mmol) were added and the reaction mixture was heated for 6 h at 70 °C. The reaction mixture was filtered through Celite eluting with MeOH. The solution was evaporated and the resulting residue was poured onto EtOAc and water. The layers were separated, the aqueous layer was further extracted with EtOAc, and the combined organic layer was discarded. The aqueous layer was rendered basic with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with 80% CH_2Cl_2/20% isopropanol (3 x 500 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude material

was purified by flash chromatography on silica gel (100% CH_2Cl_2 to 80:20:2 CH_2Cl_2/MeOH/NH_4OH). To the product was added Et_2O followed by 1 eq. of HCl in dioxane (4M) to afford the HCl salt of the title compound (0.73 g, 28%). LC-MS (ES) m/z = 194 $[M+H]^+$.

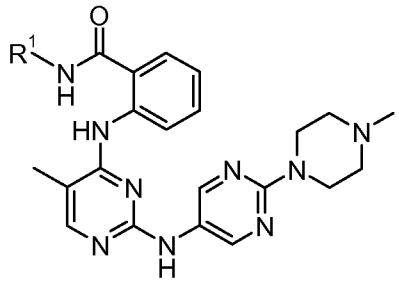
Example 29

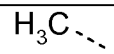
2-[(5-Chloro-2-{[2-(4-methyl-1-piperazinyl)-5-pyrimidinyl]amino}-4-pyrimidinyl)amino]-*N*-methylbenzamide



To Intermediate 19 (0.13 g, 0.44 mmol) and Intermediate 21 (0.10 g, 0.44 mmol) in isopropanol (3 mL) was added HCl (0.1 mL, 0.6 mmol, 6M) and the mixture was heated overnight at 100 °C. The reaction mixture was cooled to room temperature and diluted with Et_2O. The solvent was removed with a pipette and the remaining solid was purified by reverse phase HPLC (5% - 100% CH_3CN/H_2O w/0.1% TFA) to afford the TFA salt of the title compound (0.11 g, 42%) as a yellow solid. LC-MS (ES) m/z = 454, 456 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.61 (s, 2H), 8.56 (bs, 1H), 8.11 (s, 1H), 7.70 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.43(m, 1H), 7.18 (m, 1H), 3.61 (m, 4H), 3.16 (m, 4H), 2.97 (s, 3H), 2.93 (s, 3H).

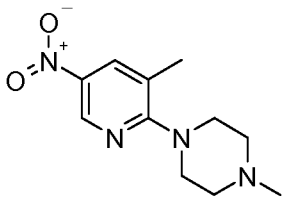
The following *N*-substituted-2-{[5-methyl-2-(4-methyl-1-piperazinyl)-4-pyrimidinyl]amino}-benzamide compounds were prepared from the corresponding 2-(4-Methyl-1-piperazinyl)-5-pyrimidinamine Intermediate 21 and the corresponding 2-[(2-Chloro-5-methyl-4-pyrimidinyl)amino]-*N*-substitutedbenzamide using a procedure similar to Example 29.



Ex. No.	R^1	Mass (m/z)
30		462
31		434

Intermediate 22

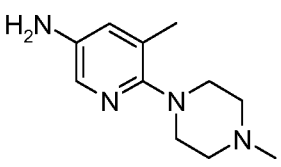
1-Methyl-4-(3-methyl-5-nitro-2-pyridinyl)piperazine



2-Chloro-3-methyl-5-nitropyridine (0.52 g, 3.0 mmol) and 1-methylpiperazine (0.3 g, 3.0 mmol) were combined in a sealed tube and heated at 80 °C for 24 h. The reaction was cooled to room temperature and Et_2O was added to the reaction mixture. The resultant yellow solid was filtered and washed with ether to afford 1-methyl-4-(3-methyl-5-nitro-2-pyridinyl)piperazine hydrochloride 408 mg (50% yield) LC-MS (ES) m/z =237 $(M+H)^+$.

Intermediate 23

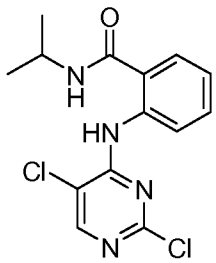
5-Methyl-6-(4-methyl-1-piperazinyl)-3-pyridinamine



A mixture of Intermediate 22 (0.24 g, 1.0 mmol), ammonium formate (0.25 g, 4.0 mmol), 5 mg Pd on charcoal (10%) and absolute ethanol (3 mL) was placed in a 5-mL Smith Process Vial ™ equipped with a magnetic stirring bar. The reaction mixture was heated at 130 °C for 130 seconds in a SmithSynthesizer. The reaction mixture was filtered, treated with 350 μL of 1M HCl· Ether and the solvents were removed to afford 5-methyl-6-(4-methyl-1-piperazinyl)-3-pyridinamine hydrochloride (0.064 g) as a tan solid LC-MS (ES) m/z = 207 $(M+H)^+$.

Intermediate 24

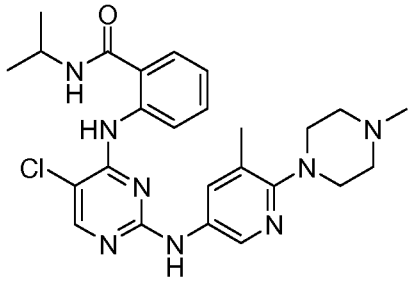
2-[(2,5-Dichloro-4-pyrimidinyl)amino]-*N*-(1-methylethyl)benzamide



A round-bottom flask was charged with 2,4,5-trichloropyrimidine (2.0 g, 6.8 mmol), Intermediate 2 (1.2 g, 7.1 mmol), di-isopropyl-ethylamine (1.4 mL, 8.1 mmol) and 30 mL isopropanol. The flask was fitted with a reflux condenser and the reaction was heated to reflux and stirred for 18 h. A white solid appeared in the reaction mixture. The reaction was cooled to 0 °C and filtered and solid was washed with Et_2O to afford 2-[(2,5-dichloro-4-pyrimidinyl)amino]-*N*-(1-methylethyl)benzamide (2.0 g, 90%)

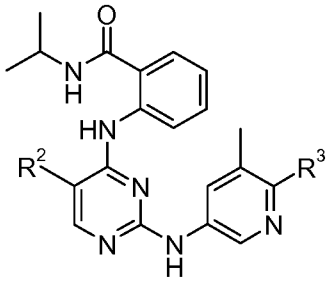
Example 32

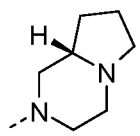
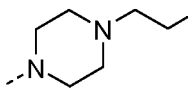
2-[(5-Chloro-2-{[5-methyl-6-(4-methyl-1-piperazinyl)-3-pyridinyl]amino}-4-pyrimidinyl)amino]-*N*-(1-methylethyl)benzamide



Intermediate 24 (100mg, 0.31 mmol) and Intermediate 23 (64mg, 0.31 mmol) were combined in a tube with 3 mL isopropanol. The vessel was sealed and heated with stirring at 110 °C for 72 h. The reaction was cooled to room temperature and the solvent was removed. Purification by reverse phase preparative HPLC afforded 50 mg (32% yield) of tan solid. The solid was dissolved in tetrahydrofuran to which 1 eq of 1M HCl· Ether was added and the resultant white solid was filtered off to afford the title compound as the HCl salt. LC-MS (ES) m/z = 496, 497 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 11.40 (s, 1H) 9.39 (s, 1H) 8.56 (d, *J* = 7.3 Hz, 1H) 8.26 (s, 1H) 8.14 - 8.22 (m, 1H) 7.88 (d, *J* = 2.5 Hz, 1H) 7.76 (d, *J* = 7.8 Hz, 1H) 7.42 - 7.49 (m, 1H) 7.15 (t, *J* = 7.7 Hz, 1H) 4.06 - 4.17 (m, 1H) 3.02 (s, 4H) 2.55 (s, 4H) 2.30 (s, 3H) 2.19 (s, 3H) 1.18 (d, *J* = 6.6 Hz, 6H).

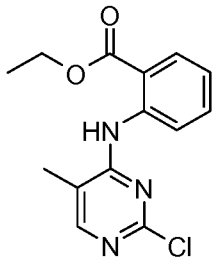
The following 2-[(5-substituted-2-{[5-methyl-6-(substituted)-3-pyridinyl]amino}-4-pyrimidinyl)amino]-*N*-(1-methylethyl)benzamide compounds were prepared from the corresponding 2-[(2-Chloro-5-substituted-4-pyrimidinyl)amino]-N-(1-methylethyl)benzamide and the corresponding 5-methyl-6-(substituted)-3-pyridinamine using a procedure similar to Example 32.



Ex. No.	R^2	R^3	Mass (M+H)+
33	Cl		522, 523
34	Me		505

Intermediate 25

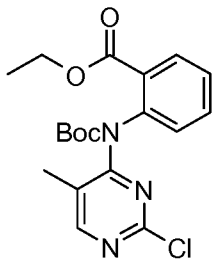
Ethyl 2-[(2-chloro-5-methyl-4-pyrimidinyl)amino]benzoate



2,4-Dichloro-5-methylpyrimidine (28.1g, 4172 mmol), ethyl 2-aminobenzoate (26.7 mL, 181 mmol), diisopropylethylamine (33 mL, 190 mmol) and ethanol (200 mL) were mixed together then equally divided and placed in two 350 mL pressure vessels. They were then capped and heated to 130 °C for three days. Upon cooling to room temperature, the precipitated product was collected and washed with ethanol followed by hexanes and then dried to give the title compound (4.5g, 9%) as an off-white solid. LC-MS (ES) m/z =293, 294 $(M+H)^+$.

Intermediate 26

Ethyl 2-((2-chloro-5-methyl-4-pyrimidinyl){[(1,1-dimethylethyl)oxy]carbonyl}amino)benzoate

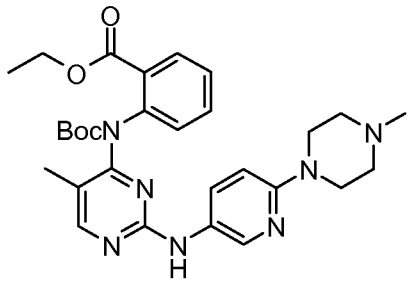


To a solution of Intermediate 25 (1.02 g, 3.50 mmol) in dry tetrahydrofuran (50 mL) under N_2 was added di-t-butyldicarbonate (Boc_2O) (0.84 g, 3.85 mmol) followed by dimethylaminopyridine (0.021 g, 0.175 mmol). The resulting solution was heated at 50 °C for 16 h. After cooling to room temperature, concentration afforded a yellow solid which dissolved in 90/10 $CHCl_3$/ethyl acetate and was purified on 90g SiO_2 (ethyl acetate/Hexanes). A second batch of product was simultaneously synthesized and purified in the exact same manner. The product fractions of both SiO_2 columns were

combined and concentrated to dryness, affording a white solid (2.35g) that was a mixture of 74% product and 26% starting material. This mixture was dissolved in dry tetrahydrofuran (40 mL) under N_2. To the resulting solution was added dimethylaminopyridine (cat.) followed by di-t-butyldicarbonate (0.40 g, 1.83 mmol). The solution was heated at 50 °C for 16 h. After cooling to room temperature, concentration afforded a yellow oil which was dissolved in fresh $CHCl_3$ and was purified on 90g SiO_2 (EtOAc/Hexanes). The product fractions were combined and concentrated to afford the title compound as a white solid (2.21 g, 81%). LC-MS (ES) m/z = 392 $(M+H)^+$.

Intermediate 27

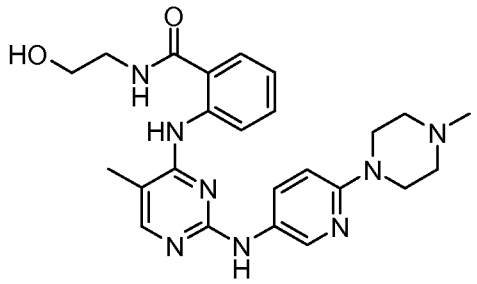
Ethyl 2-[{[(1,1-dimethylethyl)oxy]carbonyl}(5-methyl-2-{[6-(4-methyl-1-piperazinyl)-3-pyridinyl]amino}-4-pyrimidinyl)amino]benzoate



In a 75-mL sealed tube under argon were combined Intermediate 26 (1.70 g, 4.34 mmol), Intermediate 5 (1.32 g, 4.99 mmol), XANTPHOS (0.38 g, 0.65 mmol), and Cs_2CO_3 (5.66 g, 17.4 mmol) in 1,4-dioxane (40 mL). Argon was bubbled through the mixture for 15min. after which time palladium(II) acetate (0.19 g, 0.87 mmol) was added, the vessel sealed, and the reaction was heated with stirring at 50 °C for 16 h. After cooling to room temperature, the reaction was diluted with 100 mL $CHCl_3$, filtered through Celite 503, and concentrated to dryness yielding a black solid which was dissolved in 10 mL $CHCl_3$ and purified on 90 g SiO_2 ($CHCl_3$/MeOH). The product fractions were combined and concentrated to afford the title compound as a tan solid (89% pure) (1.38g, 58%). LC-MS (ES) m/z = 548 $(M+H)^+$.

Example 35

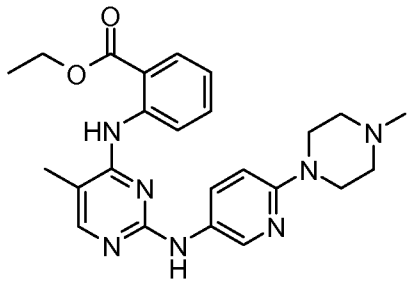
N-(2-Hydroxyethyl)-2-[(5-methyl-2-{[6-(4-methyl-1-piperazinyl)-3-pyridinyl]amino}-4-pyrimidinyl)amino]benzamide



In a 50-mL flask fitted with a reflux condenser were combined Intermediate 27 (1.38 g, 2.52 mmol) and ethanolamine (10 mL, solvent). The mixture was heated in an oil bath under N_2 at 80 °C for 4 h. Because of slow reaction progression, the temperature was increased to 85 °C for 40 h. The reaction mixture was cooled to room temperature and concentrated to dryness (12mbar, 83°C bath). The resulting yellow oil was dissolved in 90/10 H_2O/CH_3CN with 1 drop of TFA and purified by reverse-phase HPLC (C18, CH_3CN/H_2O w/ 0.1% TFA). The product fractions were combined and concentrated to dryness. The resulting light yellow solid was dissolved in 75 mL H_2O and brought to pH=12 with 1M $NaOH_{(aq)}$. The milky mixture was extracted with $CHCl_3$ (2 x 50 mL). The organics were combined, dried with $MgSO_4$, and concentrated to dryness affording the title compound as a yellow solid (0.75 g, 64%). LC-MS (ES) m/z = 463 $(M+H)^+$. ^1H NMR (400 MHz, DMSO) δ ppm 11.12 (s, 1H), 8.82-8.85 (m, 2H), 8.71-8.74 (m, 1H), 8.32-8.33 (m, 1H), 7.92 (s, 1H), 7.86-7.89 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.77-7.79 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.41-7.45 (m, 1H), 7.04-7.08 (m, 1H), 6.79-6.81 (d, *J* = 9.1 Hz, 1H), 4.75-4.78 (t, *J* = 5.8 Hz, 1H), 3.52-3.56 (m, 2H), 3.30-3.41 (m, 6H), 2.40-2.43 (m, 4H), 2.22 (s, 3H), 2.09 (s, 3H).

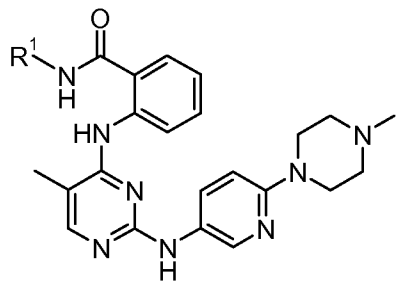
Intermediate 28

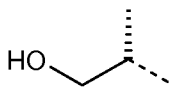
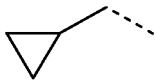
Ethyl 2-[(5-methyl-2-{[6-(4-methyl-1-piperazinyl)-3-pyridinyl]amino}-4-pyrimidinyl)amino]benzoate



Intermediate 25 (2.1 g, 7.2 mmol) and Intermediate 5 (1.65 g) were combined in isopropanol and heated to 100 °C. Reaction mixture was stirred at 100 °C for 2 days. The reaction mixture was filtered through a plug of silica and the filtrate was concentrated to a tan solid. The solid was dissolved in a mixture of water (0.1% TFA) and CH_3CN (0.1% TFA) and a insoluble precipitate was filtered off via vacuum filtration. The filtrate was concentrated to a solid, re-dissolved into a minimum amount of water with 0.1% TFA and CH_3CN with 0.1% TFA and injected onto the Varian reverse phase HPLC (C18) 5 to 95 water (0.1% TFA) to CH_3CN (0.1% TFA). Isolated product was ~80% pure. Flash chromatography with 5% MeOH:$CHCl_3$ to 10% MeOH:$CHCl_3$ afforded clean product (0.99 g). LC-MS (ES) m/z = 448 $(M+H)^+$.

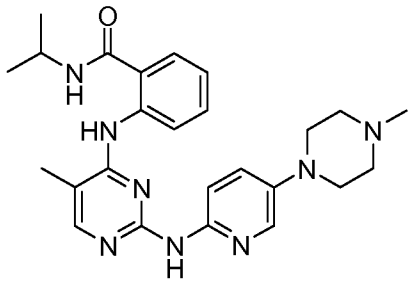
The following *N*-substituted-2-[(5-methyl-2-{[6-(4-methyl-1-piperazinyl)-3-pyridinyl]amino}-4-pyrimidinyl)amino]benzamide compounds were prepared from Intermediate 28 and the corresponding amine using a procedure similar to Example 35.



Ex. No.	R^1	Mass (m/z)
36		477
37		473
38		473

Example 39

N-(1-Methylethyl)-2-[(5-methyl-2-{[5-(4-methyl-1-piperazinyl)-2-pyridinyl]amino}-4-pyrimidinyl)amino]benzamide

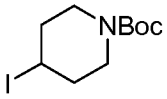


A solution of 5-(4-methyl-1-piperazinyl)-2-pyridinamine (0.29g, 0.001mol), Intermediate 3 (0.36 g, 1.0 mmol), Cs_2CO_3 (1.84g, 5 mmol), and XANTPHOS (0.089 g, 0.15 mmol) in dioxane was degassed for ~15 mins. To the degassed solution was added $Pd(OAc)_2$ (0.023 g, 0.10 mmol). The reaction mixture was heated to 70 °C for 48 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine and concentrated to a orange residue. The residue was dissolved in 50:50 H_2O(0.1% TFA):CH_3CN, the solution was injected onto the Varian RP C18 HPLC 5 to 95 40 min run. The impure product was concentrated and subjected to flash chromatography CH_2Cl_2 to 90:10:1 $CHCl_3$:MeOH:NH_4OH. Again impure product was collected. The impure material was dissolved in 0.5 mL of CH_3CN and injected onto the Gilson RP Polaris C18 HPLC 5 to 60 H_2O:CH_3CN (0.1%TFA). The oily residue was dissolved in CH_3CN and precipitated with Et_2O (9 mg). ^1H NMR

(400 M Hz, CD_3OD) δ 1.26 (d, J = 6.6 Hz, 6H), 2.33 (d, J = 1.0 Hz, 3H), 3.01 (s, 3H), 3.16 (m, 2H), 3.31 (m, 2H), 3.67 (m, 2H), 3.88 (m, 2H), 4.23 (m, 1H), 7.18 (dd, J = 9.1, 0.5 Hz, 1H), 7.33 (m, 1H), 7.64 (m, 1H), 7.70 (dd, J = 9.1, 3.0 Hz, 1H), 7.81 (dd, J = 7.8, 1.3 Hz, 1H), 7.93 (d, J = 1.3Hz, 1H), 8.13 (d, J = 2.5Hz, 1H), 8.72 (dd, J = 8.3, 1.3 Hz, 1H). LC-MS (ES) m/z = 461 $(M+H)^+$.

Intermediate 29

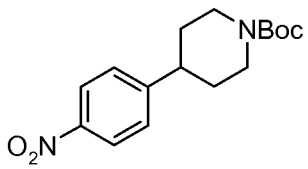
1,1-Dimethylethyl 4-iodo-1-piperidinecarboxylate



To a solution of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate (5.35 g, 26.6 mmol), imidazole (2.18 g, 32.0 mmol), and triphenylphosphine (8.45 g, 32.2 mmol) in THF (13 mL) at 0 °C under N_2 was added a solution of I_2 (8.11 g, 32.0 mmol) in THF (13 mL) dropwise. The mixture was allowed to warm to room temperature and stirred under N_2 for 17 h, then quenched with 10% aq $NaHSO_3$ (10 mL), concentrated to remove most of the THF, poured into H_2O, and extracted with hexanes (2×). The extracts were washed with H_2O, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with a gradient of hexanes to 20% EtOAc in hexanes to give the title compound as a white solid (6.32 g, 76%). LC-MS (ES) m/z = 256 $[M–C_4H_9+H]^+$.

Intermediate 30

1,1-Dimethylethyl 4-(4-nitrophenyl)-1-piperidinecarboxylate

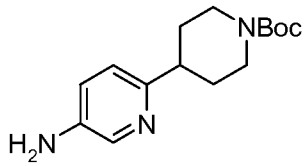


A solution of trimethylsilyl chloride (158 μL, 136 mg, 1.25 mmol) and 1,2-dibromoethane (108 μL, 235 mg, 1.25 mmol) in dry dimethyl acetamide (DMA) (5 mL) was added dropwise to a stirred suspension of Zn dust (652 mg, 9.97 mmol) in dry DMA at room temperature under N_2, which caused a 10 °C exotherm. That mixture was stirred at room temperature under N_2 for 15 minutes, then a solution of Intermediate 29 (2.345 g, 7.54 mmol) in dry DMA (5 mL) was added dropwise so as to maintain an internal

temperature below 35 °C, and stirring continued at room temperature for 30 min. Meanwhile, a suspension of 2-bromo-5-nitropyridine (1.02 g, 5.04 mmol), $Cl_2Pd(dppf)•CH_2Cl_2$ (124 mg, 0.15 mmol), and CuI (62 mg, 0.32 mmol) in dry DMA (10 mL) was degassed with N_2. The preformed alkylzinc reagent was transferred to a syringe and filtered through an acrodisc (that had been pre-rinsed with dry DMA) into the aryl bromide mixture, and the resulting dark mixture was stirred at 60 °C under N_2 for 15 h, cooled to room temperature, and quenched with 1 M aq NH_4Cl with stirring for 15 minutes. It was then made basic with sat. aq $NaHCO_3$ and extracted with EtOAc (3×). The extracts were washed repeatedly with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a dark oil. Purification by flash chromatography on silica gel eluting with a gradient of 1:1 hexanes:CH_2Cl_2 to 5:4:1 hexanes:CH_2Cl_2:CH_3CN gave the title compound (ca. 90% pure) as an orange oil (540 mg, 35%). LC-MS (ES) m/z = 208 $[M–C_5H_9O_2+H]^+$.

Intermediate 31

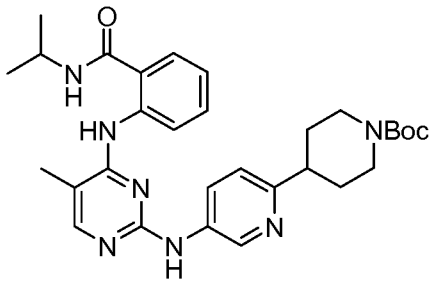
1,1-Dimethylethyl 4-(5-amino-2-pyridinyl)-1-piperidinecarboxylate



A suspension of intermediate 30 (270 mg, 0.88 mmol) and Pd (10 wt% on activated carbon, 27 mg) in MeOH (10 mL) was stirred under an atmosphere of H_2 for 6 h. Ethanol (2 mL) was added, and stirring continued under H_2 for 18 h. Another portion of Pd (10 wt% on activated carbon, 204 mg) was added, and the mixture was stirred under H_2 for 2.5 h, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a gradient of 1–8% MeOH in CH_2Cl_2 to give the title compound as an orange oil (103 mg, 42%). LC-MS (ES) m/z = 278 $[M+H]^+$.

Intermediate 32

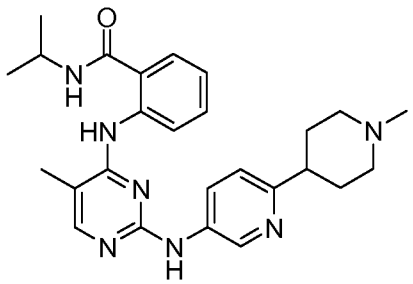
1,1-Dimethylethyl 4-[5-({5-methyl-4-[(2-{[(1-methylethyl)amino]carbonyl}phenyl)amino]-2-pyrimidinyl}amino)-2-pyridinyl]-1-piperidinecarboxylate



A mixture of Intermediate 3 (144 mg, 0.41 mmol), Intermediate 32 (114 mg, 0.41 mmol), XANTPHOS (36 mg, 0.06 mmol), and Cs_2CO_3 (402 mg, 1.23 mmol) in dioxane (4 mL) was degassed with N_2 for 15 min. $Pd(OAc)_2$ (18 mg, 0.08 mmol) was added, the vessel was sealed and stirred at 50 °C for 5 h, then at 60 °C for 15 h. LC-MS showed incomplete conversion, so more XANTPHOS (35 mg, 0.06 mmol) and Cs_2CO_3 (251 mg, 0.77 mmol) were added and the mixture was again degassed with N_2. More $Pd(OAc)_2$ (22 mg, 0.10 mmol) was added, the vessel was sealed and the mixture stirred at 80 °C for 5 h. The reaction mixture was cooled to room temperature and filtered through a pad of celite with acetone. The filtrate was partially concentrated *in vacuo* and the resulting residue was poured into half-saturated aq $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel, eluting with a gradient of CH_2Cl_2 to 90:10:1 CH_2Cl_2:MeOH:NH_4OH to give the title compound as an orange glass (ca. 80% pure, 70 mg, 31%). LC-MS (ES) m/z = 546 $[M+H]^+$.

Example 40

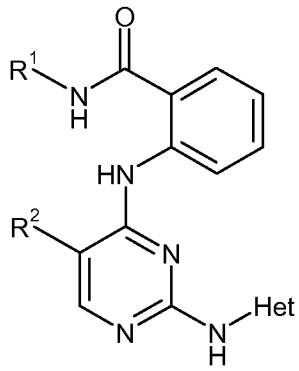
N-(1-Methylethyl)-2-[(5-methyl-2-{[6-(1-methyl-4-piperidinyl)-3-pyridinyl]amino}-4-pyrimidinyl)amino]benzamide



A solution of Intermediate 32 (70 mg, 0.13 mmol) in dioxane (10 mL) was treated with 6 M aq HCl (1 mL) and the solution was stirred at room temperature for 1.5 h, poured into sat. aq $NaHCO_3$, and extracted with 90:10 CH_2Cl_2:IPA (3×). The extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*, and the reside was dissolved in THF (2.5 mL) and treated with CH_2O (37 wt% in H_2O, 12 μL, 0.16 mmol) and $NaBH(OAc)_3$. The mixture was stirred at room temperature under N_2 for 15 h, quenched with sat. aq $NaHCO_3$, and extracted with 90:10 CH_2Cl_2:IPA (3×). The extracts were concentrated *in vacuo* and purified by reverse-phase HPLC (C18, CH_3CN/H_2O w/ 0.1% TFA). The clean fractions were concentrated *in vacuo*, and after trituration with Et_2O afforded a TFA salt of the title compound as a white solid (47 mg, 53%). LC-MS (ES) m/z = 460 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 1.26 (d, *J* = 6.6 Hz, 6H), 2.16 (m, 4H), 2.28 (d, *J* = 1.0 Hz, 3H), 2.96 (s, 3H), 3.17 (m, 3H), 3.68 (m, 2H), 4.22 (septet, *J* = 6.6 Hz, 1H), 7.30 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.44 (m, 2H), 7.79 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.83 (d, *J* = 1.0 Hz, 1H), 7.98 (dd, *J* = 8.3, 2.5 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.69 (d, *J* = 2.5 Hz, 1H).

Claims

1. A compound of the following formula:

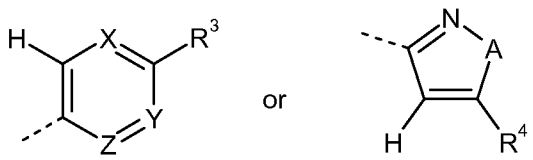


or a pharmaceutically acceptable salt thereof wherein:

R^1 is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl-CH_2-, or HO-C_1-C_6-alkyl;

R^2 is CH_3, F, or Cl;

Het is



where the dotted line represents the point of attachment; wherein

X is CR^5 or N;

Y is CR^5 or N; and

Z is CH or N; with the proviso that at least one of X, Y, and Z is N, and with the further proviso that at least one of X and Z is not N;

A is NR^6 or O;

R^3 is C_1-C_6-alkyl, OH, or $-N(R^7)_2$;

R^4 is H, CH_3, $-CH_2N(CH_3)_2$, $-CH_2$-piperazinyl, $-CH_2$-4-methylpiperazinyl, or 1-ethyl-2-pyrrolidinyl;

R^5 is H or C_1-C_6-alkyl;

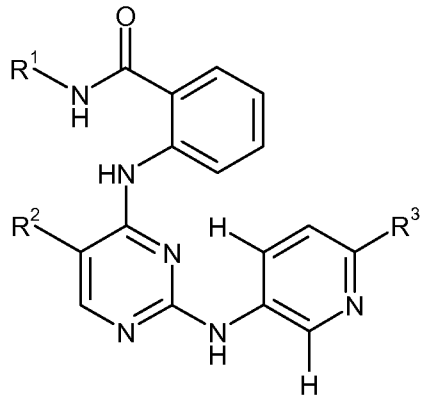
R^6 is H, $-CH_3$, or $-CH_2CH_3$; and

each R^7 is independently H, C_1-C_6-alkyl, HO-C_1-C_6-alkyl, C_1-C_3-alkyl-OC(O)-CH_2-NH-CH_2CH_2-, C_1-C_3-alkyl-O-CH_2CH_2-, or, together with the nitrogen atom to which they are attached, form a 5- or 6-membered heterocycloalkyl group or a 9- or 10-membered heterobicycloalkyl group.

2. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_1-C_6-alkyl.

3. The compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein R^2 is methyl or F.

4. The compound of Claim 3 which is represented by the following formula:



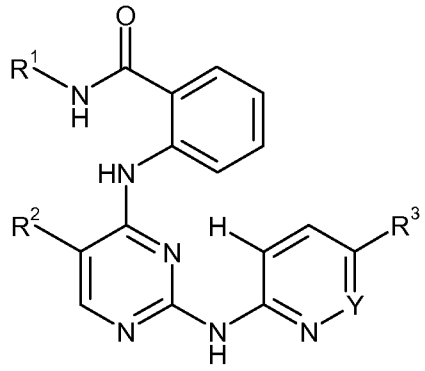
or a pharmaceutically acceptable salt thereof.

5. The compound of Claim 4, or a pharmaceutically acceptable salt thereof, wherein R^3 is $-N(R^7)_2$, where each R^7, together with the nitrogen atom to which they are attached, form a pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-hydroxyethylpiperazinyl, morpholino, or 2-oxo-piperazinyl group.

6. The compound of Claim 5, or a pharmaceutically acceptable salt thereof, wherein each R^7, together with the nitrogen atom to which they are attached, form a 4-methylpiperazinyl group.

7. The compound of Claim 6, or a pharmaceutically acceptable salt thereof, wherein R^1 is isopropyl and R^2 is methyl.

8. The compound of Claim 3 which is represented by the following formula:



wherein Y is N or CH, R^1 is C_1-C_6 alkyl; and R^3 is wherein R^3 is $-N(R^7)_2$.

9. The compound of Claim 8 where Y is CH and each R^7, together with the nitrogen atom to which they are attached, form a pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-hydroxyethylpiperazinyl, morpholino, or 2-oxo-piperazinyl group.

10. A method for treating a cancer comprising administering to a patient in need thereof the compound of Claim 1, or a pharmaceutically acceptable salt thereof.

11. The method of Claim 10 wherein the cancer is a solid tumor cancer or a hematological cancer.

12. The method of Claim 11 wherein the solid tumor cancer is lung cancer, breast cancer, colon cancer, ovarian cancer, melanoma, and pancreatic cancer.

13. The method of Claim 11 wherein the hematological cancer is leukemia, B-cell lymphoma, AML, or CML.

14. A method for treating cancer comprising the step of administering to a patient in need thereof an effective amount of a composition comprising the compound of Claim 1,

or a pharmaceutically acceptable salt thereof; and (b) at least one pharmaceutically acceptable excipient.

15. A composition comprising a) the compound of Claim 1 or a pharmaceutically acceptable salt thereof; and b) at least one pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/64446

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/54; A61K 31/505 (2008.04)
USPC - 514/269
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)
USPC: 514/269

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/269; 514/49, 227.8, 234.2, 256, 266.1, 274 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPTO.gov (PGPubs and Patents), Google, Dialog Search terms: Anthranilamide, 2-aminobenzamide, aminobenzamide, benzamide, pyrimidine, kinase, kinase inhibitors, kinase activity inhibitor, aurora kinases, o-aminobenzamide, 1,3-diazine, pyrimidinyl, anthranilic acid amides, tumor, angiogenesis, cancer.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 6,932,161 B2 (Erickson et al.) 13 September 2005 (13.09.2005) abstract; col 2-5	1-4, 10-15 --- 5-9
Y	US 7,148,357 B2 (Huth et al.) 12 December 2006 (12.12.2006) col 2, ln 5-20	5-9
A	US 7,122,544 B2 (Kois et al.) 17 October 2006 (17.10.2006) entire document	1-15
P/A	US 7,338,957 B2 (Ding et al.) 4 March 2008 (04.03.2008) entire document	1-15

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

* 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 but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 September 2008 (06.09.2008)	12 SEP 2008
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: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)