# Identification of 4-Aminopyrazolylpyrimidines as Potent Inhibitors of Trk Kinases

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*Received March 26, 2008*

The design, synthesis and biological evaluation of a series of 4-aminopyrazolylpyrimidines as potent Trk kinase inhibitors is reported. High-throughput screening identified a promising hit in the 4-aminopyrazolylpyrimidine chemotype. Initial optimization of the series led to more potent Trk inhibitors. Further optimization using two strategies resulted in significant improvement of physical properties and led to the discovery of **10z** (AZ-23), a potent, orally bioavailable Trk A/B inhibitor. The compound offers the potential to test the hypothesis that modulation of Trk activity will be of benefit in the treatment of cancer and other indications in vivo.

## Introduction

Receptor tyrosine kinases (RTKs)[a] are a subfamily of protein kinases that play a critical role in cell signaling and are involved in a variety of normal and cancer related processes including cell proliferation, survival, angiogenesis, and metastasis.[1] Currently, up to 100 different RTKs including tropomyosin-related kinases (Trks) have been identified. Trks are the high affinity receptors activated by a group of soluble growth factors called neurotrophins (NT). The Trk receptor family has three highly homologous isoforms: TrkA, TrkB, and TrkC. Among the neurotrophins, there are (i) nerve growth factor (NGF), which activates TrkA, (ii) brain-derived neurotrophic factor (BDNF) and NT-4/5, which activate TrkB, and (iii) NT-3, which activates TrkC. Each Trk receptor contains an extracellular domain (NT ligand binding), a transmembrane region, and an intracellular domain (including kinase domain). Upon binding of the ligand, the kinase catalyzes its own phosphorylation and triggers downstream signal transduction pathways.[2]

Trks are widely expressed in neuronal tissue during development where they are critical for the maintenance and survival of these cells. A postembryonic role for the Trk/neurotrophin axis, however, remains in question. There are reports showing that Trks play an important role in both the development and function of the nervous system as well as in pain sensation.[3,4]

In the past decade, a considerable number of reports linking Trk signaling with cancer have been published. For example, while Trks are expressed at low levels outside the nervous system in the adult, Trk expression is increased in late stage prostate cancers.[5] Furthermore, recent literature also shows that overexpression, activation, amplification, and/or mutation of Trks are associated with many cancers including neuroblastoma,[6–9] ovarian,[10] and colorectal cancer.[11]

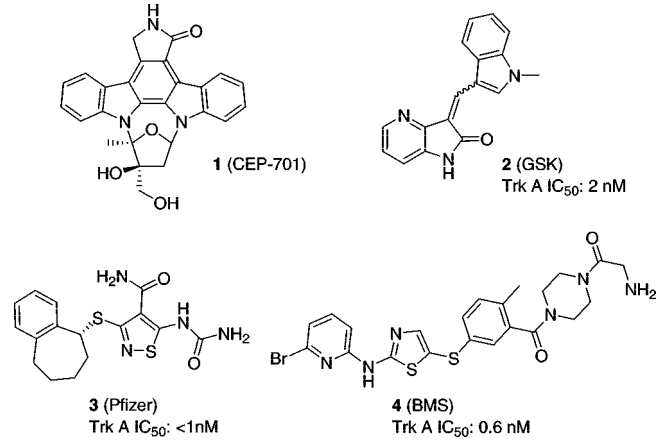


**Figure 1.** Trk inhibitors in literature.

Among the earliest inhibitors of Trk kinases was **1** (CEP-701, Figure 1) and its later analogues, which are potent inhibitors of Trks along with other kinases.[12] Other inhibitors that hit Trks along with their main targets include 1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazoles (Aurora kinases)[13] and keto-pyrrolopyrimidines (Tie-2 kinase).[14] In addition, there have been several reports of selective Trk tyrosine kinase inhibitors in the literature. Oxindole **2**, isothiazole **3**, and thiazole **4** (Figure 1) were reported as potent Trk A inhibitors.[15–17] In patent applications, aminopyrimidines,[18] pyrazolyl ureas,[19] and pyrazolyl condensed cyclic compounds[20] were described as Trk inhibitors to treat cancer or pain.

In this paper, we report the identification and optimization of a series of 4-aminopyrazolylpyrimidines as potent Trk inhibitors that exhibit excellent physical properties and good oral pharmacokinetics.

High throughput screening of the AstraZeneca compound collection against the TrkB enzyme resulted in the identification of a 4-aminopyrazolylpyrimidine derivative **5** (Figure 2) as a hit. The compound was found to have an $IC_{50}$ against TrkB of 1.1 $\mu$M and was also potent against TrkA ($IC_{50}$ = 0.27 $\mu$M). The series was attractive because 2,4-disubstituted pyrimidines

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[a] Abbreviations: RTK, receptor tyrosine kinase; Trk, tropomyosin-related kinase; NT, neurotrophin; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; HTS, high throughput screening; DIAD, diisopropylazodicarboxylate; CDK2, cyclin-dependent kinase 2; DMA, dimethylacetamide; PEG, polyethylene glycol; HPMC, hydroxypropylmethylcellulose; D5W, dextrose 5% in water; DPPF, 1,1′-bis(diphenylphosphino)ferrocene.

10.1021/jm800343j CCC: $40.75 © 2008 American Chemical Society
Published on Web 07/23/2008

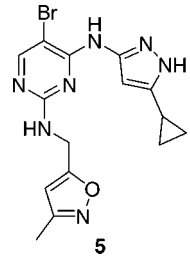
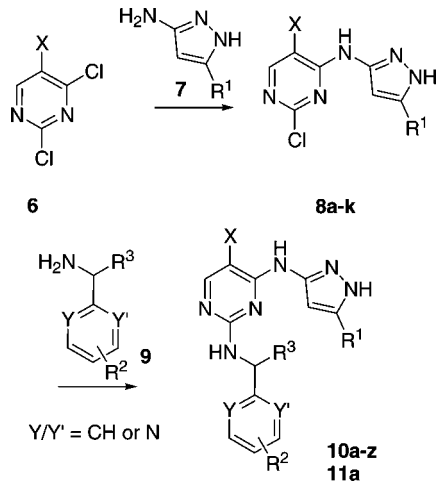



**Figure 2.** HTS hit.

**Scheme 1.** Synthesis of **10a**−**z**, **11a**




could be readily synthesized in two steps from a 2,4-dichloropyrimidine core and a convergent, modular synthetic approach allowed the rapid elucidation of SAR.

## Chemistry

The general synthetic sequence for the 2,4-disubstituted pyrimidines is shown in Scheme 1. 2,4-Dichloropyrimidines **6** were reacted with aminopyrazoles **7** in the presence of base (e.g., $NEt_3$) to give 4-substituted-2-chloropyrimidines **8**. For inactivated pyrimidines (e.g., 5-$CH_3$/H substitutions), the reaction mixture was heated to 70 °C. Nucleophilic aromatic substitution of intermediates **8** with suitable amines **9** was achieved by heating under basic conditions to provide target compounds **10a**−**z** and **11a**.

For 2,4,6-trisubstituted pyrimidines, trichloropyrimidine cores **12** were first reacted with aminopyrazoles **7** in the presence of base to give 4-substituted-2,6-dichloropyrimidines **13a**−**d** (Scheme 2). Nucleophilic aromatic substitutions of intermediates **13a**−**d** with amines **9** provided intermediates **14a**−**f** together with their regioisomers (6-adducts, separable by silica gel column chromatography). Treatment of **14a**−**f** with either alkoxide or an amine generated the target compounds **15a**−**i**.

As Scheme 3 illustrates, aminopyrazoles with alkyl substitution at the 5-position can be readily synthesized from ester **16**.[21] For alkoxyl-substituted aminopyrazoles, this method is not feasible and therefore a one-step synthesis was developed using Mitsunobu conditions. Hydroxyaminopyrazole **17** was treated with a suitable alcohol in the presence of triphenylphosphine and diisopropylazodicarboxylate (DIAD) to give the desired products **7a**−**b**. Thiomethyl analogue **7c** was synthesized from 3,3-bis(methylthio)acrylonitrile **18**[22] in the presence of hydrazine.

Most α-methyl benzylamines and α-hydroxymethyl-benzylamines are commercially available in both enantiopure forms. The synthesis of enantiopure (*S*)-1-(5-fluoropyridin-2-yl)ethanamine was initiated from compound **19** (Scheme 4). Treatment of **19** with $Zn(CN)_2$ in the presence of catalyst generated nitrile **20** in 72% yield. Grignard addition to **20** followed by acetylation gave the vinyl acetamide **21**. Catalytic asymmetric hydrogenation[23] provided the desired acetamide **22** in 88% yield and 95% enantiomeric excess. Protection of the amide N−H with Boc anhydride, followed by treatment with LiOH, resulted in the Boc protected compound **23**, which was then deprotected with HCl/1,4-dioxane to give the desired amine (*S*)-**9a**.

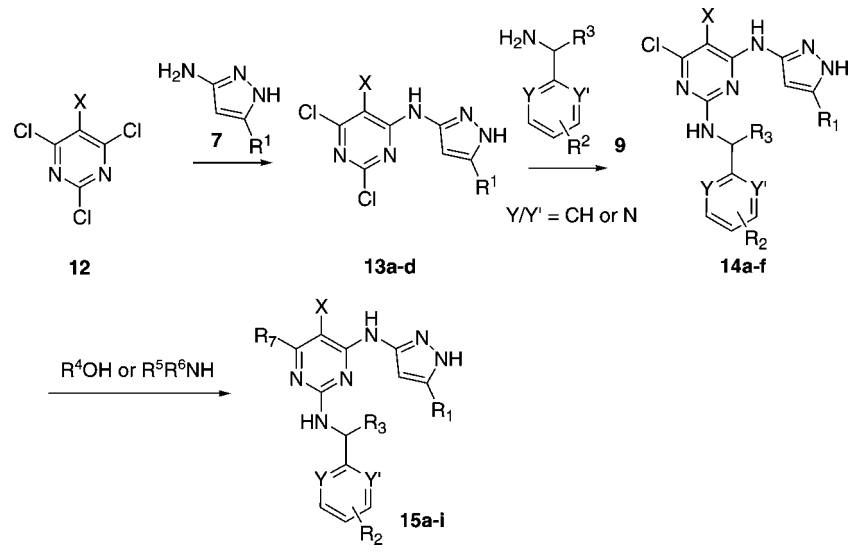
The synthetic route of the corresponding pyrimidine ring system (*S*)-**9b** (Scheme 5) began with 2-chloro-5-fluoropyrimidine **24** and followed an analogous approach to that shown in Scheme 4.

## Results and Discussion

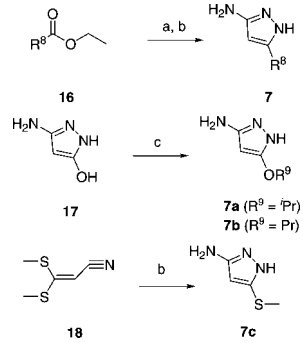
There are two potential binding modes for compound **5** to the hinge of Trk enzymes: either through the pyrimidine or pyrazole moieties. Because compound **5** is moderately potent against CDK2 enzyme ($IC_{50}$: 0.11 μM), a surrogate crystal structure of **5** with CDK2 (data not shown), which has 68% homology to TrkB in the active site, was obtained. This structure suggested that the series binds to the ATP-binding site hinge between N- and C-terminal domains through the pyrazole, and that the cyclopropyl ring would stack against the phenylalanine gatekeeper residue, which is common to both Trk and CDK2 kinases. This region of the inhibitor was then held constant and the effect of substitutions at the pyrimidine 2-position in compound **5** was evaluated. The isoxazole was replaced with a phenyl group, as benzylamines are synthetically more accessible than isoxazolylmethylamines. The benzylamine analogue **10a** exhibited an $IC_{50}$ of 0.75 μM against TrkA (for simplicity, potencies against TrkA are reported in this paper because comparable potencies against TrkA and TrkB were observed throughout this series of compounds). Next, a small library was designed to probe substitutions of the newly installed phenyl ring as exemplified in Table 1. Substitution at the 3-position of this ring with a methoxy group (**10b**) did not provide a potency improvement when compared with **10a**. At the 2-position, the methoxy group (**10d**) is preferred over chloro (**10c**). Finally, substitution with halogen groups (**10e** and **10f**) at the 4-position consistently improved potency compared to **10a**. Incorporation of a halogen atom on the aromatic ring was especially attractive because the halogen atom might reduce the potential for metabolism at this position of the molecule. In a human microsomal stability assay, compound **10e** (Clint: 28 μL/min/mg) was indeed more stable when compared with **10a** (Clint: 66 μL/min/mg).

The presence of a methylene moiety between the 2-position of the pyrimidine and the phenyl ring prompted an exploration of the SAR around this linker region. It was reasoned that this benzylic position might be prone to metabolism, and substitution at $R^3$ might result in compounds with better metabolic stability. Initial evaluation of racemic methyl-substituted compounds indicated improved potency over unsubstituted analogues (data not shown), and molecular docking of each isomer in the TrkB homology model (see experimental details, homology modeling) indicated a preference for the (*S*)-methyl enantiomer, as illustrated in Figure 3 with example **10k**. It was subsequently determined that one enantiomer is indeed more potent than the other. For instance, small groups (e.g., methyl and hydroxymethylene) (**10g** and **10j**) show improvements in enzyme potency (around 5-fold) over compound **10a** for only one of the enantiomers. The other enantiomers are less active (**10h** and **10i**). It should be noted that the preferred configuration remains

**Scheme 2.** Synthesis of **15a−i**

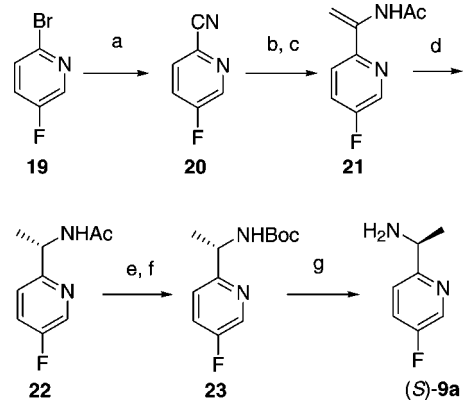



**Scheme 3.** Synthesis of Aminopyrazoles[a]




[a] Reagents and conditions: (a)$CH_3CN$, NaH, dioxane; (b)$H_2NNH_2$; (c) $R^9OH$, DIAD, $PPH_3$, $CH_2Cl_2$, heating.

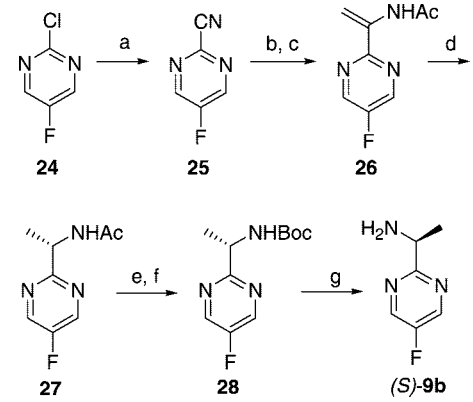
**Scheme 4.** Synthesis of (*S*)-**9a**[a]




[a] Reagents and conditions: (a) $Zn(CN)_2$, $Pd_2(dba)_3$, DPPF, Zn, DMA, 95 °C; (b) MeMgBr, THF; (c) $Ac_2O$; (d) (*S*,*S*)Rh-Et-DUPHOS-OTf, MeOH, $H_2$ (150 psi); (e) $Boc_2O$; (f) LiOH; (g) HCl/1,4-dioxane.

consistent between α-methyl and α-hydroxymethyl, but the designation switches from (*S*)-configuration for the α-methyl to (*R*)-configuration for the α-hydroxymethyl moiety. (*S*)-Methyl was equipotent when compared to (*R*)-hydroxymethyl based on the $IC_{50}$'s of compounds **10g** and **10j**. In a human microsomal stability assay, compound **10g** (Clint: 29 μL/min/mg) was also more stable when compared with **10a** (Clint: 66 μL/min/mg). This tended to support the original hypothesis that blocking the

**Scheme 5.** Synthesis of (*S*)-**9b**[a]



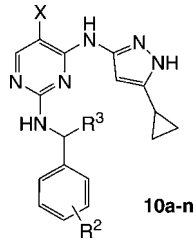

[a] Reagents and conditions: (a) $Zn(CN)_2$, $Pd_2(dba)_3$, DPPF, Zn, DMA, 100°C; (b) MeMgBr, THF; (c) $Ac_2O$, THF/DCM; (d) (*S*,*S*)Rh-Et-DUPHOS-OTf, MeOH, $H_2$ (150 psi); (e) $Boc_2O$, DMAP, THF; (f) LiOH; (g) HCl/1,4-dioxane.

benzylic position would improve metabolic stability. When substitution at the benzylic site was combined with a 4-fluorophenyl ring, extremely potent compounds such as **10k** and **10l** were identified. Slightly larger linear groups are also tolerated at the $R^3$ position (**10m** and **10n**).

As part of the evaluation of the SAR at C-5 of the pyrimidine (Table 1), replacement of 5-Br with 5-Cl retained enzyme potency while reducing the molecular weight of the compound. Alternative substitutions at the pyrimidine 5-position were also explored (**10o−q** in Table 2). Because enzyme potency for many compounds in this series had reached the low end of the enzyme assay detection limit (~0.003 μM), a modification of a published assay[24] in which phospho-TrkA inhibition in a cell line expressing a constitutive form of TrkA (MCF-10A TrkA-deletion) was evaluated.[25] For example, compound **10k** exhibited an $IC_{50}$ of 0.006 μM in the more sensitive TrkA cell assay, comparable to its enzyme assay result (0.006 μM). Based on the cellular assay, bromine and chlorine remain among the best moieties for potency at this position.

To determine whether the cyclopropyl group was optimal, other pyrazole substituents were also explored (Table 2). It was found that TrkA in vitro cell potency improved from no substitution (**10v**) to methyl (**10t**) and cyclopropyl (**10k** and

**Table 1.** SAR at $R^2$ and $R^3$ Positions




| compd | X | $R^2$ | $R^3$ | TrkA $IC_{50}$ ($\mu$M) |
|---|---|---|---|---|
| **10a** | Br | H | H | 0.75 |
| **10b** | Br | 3-OMe | H | 0.72 |
| **10c** | Br | 2-Cl | H | 1.17 |
| **10d** | Br | 2-OMe | H | 0.12 |
| **10e** | Br | 4-F | H | 0.10 |
| **10f** | Br | 4-Cl | H | 0.36 |
| **10g** | Br | H | (*S*)-Me | 0.10 |
| **10h** | Br | H | (*R*)-Me | 0.65 |
| **10i** | Br | H | (*S*)-$CH_2OH$ | 1.90 |
| **10j** | Br | H | (*R*)-$CH_2OH$ | 0.12 |
| **10k** | Br | F | (*S*)-Me | 0.006 |
| **10l** | Cl | F | (*R*)-$CH_2OH$ | 0.010 |
| **10m** | Cl | F | (*S*)-$CH_2CONMe_2$ | 0.013 |
| **10n** | Cl | F | (*S*)-$CH_2CONHMe$ | 0.015 |

**10l**) and that the position can tolerate O$^i$Pr (**10r**) and even $SCH_3$ groups (**10s**). However, further increase in linear length (**10u**) or bulk (**10w**) resulted in 45-fold and >90-fold reduction in cell potency respectively from compound **10k**. Again compounds **10k**, **10l**, and **10r** are among the most potent Trk compounds in this series.

Having achieved single-digit nanomolar in vitro cell potency, pharmacokinetic properties of the lead compounds were investigated. As shown in Table 3, compound **10k** showed promise in rodent studies having reasonable in vivo clearance, moderate half-life, and an oral bioavailability of 32%. However, the compound displayed aqueous solubility of <3 $\mu$M and over 99% plasma protein binding. Compound **10l** had a larger free-fraction in plasma, but in vivo clearance in rat was high and the aqueous solubility was 1.7 $\mu$M.

There are several known strategies to improve the physical properties of compounds with low solubility.[26] One strategy is to attach side chains to the parent molecule to improve solubility in a position where SAR is not very sensitive. For kinase inhibitors, solubilizing groups are typically introduced in the area of the molecule pointing to the kinase solvent channel, which in this case is the pyrimidine C-6 position (Figure 3). As Table 4 demonstrates, a variety of functional groups are tolerated in the TrkA kinase solvent channel including terminal basic rings (such as **15a**) and neutral linear (**15c**) and branched hydroxyl side chains (**15b**, **15d**−**g**). Cellular potencies were all comparable to that of **10l** (except for methylpyrazole **15f**, $EC_{50}$: 0.06 $\mu$M). However, the solubilities of **15a**−**g** were generally 10-fold higher than **10l** (except for **15c**). These data demonstrate that attachment of solubilizing side chains is a reasonable way of improving physical properties. Two potential issues associated with this approach are that the newly added side chains might be accessible for metabolism and the modified compounds have higher molecular weights.

The second strategy used to improve physical properties was to modify the "core template" so that the resulting compounds were more soluble without the additional solvent channel side chains. As heterocycles typically have lower logD compared to phenyl rings, we reasoned that this change would improve the solubility of the resulting compounds. Indeed the original HTS hit compound **5** contained a heterocycle (isoxazole), this area of chemistry was further explored, with a focus on pyridyl and pyrimidyl moieties as a replacement for the phenyl group.

As Table 5 shows, introduction of nitrogens at the 2 and/or 6 position of the phenyl ring was tolerated in terms of cellular potency and compound solubilities all demonstrated significant improvement to greater than 100 $\mu$M, with the trend of phenyl < 2-pyridyl < 2-pyrimidyl (the solubility for **10r** is 4 $\mu$M, as compared to 100 $\mu$M for **10z** (AZ-23) and 440 $\mu$M for **11a**). In a human plasma protein-binding assay, **10z** was found to have 6.9% free drug in plasma. A combination of the heterocycle replacement and C-6 soluble side chain approach further increased the solubility (compounds **15h** and **15i**).

On the basis of the SAR obtained in this series, several lead compounds were selected for in vivo PK profiling. As Table 6 shows, the clearance of **10y**, **10z** was low to moderate across two species (rat and dog). Half-lives (iv dosing) are somewhat short in rat but reasonable in dog. Compound **15i** also showed a reasonable profile in rat (iv and po) and dog PK (iv) studies, indicating that the potential metabolism of the solubilizing side chains was not problematic in these species. The oral bioavailabilities for all three compounds ranged from 24% to 60% in rat. On the basis of further evaluation in a pharmacodynamic model and selectivity,[27] compound **10z** was chosen for progression into in vivo disease models.

In summary, a series of 4-aminopyrazolylpyrimidines has been discovered as highly potent TrkA/B inhibitors. SAR exploration started from an HTS hit, compound **5**, and in vitro potency was quickly improved to the single digit nM level (e.g., compounds **10k** and **10l**). Subsequently, two strategies were utilized to improve the physical properties resulting in compounds like **10z** that has excellent overall properties in PK, physical properties, and also retains the target potency. Being a potent, orally bioavailable inhibitor, **10z** offers the potential to test the hypothesis that modulation of Trk activity will be of benefit in the treatment of cancer and other indications in vivo. The evaluation of such compounds (including **10z**) will be reported in due course.

## Experimental Section

**General.** $^1$H NMR spectra were recorded on Bruker 300 MHz or 400 MHz NMR spectrometers. Chemical shifts are expressed in part per million (ppm, $\delta$ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), dd (doublet-doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet). LC-MS analyses were performed with an Agilent 1100 equipped with Waters columns eluted with a gradient mixture of $H_2O$−acetonitrile with formic acid and ammonium acetate. All compounds analyzed were ≥95% pure. HRMS were recorded on a Waters LCT TOF mass spectrometer. Reverse phase chromatography was performed with Gilson systems using a YMC-AQC18 reverse phase HPLC column with dimensions 20 mm/100 and 50 mm/250 in water/MeCN with 0.1% TFA as mobile phase. HPLC retention times ($R_t$) are reported in minutes. Elemental analyses (C, H, N) were performed by QTI, P.O. Box 470, 291 Route 22 East, Salem Industrial Park, Building 5, Whitehouse, NJ 08888. Most of the reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light or LC-MS. Flash column chromatography was performed on ISCO Combi-flash systems (4700 Superior Street, Lincoln, NE) unless otherwise mentioned using silica gel cartridges.

**TrkB Enzyme Assay.** TrkB kinase activity was measured against its ability to phosphorylate synthetic tyrosine residues within a generic polypeptide substrate using homogeneous time-resolved

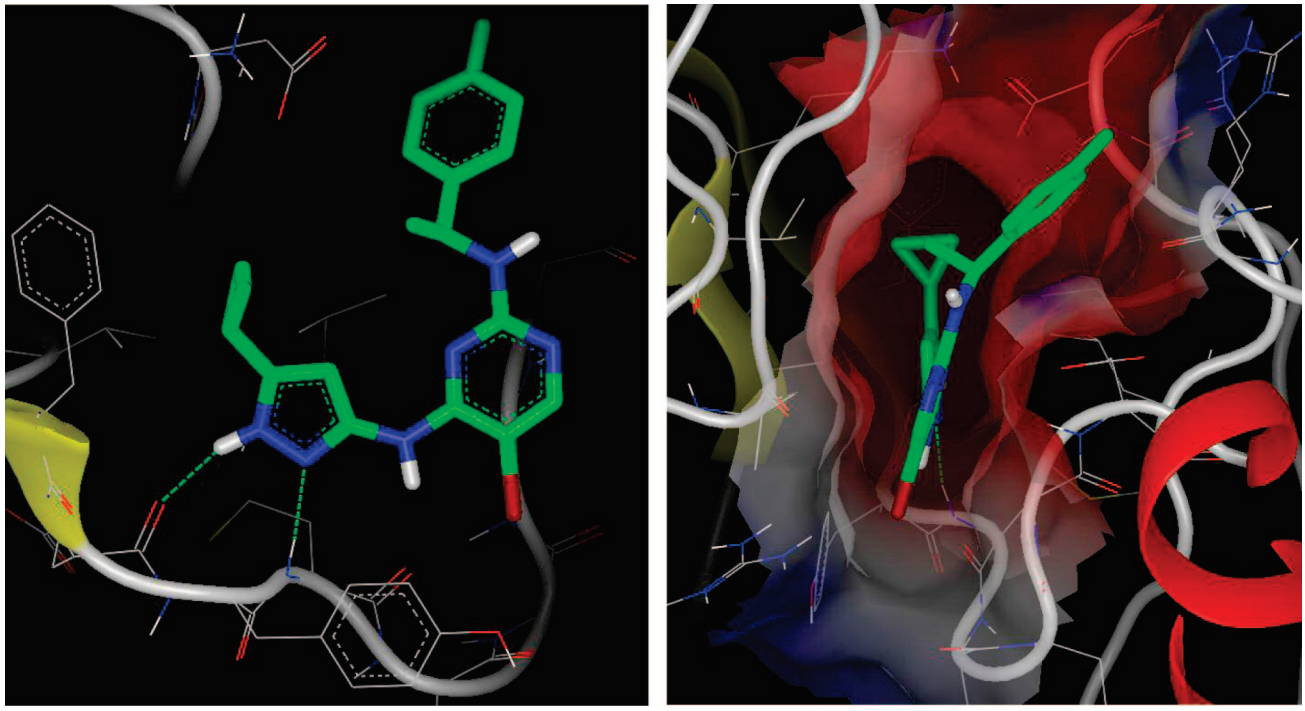
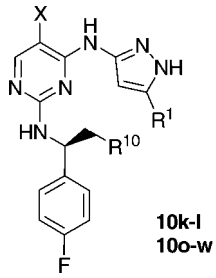


**Figure 3.** (A) Predicted binding through the pyrazole motif for compound **10k** docked into a homology model of TrkB (only polar hydrogen atoms shown). The cyclopropyl moiety stacks against the phenylalanine gatekeeper residue. The pyrimidine C6-position is solvent-accessible. (B) View from solvent channel into the ATP-binding site. The (*S*)-methyl configuration of **10k** is preferred over the (*R*)-methyl analogue.

**Table 2.** SAR at X and $R^1$ Positions




**10k-l**
**10o-w**

| compd | X | $R^{10}$ | $R^1$ | Trk A $EC_{50}$ ($\mu$M) |
|---|---|---|---|---|
| **10k** | Br | H | cyclopropyl | 0.006 |
| **10o** | H | H | cyclopropyl | 0.02 |
| **10p** | F | H | cyclopropyl | 0.017 |
| **10q** | Me | H | cyclopropyl | 0.01 |
| **10l** | Cl | OH | cyclopropyl | 0.004 |
| **10r** | Cl | H | O$^i$Pr | 0.006 |
| **10s** | Cl | OH | SMe | 0.036 |
| **10t** | Cl | H | Me | 0.081 |
| **10u** | Cl | OH | OPr | 0.28 |
| **10v** | Cl | OH | H | 1.5 |
| **10w** | Cl | H | $^t$Bu | 3 |

**Table 3.** Rat Pharmacokinetics Data[a]

| | clearance (iv, mL/min/kg) | volume of distribution (L/kg) | half-life (iv, h) | oral bioavailability (%) | solubility ($\mu$M) | human plasma free (%) |
|---|---|---|---|---|---|---|
| **10k** | 9.5 | 0.84 | 1.5 | 32 | <3 | <1 |
| **10l** | 87 | 6.9 | 1.9 | 71 | 1.7 | 4.4 |

[a] Han Wistar Rat male; 10 mg/kg po (0.1% HPMC); 3 mg/kg iv (DMA/PEG/saline = 40/40/20).

fluorescence (HTRF) technology. The intracellular domain of human TrkB kinase was HIS tagged, expressed in SF9 insect cells, and purified using standard nickel column chromatography. The kinase assay (400 ng/mL of recombinant TrkB, 10 mM HEPES, 0.005% BSA, 10 mM $MnCl_2$, 60 $\mu$M ATP, and 50nM biotinylated Poly EAY) was incubated for 50 min at room temperature, and the kinase reaction stopped by the addition of 60 mM ethylenediaminetetraacetic acid (EDTA). Reaction products are detected with the addition of strepavidin-linked and phosphotyrosine-specific antibodies using the Tecan Ultra Evolution microplate fluorometer after additional 3 h incubation at room temperature.

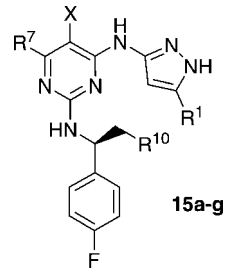
**TrkA Enzyme Assay.** TrkA kinase activity was determined by measuring the kinase's ability to phosphorylate synthetic tyrosine residues within a generic polypeptide substrate using amplified luminescent proximity assay (Alphascreen) technology (Perkin-Elmer, 940 Winter Street, Waltham, MA).

The intracellular domain of human TrkA kinase was HIS tagged, expressed in SF9 insect cells, and purified using standard nickel column chromatography. The kinase assay (0.838 ng/mL Trk A, 9 mM HEPES, 45 $\mu$g/mL BSA, 10 mM $MnCl_2$, 5 nM Poly EY, 0.01% Triton X-100, 70 $\mu$M ATP) was incubated for 20 min at room temperature and the reaction was stopped by the addition of 30 mM ethylenediaminetetraacetic acid (EDTA). The reaction products were detected with the addition of streptavidin coated donor beads and phosphotyrosine-specific antibodies coated acceptor beads. Plates were read using the EnVision Multilabel plate reader after an overnight incubation at room temperature.

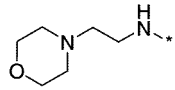
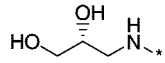
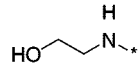
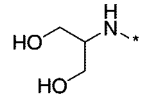
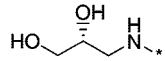
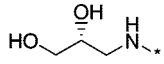
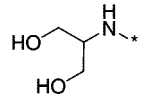
**TrkA Mechanism of Action (MOA) Cell Assay.** This is a cell-based assay for evaluating inhibitors of TrkA phosphorylation in MCF10A overexpressing TrkA deletion mutant cell line made in house.[25] A cDNA encoded a TrkA protein that contained a 75-aa deletion in the extracellular domain of the receptor and was named ΔTrkA. The deletion resulted in activation of the tyrosine kinase domain, leading to constitutive tyrosine phosphorylation of TrkA. MCF10A cells were infected with retrovirus made from an in-house retroviral vector that has the ΔTrkA cDNA insertion.

After cells have been treated with different doses of TrkA inhibitor for 75 min, the TrkA receptor was captured from cell lysates in microtiter plates coated with an antitrk antibody (C-14) from Santa Cruz. The amount of TrkA phosphorylation was then measured using europium-labeled antiphosphotyrosine antibody (P-Tyr-100 from Perkin-Elmer) with fluorometric detection. (This assay was modified based on a TRF-based TrkA intact cell assay.[24]

**Table 4.** SAR at $R^7$ Positions



**15a-g**

| Compound | $R^7$ | X | $R^{10}$ | $R^1$ | $EC_{50}$ (μM) | Solubility (μM) |
|---|---|---|---|---|---|---|
| **15a** |  | Cl | OH | Cp | 0.012 | 45 |
| **15b** |  | Cl | H | Cp | 0.009 | 19 |
| **15c** |  | Cl | H | Cp | 0.003 | 2 |
| **15d** |  | Cl | H | Cp | 0.003 | 82 |
| **15e** |  | H | H | Cp | 0.024 | 210 |
| **15f** |  | H | H | Me | 0.06 | 646 |
| **15g** |  | Cl | H | O$^i$Pr | 0.004 | 82 |

**Homology Modeling.** The program Modeler as implemented in the Accelrys Insight II package[28] was used to generate the TrkB homology model. Considering the flexibility of some of the structural elements in the ATP binding site, five template kinases were chosen as described below. As a result, the homology model is less likely biased by any single kinase structure. The overall reliability of the model is very good, especially at places where the structures are best conserved among all kinases such as residues involved in ATP binding.

A BLAST search using the TrkB sequence against all kinases with crystal structure information at that time provided the top kinases with the most sequence similarity. Insulin receptor kinase (1IR3),[29] fibroblast growth-factor receptor kinase (1FGK),[30] LCK2 (1QPC),[31] and c-Src kinase (2SRC)[32] were each among the top 10 most similar kinases to TrkB and all were crystallized with ATP analogues. A structure of CDK2 (1H08)[33] crystallized with a bisanilinopyrimidine inhibitor **29** was included as the fifth template due to the abundance of structural information for its inhibitors. The five template kinases were superimposed and their sequences aligned based on their structures. The TrkB sequence was then aligned to the group, and Modeler generated three homology models. The backbone of the three models varied only at the two termini and in one extended loop region away from the ATP binding site. There were variations at the side chain level but not so much as to affect ATP binding. Therefore, one of the models was chosen for further refinement.

An HTS hit (**30**, TrkB $IC_{50} = 0.646\ \mu M$) of very similar structure to **29** (Figure 4) was modeled into the ATP pocket of TrkB based on the overlay of the CDK2−**29** complex and the TrkB model. The protein/inhibitor complex then went through limited, binding site-focused minimization with CHARMm[28] to optimize the inhibitor/protein interactions.

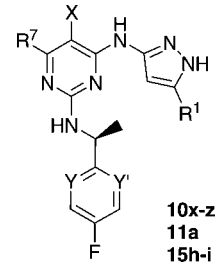
**Docking.** Docking studies were carried out with Glide.[34] The TrkB homology model complexed with **30** was prepared for docking by first modifying the atom and bond types of **30** to be compatible with Schrödinger software and adding hydrogen atoms. The Schrödinger protein preparation utilities *pprep* and *impref* were run to select appropriate side-chain protonation states, refine, and minimize the structure. Within Glide, docking grids were generated using a 12 Å search box and 30 Å grid (defaults), with one constraint defined such that docked ligands were each required to form a hydrogen bond with the backbone amide NH of the hinge methionine residue.

Three-dimensional stereoisomeric structures (with hydrogens) for ligands such as **10k** were generated from SMILES using CORINA,[35,36] and these conformations were then minimized using the MMFF force field in the Schrödinger environment using the utility scripts *sdconvert* and *premin*.

The GlideXP docking protocol employed docked each ligand flexibly and incorporated a van der Waals radius scaling factor of 0.8 for atoms with partial charge less than 0.15 to soften the potential. A maximum of 100 poses were stored for each ligand, and poses were discarded as duplicates if the rmsd was less than 1.5 Å or the maximum atomic displacement was less than 1.3 Å. Poses were then ranked by their computed GlideXP score.

**Synthesis of Aminopyrazoles 7. 5-Propan-2-yloxy-1*H*-pyrazol-3-amine (7a).** A mixture of triphenylphosphine (1.6 g, 6.1 mmol), diisopropylazodicarboxylate (1.2 mL, 6.1 mmol) in DCM (20 mL)

**Table 5.** SAR at Y/Y′ Positions




**10x-z**
**11a**
**15h-i**

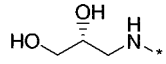
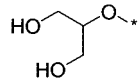
| Compound | $R^7$ | X | Y/Y' | $R^1$ | $EC_{50}$ (μM) | Solubility (μM) |
|---|---|---|---|---|---|---|
| **10x** | H | F | CH/N | Cp | 0.007 | 200 |
| **10y** | H | Cl | CH/N | Cp | 0.001 | 180 |
| **10z** | H | Cl | CH/N | O$^i$Pr | 0.001 | 100 |
| **15h** |  | Cl | CH/N | O$^i$Pr | 0.001 | 470 |
| **15i** |  | Cl | CH/N | O$^i$Pr | 0.002 | 310 |
| **11a** | H | Cl | N/N | O$^i$Pr | 0.002 | 440 |

**Table 6.** Pharmacokinetics of Lead Compounds[a]

| compd | species | iv clearance (mL/min/kg) | $T_{1/2}$ (h) | *F* % |
|---|---|---|---|---|
| **10y** | rat | 7.2 | 1.3 | 60 |
| **10y** | dog | 8.5 | 10.3 | NT |
| **10z** | rat | 17 | 1.4 | 31 |
| **10z** | dog | 9 | 7.5 | 60 |
| **15i** | rat | 23 | 1.6 | 24 |
| **15i** | dog | 9.8 | 8.3 | NT |

[a] Han Wistar rat male; 10 mg/kg po (0.1% HPMC); 3 mg/kg iv (DMA/PEG/saline = 40/40/20). Beagle dog male; 10 mg/kg po (0.1% HPMC); 3 mg/kg iv (50% PEG/D5W).

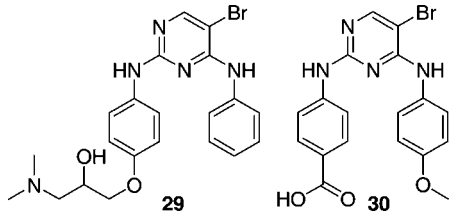



**Figure 4.** Compound **29** from CDK2 structure, **30** from TrkB HTS hit.

was stirred at room temperature for 20 min. The mixture was then cooled to 0 °C and to the mixture was added 5-amino-2*H*-pyrazole-3-ol (compound **17**, 0.55 g, 5.6 mmol) and 2-propanol (0.34 g, 5.6 mmol) and the mixture was stirred at room temperature for 2 days. Solid was filtered off, and the filtrate was concentrated. Flash column chromatography on silica gel gave the desired product 5-propan-2-yloxy-1*H*-pyrazol-3-amine as a white solid (197 mg, 25%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 10.25 (br s, 1H), 7.67 (m, 1H), 4.84 (m, 1H), 4.64 (s, 1H), 4.54 (m, 1H), 1.19 (d, $J$ = 6 Hz, 6H).

**5-Propoxy-1*H*-pyrazol-3-amine (7b).** Following a similar procedure to that for **7a**, compound **7c** was synthesized from 5-amino-2*H*-pyrazol-3-ol and 1-propanol. MS: calcd, 141; found, $[M + H]^+$ 142.

**5-Methylsulfanyl-1*H*-pyrazol-3-amine (7c).** 3,3-Bis(methylthio)-acrylonitrile (compound **18**; 300 mg, 2 mmol) in $H_2NNH_2H_2O$ (1 mL) was heated at 120 °C for 1 h. Hydrazine was removed under vacuum to give a pale-green oil (267 mg). The crude product was used without purification.

**General Synthetic Procedure for Compounds 8a−k.** A solution of pyrimidine **6** (1.0 equiv), aminopyrazole **7** (1.0 equiv), and triethylamine (1.5 equiv) in EtOH was stirred at room temperature for 10 h (or at 60 °C for inactivated pyrimidines). Solvent was removed, and EtOAc was added. The solution was washed with water, dried over anhydrous sodium sulfate, and concentrated. Flash column chromatography (30−100% EtOAc in hexanes) gave the desired compound as a solid.

**5-Bromo-2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (8a).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 12.34 (br s, 1H), 8.41 (m, 1H), 6.15 (m, 1H), 1.89 (m, 1H), 0.91 (m, 2H), 0.67 (m, 2H).

**2,5-Dichloro-*N*-(3-cyclopropyl-1*H*-pyrazol-5-yl)pyrimidin-4-amine (8b).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 12.60 (s, 1H), 9.90 (s, 1H), 8.60 (s, 1H), 6.40 (s, 1H), 2.18 (m, 1H), 1.20 (m, 2H), 0.92 (m, 2H).

**2-Chloro-*N*-(3-cyclopropyl-1*H*-pyrazol-5-yl)pyrimidin-4-amine (8c).** The reaction is similar to that for **8a** except that the reaction was performed at 70 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 12.14 (s, 1H), 10.22 (s, 1H), 8.14 (m, 1H), 5.90 (m, 1H), 1.86 (m, 1H), 0.92 (m, 2H), 0.66 (m, 2H).

**2-Chloro-*N*-(3-cyclopropyl-1*H*-pyrazol-5-yl)-5-fluoropyrimidin-4-amine (8d).** $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 12.28 (br s, 1H), 10.38 (s, 1H), 8.23 (s, 1H), 6.27 (s, 1H), 1.92 (m, 1H), 0.94 (m, 2H), 0.70 (m, 2H).

**2-Chloro-*N*-(3-cyclopropyl-1*H*-pyrazol-5-yl)-5-methylpyrimidin-4-amine (8e).** The reaction is similar to that for **8a** except that the reaction was performed at 70 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 12.18 (br, s, 1H), 9.29 (s, 1H), 7.97 (s, 1H), 6.27 (s, 1H), 2.11 (s, 3H), 1.91 (m, 1H), 0.93 (m, 2H), 0.70 (m, 2H).

**2,5-Dichloro-*N*-(5-propan-2-yloxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (8f).** $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 10.00 (br, s, 1H), 8.40 (s, 1H), 5.77 (s, 1H), 4.67 (m, 1H), 1.28 (m, 6H).

**2,5-Dichloro-*N*-[5-(methylthio)-1*H*-pyrazol-3-yl]pyrimidin-4-amine (8g).** $^1$H NMR (300 MHz, $CD_3OD$): $\delta$ ppm 8.24 (s, 1H), 6.72 (s, 1H), 2.49 (s, 3H).

**2,5-Dichloro-*N*-(5-methyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (8h).** $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 12.27 (br, s, 1H), 9.21 (s, 1H), 8.39 (s, 1H), 6.23 (s, 1H), 2.23 (s, 3H).

**2,5-Dichloro-*N*-(5-propoxy-2*H*-pyrazol-3-yl)pyrimidin-4-amine (8i).** $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ ppm 8.28 (br s, 1H), 5.60 (br s, 1H), 4.06 (m, 2H), 1.78 (m, 2H), 1.02 (t, $J$ = 7.5 Hz, 3H).

**2,5-Dichloro-*N*-(1*H*-pyrazol-5-yl)pyrimidin-4-amine (8j).** $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 12.64 (br s, 1H), 9.83 (br s, 1H), 8.35 (s, 1H), 7.74 (d, $J$ = 2 Hz, 1H), 6.51 (d, $J$ = 2 Hz, 1H).

***N*-(3-*tert*-Butyl-1*H*-pyrazol-5-yl)-2,5-dichloropyrimidin-4-amine (8k).** $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 12.37 (br s, 1H), 9.68 (br s, 1H), 8.33 (s, 1H), 6.29 (s, 1H), 1.29 (m, 9H).

**General Procedure for Compounds 10.** A mixture of compound **8** (1 equiv), DIPEA (1.5 equiv), and a suitable amine **9** (1.1 equiv) in *n*-butanol was heated at 110 °C for 18 h (or for 4 h at 165 °C in microwave). The solvent was removed, and EtOAc was added. The solution was washed with water and was concentrated. Flash column chromatography or semiprep HPLC (Gilson system) provided product as a solid.

Compounds **10a**−**k** were all synthesized from 5-bromo-2-chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**8a**).

***N*-Benzyl-5-bromo-*N*′-(5-cyclopropyl-2*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (10a).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 9.53 (br s, 1H), 8.43 (br s, 1H), 8.22 (s, 1H), 7.3 (m, 5H), 6.32 (br s, 1H), 5.94 (s, 1H), 4.48 (s, 2H), 1.81 (m, 1H), 0.88 (m, 2H), 0.67 (m, 1H), 0.47 (m, 1H). HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}BrN_6$ 385.0776; found 385.0786 ($\Delta$ = 2.6 ppm). Anal. ($C_{17}H_{17}BrN_6 \cdot 1.35C_2HF_3O_2$) C, H, N.

**5-Bromo-*N*′-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*-[(3-methoxyphenyl)methyl]pyrimidine-2,4-diamine (10b).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 11.81 (s, 1H), 7.72 (m, 2H), 7.28 (m, 1H), 7.03 (m, 1H), 6.50−6.70 (m, 3H), 4.18 (m, 2H), 3.52 (s, 3H), 1.81 (m, 1H), 0.92 (m, 2H), 0.61 (m, 2H). Anal. ($C_{18}H_{19}BrN_6O$) C, H, N.

**5-Bromo-*N*-[(2-chlorophenyl)methyl]-*N*′-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (10c).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 12.08 (br s, 1H), 8.01 (m, 2H), 7.20−7.60 (m, 5H), 5.72 (m, 1H), 4.48 (m, 2H), 1.79 (m, 1H), 0.90 (m, 2H), 0.61 (m, 2H). HRMS (ESI) *m*/*z* calcd for $C_{17}H_{16}BrClN_6$ 419.0386; found 419.0382 ($\Delta$ = − 0.9 ppm). HPLC analysis using a Waters Atlantis T3 column (3 $\mu$m, 2.1 mm × 50 mm) with $CH_3CN/H_2O$ as solvents (5−95% $CH_3CN$, flow rate: 1 mL/min, UV at 220 and 254 nm) showed ≥95% purity.

**5-Bromo-*N*′-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*-[(2-methoxyphenyl)methyl]pyrimidine-2,4-diamine (10d).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 12.10 (s, 1H), 7.90−8.00 (m, 2H), 6.81−7.42 (m, 5H), 5.78 (m, 1H), 4.39 (s, 2H), 3.76 (s, 3H), 1.80 (m, 1H), 0.91 (m, 2H), 0.61 (m, 2H). Anal. ($C_{18}H_{19}BrN_6O$) C, H, N.

**5-Bromo-*N*′-(5-cyclopropyl-2*H*-pyrazol-3-yl)-*N*-[(4-fluorophenyl-)methyl]pyrimidine-2,4-diamine (10e).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 12.10 (m, 1H), 8.01 (m, 2H), 7.62 (m, 1H), 7.10−7.30 (m, 4H), 6.19 (m, 1H), 4.38 (m, 2H), 1.78 (m, 1H), 0.91 (m, 2H), 0.61 (m, 2H). Anal. ($C_{17}H_{16}BrFN_6 \cdot 0.1H_2O$) C, H, N.

**5-Bromo-*N*-[(4-chlorophenyl)methyl]-*N*′-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (10f).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 12.12 (m, 1H), 8.00 (m, 2H), 7.61 (m, 1H), 7.20−7.40 (m, 4H), 5.88 (m, 1H), 4.36 (m, 2H), 1.76 (m, 1H), 0.92 (m, 2H), 0.61 (m, 2H). HRMS (ESI) *m*/*z* calcd for $C_{17}H_{16}BrClN_6$ 419.0386; found 419.0384 ($\Delta$ = − 0.5 ppm). Anal. ($C_{17}H_{16}BrClN_6$) C, H, N.

**5-Bromo-*N*′-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*-[(1*S*)-1-phenylethyl]pyrimidine-2,4-diamine (10g).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 12.14 (s, 1H), 8.01 (s, 1H), 7.95 (s, 1H), 7.20−7.44 (m, 5H), 5.88 (br s, 1H), 5.04 (m, 1H), 1.92 (m, 1H), 1.46 (m, 3H), 0.99 (m, 1H), 0.87 (m, 1H), 0.66 (m, 2H). Anal. ($C_{18}H_{19}N_6Br$) C, H, N.

**5-Bromo-*N*′-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*-[(1*R*)-1-phenylethyl]pyrimidine-2,4-diamine (10h).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 12.08 (s, 1H), 7.97 (m, 2H), 7.20−7.44 (m, 5H), 5.80−6.00 (m, 1H), 5.00 (m, 1H), 1.86 (m, 1H), 1.42 (m, 3H), 0.93 (m, 2H), 0.63 (m, 2H). HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}BrN_6$ 399.0933; found 399.0949 ($\Delta$ = 4.1 ppm). Anal. ($C_{18}H_{19}BrN_6 \cdot 0.85H_2O$) C, H, N.

**(2*S*)-2-[[5-Bromo-4-[(5-cyclopropyl-2*H*-pyrazol-3-yl)amino]pyrimidin-2-yl]amino]-2-phenylethanol (10i).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 10.11 (m, 1H), 8.70 (s, 1H), 8.12 (m, 1H), 7.30−7.40 (m, 5H), 6.23 (m, 1H), 5.32 (m, 1H), 4.18 (m, 1H), 4.11 (m, 2H), 2.04 (m, 1H), 1.20 (m, 2H), 0.91 (m, 2H). HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}BrN_6O$ 415.0882; found 415.0886 ($\Delta$ = 1.0 ppm). Anal. ($C_{18}H_{19}BrN_6O \cdot 0.3C_4H_8O_2$) C, H, N.

**(2*R*)-2-[[5-Bromo-4-[(5-cyclopropyl-2*H*-pyrazol-3-yl)amino]pyrimidin-2-yl]amino]-2-phenylethanol (10j).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 9.45 (br s, 1H), 8.40 (br s, 1H), 8.22 (s, 1H), 7.30 (m, 5H), 5.95 (s, 1H), 4.93 (m, 1H), 3.68 (m, 2H), 1.90 (m, 1H), 0.95 (m, 2H), 0.69 (m, 2H). HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}BrN_6O$ 415.0882; found 415.0901 ($\Delta$ = 4.6 ppm). Anal. ($C_{18}H_{19}BrN_6O \cdot 1.6C_2HF_3O_2$) C, H, N.

**5-Bromo-*N*′-(5-cyclopropyl-2*H*-pyrazol-3-yl)-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]pyrimidine-2,4-diamine (10k).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 9.23 (br s, 1H), 8.92 (br s, 1H), 8.27 (s, 1H), 8.14 (s, 1H), 7.31 (m, 2H), 7.12 (m, 2H), 5.95 (s, 1H), 4.95 (m, 1H), 1.88 (m, 1H), 1.44 (m, 3H), 0.92 (m, 2H), 0.66 (s, 2H). Anal. ($C_{18}H_{18}BrFN_6$) C, H, N.

**(2*R*)-2-[[5-Chloro-4-[(5-cyclopropyl-2*H*-pyrazol-3-yl)amino]pyrimidin-2-yl]amino]-2-(4-fluorophenyl)ethanol (10l).** The title compound was synthesized from 2,5-dichloro-*N*-(3-cyclopropyl-1*H*-pyrazol-5-yl)pyrimidin-4-amine (**8b**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 12.08 (s, 1H), 8.36 (s, 1H), 7.89 (s, 1H), 7.35 (m, 2H), 7.10 (m, 2H), 6.07−6.47 (m, 1H), 5.79 (s, 1H), 4.88−4.93 (m, 2H), 3.60 (m, 2H), 1.88 (m, 1H), 0.82−0.94 (m, 2H), 0.62−0.71 (m, 2H). HRMS (ESI) *m*/*z* calcd for $C_{18}H_{18}ClFN_6O$ 389.1293; found 389.1302 ($\Delta$ = 2.3 ppm). Anal. ($C_{18}H_{18}ClFN_6O \cdot 2.4H_2O$) C, H, N.

**(3*S*)-3-[[5-Chloro-4-[(5-cyclopropyl-1*H*-pyrazol-3-yl)amino]pyrimidin-2-yl]amino]-3-(4-fluorophenyl)-*N*,*N*-dimethylpropanamide (10m).** The title compound was synthesized from (3*S*)-3-amino-3-(4-fluorophenyl)-*N*,*N*-dimethylpropanamide (**31**) and 2,5-dichloro-*N*-(3-cyclopropyl-1*H*-pyrazol-5-yl)pyrimidin-4-amine (**8b**). $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ ppm 7.93 (s, 1H), 7.30 (m, 2H), 6.80 (m, 2H), 6.30 (m, 1H), 5.60 (br s, 1H), 5.07 (m, 1H), 2.95 (m, 2H), 2.60−2.80 (m, 6H), 1.80 (m, 1H), 0.90 (m, 2H), 0.60 (m, 2H). HRMS (ESI) *m*/*z* calcd for $C_{21}H_{23}ClFN_7O$ 444.1715; found 444.1703 ($\Delta$ = − 2.7 ppm). HPLC analysis using a Waters Atlantis T3 column (3 $\mu$m, 2.1 mm × 50 mm) with $CH_3CN/H_2O$ as solvents (5−95% $CH_3CN$, flow rate: 1 mL/min, UV at 220 and 254 nm) showed ≥95% purity.

**(3*S*)-3-Amino-3-(4-fluorophenyl)-*N*,*N*-dimethylpropanamide (31).** A mixture of (3*S*)-3-[(*tert*-butoxycarbonyl)amino]-3-(4-fluorophenyl)propanoic acid (200 mg, 0.74 mmol), EDCI (184 mg, 0.96 mmol), HOBT (160 mg, 1.2 mmol), and dimethylamine (2.0 M in THF, 0.48 mL, 0.96 mmol) was stirred at room temperature for 48 h. To the mixture was added water and the mixture was extracted with DCM. The combined organic layers were dried and concentrated. Reverse phase HPLC (Gilson) purification (monitored at 220 nm) gave the desired product as a white solid (506 mg, 90%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm 7.40 (m, 2H), 7.10 (m, 2H), 5.15 (m, 1H), 3.10 (m, 6H), 2.90 (m, 2H), 1.50 (s, 9H).

To a solution of above solid in DCM (5 mL) was added trifluoroacetic acid (5 mL), and the reaction mixture was stirred for 2 h. Solvent was removed and the residue was basified with $K_2CO_3/H_2O$. The mixture was extracted with $CHCl_3$/2-propanol (3:1). The combined organic layers were concentrated to give a yellow oil (130 mg, 93%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm 7.30 (m, 2H), 6.90 (m, 2H), 4.45 (m, 1H), 2.90 (m, 6H), 2.50 (m, 2H), 1.80 (s, 2H).

**(3*S*)-3-({5-Chloro-4-[(5-cyclopropyl-1*H*-pyrazol-3-yl)amino]pyrimidin-2-yl}amino)-3-(4-fluorophenyl)-*N*-methylpropanamide (10n).** The title compound was synthesized from (3*S*)-3-amino-3-(4-fluorophenyl)-*N*-methylpropanamide (**32**) and 2,5-dichloro-*N*-(3-cyclopropyl-1*H*-pyrazol-5-yl)pyrimidin-4-amine (**8b**). $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ ppm 8.23 (s, 1H), 7.40 (m, 2H), 7.20 (m, 2H), 6.30 (m, 1H), 5.60 (br s, 1H), 5.07 (m, 1H), 2.95 (m, 2H), 2.80 (m, 3H), 2.10 (m, 1H), 1.25 (m, 2H), 0.90 (m, 2H). HRMS (ESI) *m*/*z* calcd for $C_{20}H_{21}ClFN_7O$ 430.1558; found 430.1537 ($\Delta = -4.9$ ppm). Anal. ($C_{20}H_{21}ClFN_7O \cdot 1.55C_2HF_3O_2$) C, H, N.

**(3*S*)-3-Amino-3-(4-fluorophenyl)-*N*-methylpropanamide (32).** The title compound was synthesized in a similar way to compound **31**. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm 7.40 (m, 2 H), 7.08 (m, 2H), 6.65 (br s, 1H), 4.80 (br s, 1H), 3.27 (m, 1H), 2.82 (m, 3H), 1.52 (m, 2H).

***N*′-(5-cyclopropyl-2*H*-pyrazol-3-yl)-*N*-[(1*S*)-1-(4-fluorophenyl-)ethyl]pyrimidine-2,4-diamine (10o).** The title compound was synthesized from 2-chloro-*N*-(3-cyclopropyl-1*H*-pyrazol-5-yl)pyrimidin-4-amine (**8c**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 12.02 (br s, 1H), 11.11 (s, 1H), 8.91 (br s, 1H), 7.83 (m, 1 H), 7.41 (m, 2H), 7.19 (m, 2H), 6.28 (m, 1H), 6.06 (s, 1H), 5.12 (m, 1H), 1.86 (m, 1H), 1.52 (m, 3H), 0.95 (m, 2H), 0.66 (m, 2H). HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}FN_6$ 339.1733; found 339.1724 ($\Delta = -2.7$ ppm). Anal. ($C_{18}H_{19}FN_6 \cdot 1.55C_2HF_3O_2$) C, H, N.

***N*′-(5-Cyclopropyl-2*H*-pyrazol-3-yl)-5-fluoro-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]pyrimidine-2,4-diamine (10p).** The title compound was synthesized from 2-chloro-*N*-(3-cyclopropyl-1*H*-pyrazol-5-yl)-5-fluoropyrimidin-4-amine (**8d**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 8.04 (s, 1 H), 7.38 (m, 2H), 7.15 (m, 2H), 6.07 (br s, 1H), 4.98 (m, 1H), 1.88 (m, 1H), 1.46 (m, 3 H), 0.95 (m, 2H), 0.66 (m, 2H). HRMS (ESI) *m*/*z* calcd for $C_{18}H_{18}F_2N_6$ 357.1639; found 357.1625 ($\Delta = -3.9$ ppm). Anal. ($C_{18}H_{18}F_2N_6 \cdot 0.25C_4H_8O_2$) C, H, N.

***N*′-(5-Cyclopropyl-2*H*-pyrazol-3-yl)-*N*-[(1*S*)-1-(4-fluorophenyl-)ethyl]-5-methylpyrimidine-2,4-diamine (10q).** The title compound was synthesized from 2-chloro-*N*-(3-cyclopropyl-1*H*-pyrazol-5-yl)-5-methylpyrimidin-4-amine (**8e**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 12.01 (br s, 1H), 10.04 (s, 1H), 8.65 (br s, 1H), 7.70 (s, 1 H), 7.35 (m, 2H), 7.16 (m, 2H), 6.03 (br s, 1H), 5.01 (m, 1H), 2.05 (s, 3H), 1.90 (m, 1H), 1.49 (d, 3H), 0.95 (m, 2H), 0.66 (m, 2H). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{21}FN_6$ 353.1890; found 353.1894 ($\Delta = 1.1$ ppm). Anal. ($C_{19}H_{21}FN_6 \cdot 0.2H_2O$) H, C calcd, 64.10, found 63.67; N: calcd, 23.61, found, 24.13.

**5-Chloro-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]-*N*′-(5-propan-2-yloxy-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (10r).** The title compound was synthesized from 2,5-dichloro-*N*-(5-propan-2-yloxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**8f**). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 11.94 (br s, 1H), 9.66 (br s, 1H), 7.95 (s, 2H), 7.37 (d, $J$ = 5.5 Hz, 2H), 7.13 (t, $J$ = 8.3 Hz, 2H), 5.52 (d, $J$ = 1.3 Hz, 1H), 4.88−5.05 (m, 1H), 4.52−4.74 (m, 1H), 1.42 (d, $J$ = 7.1 Hz, 3H), 1.27 (d, $J$ = 6.1 Hz, 6 H). HRMS (ESI) *m*/*z* calcd for $C_{18}H_{20}ClFN_6O$ 391.1449; found 391.1445 ($\Delta = -1.0$ ppm). Anal. ($C_{18}H_{20}ClFN_6O \cdot 0.25H_2O$) C, H, N.

**(2*R*)-2-[[5-Chloro-4-[(5-methylsulfanyl-2*H*-pyrazol-3-yl)amino]pyrimidin-2-yl]amino]-2-(4-fluorophenyl)ethanol (10s).** The title compound was synthesized from 2,5-dichloro-*N*-[5-(methylthio)-1*H*-pyrazol-3-yl]pyrimidin-4-amine (**8g**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 9.74 (br s, 1H), 8.17 (s, 1H), 7.98 (s, 1H), 7.39 (m, 2H), 7.13 (m, 2H), 6.25 (s, 1H), 4.94 (m, 1H), 3.64 (m, 2H), 2.45 (s, 3H). HRMS (ESI) *m*/*z* calcd for $C_{16}H_{16}ClFN_6OS$ 395.0857; found 395.0851 ($\Delta = -1.5$ ppm). Anal. ($C_{16}H_{16}ClFN_6OS \cdot 1.15C_2HF_3O_2$) C, H, N.

**5-Chloro-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]-*N*′-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (10t).** The title compound was synthesized from 2,5-dichloro-*N*-(5-methyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**8h**). $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ ppm 8.02 (s, 1H), 7.33 (m, 2H), 7.07 (m, 2H), 6.08 (br s, 1H), 5.05 (m, 1H), 2.34 (s, 3H), 1.57 (m, 3H). HRMS (ESI) *m*/*z* calcd for $C_{16}H_{16}FClN_6$ 347.1187; found 347.1199 ($\Delta = 3.4$ ppm). Anal. ($C_{16}H_{16}FClN_6 \cdot 0.8C_2HF_3O_2$) C, H, N.

**(2*R*)-2-[[5-Chloro-4-[(5-propoxy-2*H*-pyrazol-3-yl)amino]pyrimidin-2-yl]amino]-2-(4-fluorophenyl)ethanol (10u).** The title compound was synthesized from 2,5-dichloro-*N*-(5-propoxy-2*H*-pyrazol-3-yl)pyrimidin-4-amine (**8i**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 9.86 (br s, 1H), 8.27 (br s, 1H), 7.99 (s, 1H), 7.38 (m, 2H), 7.14 (m, 2H), 5.61 (s, 1H), 4.94 (m, 1H), 4.00 (m, 2H), 3.64 (m, 2H), 1.70 (m, 2H), 0.95 (m, 3H). HRMS (ESI) *m*/*z* calcd for $C_{18}H_{20}ClFN_6O_2$ 407.1398; found 407.1393 ($\Delta = -1.2$ ppm). Anal. ($C_{18}H_{20}ClFN_6O_2 \cdot 1.25C_2HF_3O_2$) C, H, N.

**(2*R*)-2-[[5-Chloro-4-(2*H*-pyrazol-3-ylamino)pyrimidin-2-yl]amino]-2-(4-fluorophenyl)ethanol (10v).** The title compound was synthesized from 2,5-dichloro-*N*-(1*H*-pyrazol-5-yl)pyrimidin-4-amine (**8j**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 10.14 (s, 1H), 8.18 (s, 1H), 7.73 (s, 1H), 7.28 (m, 2H), 7.13 (m, 2H), 6.23 (s, 1H), 4.88 (m, 1H), 3.65 (m, 2H). HRMS (ESI) *m*/*z* calcd for $C_{15}H_{14}ClFN_6O$ 349.0980; found 349.0972 ($\Delta = -2.3$ ppm). Anal. ($C_{15}H_{14}ClFN_6O \cdot 1.25C_2HF_3O_2$) C, H, N.

***N*′-(5-*tert*-Butyl-1*H*-pyrazol-3-yl)-5-chloro-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]pyrimidine-2,4-diamine (10w).** The title compound was synthesized from *N*-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-2,5-dichloropyrimidin-4-amine (**8k**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 8.07 (s, 1H), 7.32 (m, 2H), 7.11 (m, 2H), 6.22 (br s, 1H), 5.01 (m, 1H), 1.46 (m, 3H), 1.26 (s, 9H). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{22}ClFN_6$ 389.1656; found 389.1674 ($\Delta = 4.6$ ppm). Anal. ($C_{19}H_{22}ClFN_6 \cdot 1.05C_2HF_3O_2$) C, H, N.

**(*S*)-5-Fluoro-*N*$^4$-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*$^2$-(1-(5-fluoropyridin-2-yl)ethyl)pyrimidine-2,4-diamine (10x).** A mixture of 2-chloro-*N*-(3-cyclopropyl-1*H*-pyrazol-5-yl)-5-fluoropyrimidin-4-amine (compound **8d**, 0.200 g, 0.788 mmol), (*S*)-1-(5-fluoropyridin-2-yl)ethanamine (compound (*S*)-**9a**; 0.116 g, 0.828 mmol), and DIPEA (0.17 mL, 0.946 mmol) in *n*-BuOH (2 mL) was heated in a sealed tube at 175 °C for 40 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (hexanes:EtOAc = 1:1) to give the title compound as a white solid (0.175 g, 62%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 12.47 (s, 1H), 10.15 (s, 1H), 8.48 (s, 1H), 7.89 and 7.81 (s, 1H), 7.65 (m, 1H), 7.42 (b, 1H), 7.20 (b, 1H), 5.76 (s, 1H), 5.00 (m, 1H), 1.85 (m, 1H), 1.44 (d, $J$ = 6.8 Hz, 3H), 0.95 (m, 1H), 0.85 (m, 1H), 0.74 (m, 1H), 0.63 (m, 1H). HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}F_2N_7$ 358.1591; found 358.1577 ($\Delta = -3.8$ ppm). Anal. ($C_{17}H_{17}F_2N_7 \cdot 0.35CH_4O$) C, H, N.

**(*S*)-5-Chloro-*N*$^4$-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*$^2$-(1-(5-fluoropyridin-2-yl)ethyl)pyrimidine-2,4-diamine (10y).** In a similar way described for **10x**, compound **10y** was synthesized from 2,5-dichloro-4-(5-cyclopropyl-1*H*-pyrazole-3-ylamino)pyrimidine (**8b**). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm$\delta$ 12.09−12.51 (m, 1H), 9.64−9.70 (m, 1H), 8.49 (s, 1H), 8.38 (s, 1H), 7.93−8.02 (m, 1H), 7.63 (m, 1H), 7.40 (m, 1H), 5.80−5.93 (m, 1H), 5.06 (m, 1H), 1.83 (m, 1H), 1.45 (d, $J$ = 6.8 Hz, 3H), 0.94 (m, 1H), 0.84 (m, 1H), 0.74 (m, 1H), 0.63 (m, 1H). Anal. ($C_{17}H_{17}ClFN_7 \cdot 0.45H_2O$) C, H, N.

**5-Chloro-*N*$^2$-[(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]-*N*$^4$-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (10z).** In a similar way described for **10x**, compound **10z** was synthesized from 2,5-dichloro-*N*-(5-propan-2-yloxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**8f**). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm 8.45 (s, 1H), 7.90 (s, 1H), 7,35 (m, 2H), 6.30 (br s, 1H), 5.40 (s, 1H), 5.15 (m, 1H), 4.80 (m, 1H), 1.60 (m, 3H), 1.35 (m, 6H). Anal. ($C_{17}H_{19}ClFN_7O \cdot 0.2H_2O$) C, H, N.

**5-Chloro-*N*-[(1*S*)-1-(5-fluoropyrimidin-2-yl)ethyl]-*N*′-(5-propan-2-yloxy-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (11a).** In a similar way described for **10x**, compound **11a** was synthesized from 2,5-dichloro-*N*-(5-propan-2-yloxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**8f**) and (*S*)-1-(5-fluoropyrimidin-2-yl)ethanamine (*S*)-**9b.** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm 8.50 (s, 2H), 7.75 (s, 1H), 5.50 (s, 1H), 5.20 (m, 1H), 4.68 (m, 1H), 1.55 (m, 3H), 1.20 (m, 6H). Anal. ($C_{16}H_{18}ClFN_8O$) C, H, N.

**General Procedure for the Synthesis of Intermediates 13.** Following a procedure similar to that of compounds **8**, compounds **13a**−**d** were synthesized.

**2,5,6-Trichloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (13a).** $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 12.40 (s, 1H), 9.98 (s, 1H), 6.17 (d, $J$ = 2.0 Hz, 1H), 1.92 (m, 1H), 0.88−0.99 (m, 2H), 0.70 (dd, $J$ = 4.9, 2.1 Hz, 2H).

**2,5,6-Trichloro-*N*-(5-propan-2-yloxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (13b).** $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.25 and 11.46 (s, 1H), 10.23 and 9.94 (s, 1H), 5.85 and 5.75 (s, 1H), 4.69 and 4.45 (m, 1H), 1.30 (d, $J$ = 6.0 Hz, 3H), 1.27 (d, $J$ = 6.0 Hz, 3H). MS: calcd 321; found $[M + H]^+$ 322.

**2,6-Dichloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (13c).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 12.28 (s, 1H), 10.66 (s, 1H), 7.76 and 6.80 (br s, 1H), 6.30 and 5.66 (br s, 1H), 1.88 (m, 1H), 0.92 (m, 2H), 0.68 (m, 2H).

**2,6-Dichloro-*N*-(5-methyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (13d).** $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 12.20 (s, 1H), 10.67 (s, 1H), 9.56 and 7.73 (m, 1 H), 6.75 and 5.81 (m, 1 H), 2.22 (s, 3 H).

**General Procedure for the Synthesis of Compounds 14a−f.** Following a procedure similar to that of compounds **10**, compounds **14a−f** were synthesized.

**5,6-Dichloro-*N*′-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]pyrimidine-2,4-diamine (14a).** The title compound was synthesized from 2,5,6-trichloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**13a**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 9.19 (br s, 1H), 8.83 (br s, 1H), 7.95 (m, 1H), 7.33 (m, 2H), 7.10 (m, 2H), 5.93−6.21 (m, 1H), 4.92 (m, 1H), 1.87 (m, 1H), 1.39 (m, 3H), 0.92 (m, 2H), 0.67 (m, 2H).

**5,6-Dichloro-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]-*N*′-(5-propan-2-yloxy-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (14b).** The title compound was synthesized from 2,5,6-trichloro-*N*-(5-propan-2-yloxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**13b**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 11.89 (br s, 1H), 9.86 (br s, 1H), 8.18 (m, 1H), 7.40 (m, 2H), 7.14 (m, 2H), 5.55 (m, 1H), 4.95 (m, 1H), 4.66 (m, 1H), 1.41 (m, 1H), 1.26 (m, 6H).

**6-Chloro-*N*′-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]pyrimidine-2,4-diamine (14c).** The title compound was synthesized from 2,6-dichloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**13c**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 9.63 (br s, 1H), 7.78 (br s, 1H), 7.38 (m, 2H), 7.12 (m, 2H), 5.93−6.17 (m, 1H), 5.03 (m, 1H), 1.84 (m, 1H), 1.40 (m, 3H), 0.92 (m, 2H), 0.66 (m, 2H).

**6-Chloro-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]-*N*′-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (14d).** The title compound was synthesized from 2,6-dichloro-*N*-(5-methyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**13d**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 8.60 (m, 1H), 7.80 (m, 1H), 7.40 (m, 2H), 7.10 (m, 2H), 5.85−6.10 (m, 2H), 5.10 (m, 1H), 2.20 (m, 3H), 1.45 (s, 3H).

**(2*R*)-2-[[4,5-Dichloro-6-[(5-cyclopropyl-1*H*-pyrazol-3-yl)amino]pyrimidin-2-yl]amino]-2-(4-fluorophenyl)ethanol (14e).** The title compound was synthesized from 2,5,6-trichloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**13a**). $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ ppm 7.37 (m, 2H), 7.04 (m, 2H), 6.05 (br s, 1H), 5.00 (m, 1H), 3.76 (m, 2H), 1.90 (m, 1H), 0.97 (m, 2H), 0.73 (m, 2H).

**5,6-Dichloro-*N*-[(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]-*N*′-(5-propan-2-yloxy-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (14f).** The title compound was synthesized from 2,5,6-trichloro-*N*-(5-propan-2-yloxy-1*H*-pyrazol-3-yl)pyrimidin-4-amine (**13b**). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 11.96 (s, 1H), 9.86 (s, 1H), 8.53 (bs, 1H), 8.31 (d, $J$ = 8.0 Hz, 1H), 7.68 (m, 1H), 7.46 (m, 1H), 5.56 (s, 1H), 5.05 (m, 1H), 4.68 (m, 1H), 1.46 (d, $J$ = 6.8 Hz, 3H), 1.28 (d, $J$ = 6.0 Hz, 6H). MS: calcd 425; found $[M + H]^+$ 426.

**(2*R*)-2-({5-Chloro-4-[(3-cyclopropyl-1*H*-pyrazol-5-yl)amino]-6-[(2-morpholin-4-ylethyl)amino] pyrimidin-2-yl}amino)-2-(4-fluorophenyl)ethanol (15a).** A mixture of (2-morpholin-4-ylethyl)amine (44 $\mu$L, 0.34 mmol), (2*R*)-2-[[4,5-dichloro-6-[(5-cyclopropyl-1*H*-pyrazol-3-yl)amino]pyrimidin-2-yl]amino]-2-(4-fluorophenyl)ethanol (**14e**, 70 mg, 0.16 mmol) in *n*-butanol (1.0 mL) was heated at 120 °C for 18 h. The solvent was removed and EtOAc was added. The solution was washed with water and was concentrated. Semiprep HPLC (Gilson system) provided product as a solid (92 mg). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm 9.54 (br s, 1H), 9.15 (br s, 1H), 7.95 (br s, 1H), 7.38 (m, 2H), 7.14 (m, 2H), 5.93 (s, 1H), 4.89 (m, 1H), 3.98 (m, 2H), 3.86 (m, 2H), 3.63 (m, 4H), 3.46 (m, 2H), 3.22 (m, 2H), 3.01 (m, 2H), 1.86 (m, 1H), 0.92 (m, 2H), 0.67 (m, 2H). HRMS (ESI) *m/z* calcd for $C_{24}H_{30}ClFN_8O_2$ 517.2242; found 517.2224 ($\Delta$ = − 3.4 ppm). Anal. ($C_{24}H_{30}ClFN_8O_2 \cdot 2C_2HF_3O_2 \cdot 1.2H_2O$) C, H, N.

**(2*R*)-3-[[5-Chloro-6-[(5-cyclopropyl-2*H*-pyrazol-3-yl)amino]-2-[[(1*S*)-1-(4-fluorophenyl)ethyl]amino]pyrimidin-4-yl]amino]propane-1,2-diol (15b).** The title compound was synthesized from 5,6-dichloro-*N*′-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]pyrimidine-2,4-diamine (**14a**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 9.81 (br s, 1H), 8.67 (br s, 1H), 7.42 (m, 2H), 7.14 (m, 2H), 5.86 (s, 1H), 5.02 (m, 1H), 3.30−3.54 (m, 5H), 1.93 (m, 1H), 1.45 (m, 3H), 0.98 (m, 2H), 0.69 (m, 2H). HRMS (ESI) *m/z* calcd for $C_{21}H_{25}ClFN_7O_2$ 462.1820; found 462.1833 ($\Delta$ = 2.8 ppm). HPLC analysis using a Waters Atlantis T3 column (3 $\mu$m, 2.1 mm × 50 mm) with $CH_3CN/H_2O$ as solvents (5−95% $CH_3CN$, flow rate: 1 mL/min, UV at 220 and 254 nm) showed ≥95% purity.

**2-[[5-Chloro-6-[(5-cyclopropyl-2*H*-pyrazol-3-yl)amino]-2-[[(1*S*)-1-(4-fluorophenyl)ethyl]amino]pyrimidin-4-yl]amino]ethanol (15c).** The title compound was synthesized from 5,6-dichloro-*N*′-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]pyrimidine-2,4-diamine (**14a**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 9.72 (br s, 1H), 8.59 (br s, 1H), 7.47 (br s, 1H), 7.39 (m, 2H), 7.14 (m, 2H), 5.85 (s, 1H), 4.97 (m, 1H), 3.37−3.54 (m, 4H), 1.90 (m, 1H), 1.45 (m, 3H), 0.96 (m, 2H), 0.68 (m, 2H). HRMS (ESI) *m/z* calcd for $C_{20}H_{23}ClFN_7O$ 432.1715; found 462.1710 ($\Delta$ = − 1.2 ppm). Anal. ($C_{20}H_{23}ClFN_7O \cdot 1.35C_2HF_3O_2$) C, H, N.

**2-[[5-Chloro-6-[(5-cyclopropyl-2*H*-pyrazol-3-yl)amino]-2-[[(1*S*)-1-(4-fluorophenyl)ethyl]amino]pyrimidin-4-yl]amino]propane-1,3-diol (15d).** The title compound was synthesized from 5,6-dichloro-*N*′-(5-cyclopropyl-1H-pyrazol-3-yl)-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]pyrimidine-2,4-diamine (**14a**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 9.73 (br s, 1H), 8.54 (br s, 1H), 7.42 (m, 2H), 7.14 (m, 2H), 6.68 (br s, 1H), 5.86 (s, 1 H), 4.98 (m, 1H), 4.04 (m, 1H), 3.33−3.56 (m, 4H), 1.91 (m, 1H), 1.45 (m, 3H), 0.96 (m, 2H), 0.68 (m, 2H). HRMS (ESI) *m/z* calcd for $C_{21}H_{25}ClFN_7O_2$ 462.1820; found 462.1805 ($\Delta$ = − 3.2 ppm). Anal. ($C_{21}H_{25}ClFN_7O_2 \cdot 2HCl$) C, H, N.

**(2*R*)-3-[[6-[(5-Cyclopropyl-1*H*-pyrazol-3-yl)amino]-2-[[(1*S*)-1-(4-fluorophenyl)ethyl]amino]pyrimidin-4-yl]amino]propane-1,2-diol (15e).** The title compound was synthesized from 6-chloro-*N*′-(5-cyclopropyl-1*H*-pyrazol-3-yl)-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]pyrimidine-2,4-diamine (**14c**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 11.45 (br s, 1H), 10.20 (br s, 1H), 8.70 (s, 1H), 8.10 (s, 1H), 7.35 (m, 2H), 7.10 (m, 2H), 5.45 (m, 1H), 5.35 (s, 1H), 4.95 (br s, 1H), 3.10−3.50 (m, 5H), 1.80 (m, 1H), 1.45 (m, 3H), 0.90 (m, 2H), 0.65 (m, 2H). HRMS (ESI) *m/z* calcd for $C_{21}H_{26}FN_7O_2$ 428.2210; found 428.2195 ($\Delta$ = − 3.5 ppm). Anal. ($C_{21}H_{26}FN_7O_2 \cdot 2C_2HF_3O_2$) C, H, N.

**(2*R*)-3-[[2-[[(1*S*)-1-(4-Fluorophenyl)ethyl]amino]-6-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrimidin-4-yl]amino]propane-1,2-diol (15f).** The title compound was synthesized from 6-chloro-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]-*N*′-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (**14d**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 11.55 (br s, 1H), 10.20 (br s, 1H), 8.78 (s, 1 H), 8.10 (s, 1H), 7.35 (m, 2H), 7.10 (m, 2H), 5.65 (m, 1H), 5.35 (s, 1H), 4.95 (br s, 1H), 3.10−3.90 (m, 5H), 2.15 (s, 3H), 1.40 (m, 3H). HRMS (ESI) *m/z* calcd for $C_{19}H_{24}FN_7O_2$ 402.2054; found 402.2043 ($\Delta$ = − 2.7 ppm). Anal. ($C_{19}H_{24}FN_7O_2 \cdot 0.75CH_2Cl_2$) C, H, N.

**2-[[5-Chloro-2-[[(1*S*)-1-(4-fluorophenyl)ethyl]amino]-6-[(5-propan-2-yloxy-1*H*-pyrazol-3-yl)amino]pyrimidin-4-yl]amino]propane-1,3-diol (15g).** The title compound was synthesized from 5,6-dichloro-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]-*N*′-(5-propan-2-yloxy-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (**14b**). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 9.97 (br s, 1H), 8.81 (br s, 1H), 7.40 (m, 2H), 7.13 (m, 2H), 6.70 (br s, 1H), 5.63 (s, 1H), 4.98 (m, 1H), 4.55 (m, 1H), 4.04 (m, 1H), 3.33−3.55 (m, 4H), 1.46 (m, 3H), 1.30 (m, 6H). Anal. ($C_{21}H_{27}ClFN_7O_3$) C, H, N.

**(*R*)-3-(5-Chloro-2-((*S*)-1-(5-fluoropyridin-2-yl)ethylamino)-6-(5-isopropoxy-1*H*-pyrazol-3-ylamino)pyrimidin-4-ylamino)propane-1,2-diol (15h).** In a similar way described for **15a**, compound **15h** was synthesized from (*S*)-5,6-dichloro-$N^2$-(1-(5-fluoropyridin-2-yl)ethyl)-$N^4$-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (**14f**). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 11.91 (s, 1H), 9.02 (s, 1H), 8.47 (s, 1H), 7.64 (m, 2H), 7.43 (m, 1H), 6.24 (t, $J$ = 5.6 Hz, 1H), 5.37 (d, $J$ = 1.6 Hz, 1H), 4.99 (m, 1H), 4.72 (m, 1H), 4.65 (m, 1H), 4.55 (m, 1H), 3.43 (m, 1H), 3.37 (m, 1H), 3.26 (m, 2H), 3.10 (m, 1H), 1.43 (d, $J$ = 6.8 Hz, 3H), 1.26 (d, $J$ = 6.0 Hz, 6H). Anal. ($C_{20}H_{26}ClFN_8O_3 \cdot 0.35H_2O$) C, H, N.

**2-[5-Chloro-2-[[(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]amino]-6-[(5-propan-2-yloxy-1*H*-pyrazol-3-yl)amino]pyrimidin-4-yl]oxypropane-1,3-diol (15i).** In a slightly different way described for **15a**, compound **15i** was synthesized from 5,6-dichloro-*N*-[(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]-*N*′-(5-propan-2-yloxy-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (**14f**) and 2-phenyl-1,3-dioxan-5-ol: sodium hydride (1.1 equiv) was added to a suspension of 2-phenyl-1,3-dioxan-5-ol in toluene followed by addition of **14f**. The mixture was heated overnight and to the mixture was added water. Solvent was removed and excess TFA was added. Flash column chromatography on silica gel provided the desired product. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 11.90 (s, 1H), 9.36 (s, 1H), 8.49 (s, 1H), 7.98 (d, $J$ = 7.2 Hz, 1H), 7.66 (m, 1H), 7.43 (m, 1H), 5.45 (s, 1H), 4.97 (m, 1H), 4.71 (m, 1H), 4.64 (m, 1H), 4.56 (m, 1H), 3.43 (m, 1H), 3.61 (m, 2H), 3.30 (m, 2H), 1.46 (d, $J$ = 7.2 Hz, 3H), 1.27 (d, $J$ = 6.0 Hz, 6H). HRMS (ESI) $m/z$ calcd for $C_{20}H_{25}FClN_7O_4$ 482.1719; found 482.1709 ($\Delta$ = − 2.1 ppm). Anal. ($C_{20}H_{25}ClFN_7O_4 \cdot 0.1H_2O$) C, H, N.

**5-Fluoropicolinonitrile (20).** A mixture of 2-bromo-5-fluoropyridine (compound **19,** 93.0 g, 528 mmol), Zn dust (8.29 g, 127 mmol), zinc cyanide (40.3 g, 343 mmol), DPPF (11.7 g, 21.1 mmol), and $Pd_2(dba)_3$ (9.68 g, 10.6 mmol) in anhydrous dimethylacetamide (300 mL) was heated at 95 °C for 3 h. After cooling to room temperature, brine (100 mL) and ether (500 mL) were added. The solid formed was removed by filtration and washed with ether (300 mL). The organic layer was separated, washed with brine (200 mL), and was dried over anhydrous sodium sulfate and concentrated. The crude product was purified by flash column chromatography (hexanes:DCM = 1:1) to give 5-fluoropicolinonitrile as a white solid (49 g, 72%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.82 (d, $J$ = 2.8 Hz, 1H), 8.21 (dd, $J$ = 4.4 and 8.8 Hz, 1H), 8.05 (dd, $J$ = 2.8 and 8.8 Hz, 1H).

***N*-(1-(5-Fluoropyridin-2-yl)vinyl)acetamide (21).** A solution of MeMgBr (170.3 mL, 510.98 mmol) in ether was diluted with 170 mL of anhydrous THF and cooled to 0 °C. 5-Fluoropicolinontrile (compound **20**, 53.6 g, 425.82 mmol) in THF (170 mL) was added dropwise. The reaction was stirred at 0 °C for 30 min and then diluted with DCM (170 mL). Acetic anhydride (48.3 mL, 510.98 mmol) in DCM (100 mL) was added dropwise at 0 °C. After addition, the reaction was warmed to room temperature and stirred at room temperature for 8 h. Saturated sodium bicarbonate solution (50 mL) was added and extracted with ethyl acetate (2 × 200 mL). The combined organic was dried over sodium sulfate. After removal of solvent, the resulting residue was purified by flash column chromatography (hexanes:EtOAc = 2.5:1) to give *N*-(1-(5-fluoropyridin-2-yl)vinyl)acetamide as a white solid (26.6 g, 35%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 9.37 (s, 1H), 8.57 (d, $J$ = 2.8 Hz, 1H), 7.81 (m, 2H), 6.01 (s, 1H), 5.52 (s, 1H), 2.08 (s, 3H). MS: calcd 180; found $[M + H]^+$ 181.

**(*S*)-*N*-(1-(5-Fluoropyridin-2-yl)ethyl)acetamide (22).** To a solution of *N*-(1-(5-fluoropyridin-2-yl)vinyl)acetamide (compound **21**, 11.0 g, 61.1 mmol) in MeOH (120 mL) under $N_2$ was added (+)-1,2-bis((2*S*, 5*S*)-2,5-diethylphospholano)benzene (cyclooctadiene)rhodium(I) trifluoromethanesulfonate (0.441 g, 0.611 mmol). The solution was transferred to a high pressure bomb and charged 150 psi $H_2$. The reaction was stirred at room temperature and maintained inside pressure between 120−150 psi for 7 h. The solvent was removed, and the resulting residue was purified by flash column chromatography (EtOAc) to give (*S*)-*N*-(1-(5-fluoropyridin-2-yl)-ethyl)acetamide as a white solid (9.8 g, 88%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.49 (d, $J$ = 2.4 Hz, 1H), 8.32 (d, $J$ = 7.6 Hz, 1H), 7.66 (m, 1H), 7.39 (dd, $J$ = 4.4 and 8.8 Hz, 1H), 4.95 (m, 1H), 1.85 (s, 3H), 1.34 (d, $J$ = 7.2 Hz, 3H). MS: calcd 182; found: $[M + H]^+$ 183. Enantiomeric excess determined by HPLC (Chiralpak IA 250 mm × 4.6 mm; solvent 70:30 $CO_2$/MeOH, isocratic; run: 2 mL/min, 10 min run; pressure: 120 bar; temperature: 45 °C; wavelength: 220 nm; retention time: 1.77 and 2.19 min (desired enantiomer) 95.3% ee).

**(*S*)-*tert*-Butyl-1-(5-fluoropyridin-2-yl)ethylcarbamate (23).** A solution of (*S*)-*N*-(1-(5-fluoropyridin-2-yl)ethyl)acetamide (compound **22**, 11.0 g, 60.37 mmol), DMAP (1.48 g, 12.07 mmol), and $Boc_2O$ (26.35 g, 120.7 mmol) in THF (100 mL) was stirred at 50 °C for 20 h. After cooling to room temperature, lithium hydroxide monohydrate (5.19 g, 123.8 mmol) and water (100 mL) were added. The reaction was stirred at room temperature for 5 h and diluted with ether (200 mL). The organic layer was separated, washed with brine (100 mL), and dried over sodium sulfate. After removal of solvent, the resulting residue was purified by flash column chromatography (hexanes:EtOAc = 5:1) to give (*S*)-*tert*-butyl-1-(5-fluoropyridin-2-yl)ethylcarbamate as a pale-yellow oil (13.6 g, 94%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.46 (d, $J$ = 2.8 Hz, 1H), 7.69 (m, 1H), 7.35−7.41 (m, 2H), 4.67 (m, 1H), 1.37 (s, 9H), 1.32 (d, $J$ = 7.2 Hz, 3H). MS: calcd 240; found $[M + H]^+$ 241.

**(*S*)-1-(5-Fluoropyridin-2-yl)ethanamine (*S*)-9a.** To the solution of (*S*)-*tert*-butyl-1-(5-fluoropyridin-2-yl)ethylcarbamate (compound **23**, 12.8 g, 53.3 mmol) in DCM (100 mL) was added HCl/dioxane solution (107 mL, 4 N, 428 mmol). The reaction was stirred at room temperature for 3 h. The solvent was removed and 50 mL of saturated sodium bicarbonate was added. The resulting aqueous solution was extracted with ether (6 × 400 mL), dried over sodium sulfate, and concentrated to give (*S*)-1-(5-fluoropyridin-2-yl)ethanamine (7.30 g, 98%) as a pale-yellow oil. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.44 (d, $J$ = 2.8 Hz, 1H), 7.66 (m, 1H), 7.53 (m, 1H), 4.01 (q, $J$ = 6.8 Hz, 1H), 1.94 (m, 2H), 1.26 (d, $J$ = 6.8 Hz, 3H). MS: calcd 140; found: $[M + H]^+$ 141.

**5-Fluoropyrimidine-2-carbonitrile (25).** A 10 mL microwave vial was charged with 2-chloro-5-fluoropyrimidine (compound **24**, 2.0 g, 15.09 mmol), $Pd_2(dba)_3$ (0.549 g, 0.6 mmol), DPPF (0.67 g, 1.21 mmol), zinc cyanide (1.15 g, 9.81 mmol), and zinc dust (0.237 mg, 3.62 mmol). The flask was evacuated and backfilled with $N_2$ and anhydrous dimethylacetamide. The vial was mounted onto a Personal Chemistry microwave reactor and heated at 100 °C for 10 h. The reaction mixture was diluted with EtOAc and then washed with brine three times. The organic layer was obtained and evaporated to dryness. The dried residue was purified by silica gel chromatography (by ISCO Combiflash with gradient EtOAc and hexanes) to afford the title compound as an off-white solid (1.50 g, 80%). GC-MS: 123 (M); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ ppm 8.80 (s, 2H).

***N*-(1-(5-Fluoropyrimidin-2-yl)vinyl)acetamide (26).** To a solution of 5-fluoropyrimidine-2-carbonitrile (compound **25**, 1.0 g, 8.1 mmol) in THF (10 mL) was added a solution of MeMgBr (3.3 mL, 9.75 mmol) in ether dropwise at 0 °C. After addition, the reaction was warmed to room temperature, stirred at room temperature for 1 h, and then diluted with DCM (10 mL). Acetic anhydride (1.23 mL, 13.0 mmol) was added in one portion. The reaction was stirred at room temperature for 1 h and 40 °C for 1 h. Saturated sodium bicarbonate solution (10 mL) was added and extracted with ethyl acetate (2 × 20 mL). The combined organic was dried over sodium sulfate. After removal of solvent, the resulting residue was purified by flash column chromatography (hexanes:EtOAc = 2.5:1) to give *N*-(1-(5-fluoropyrimidin-2-yl)vinyl)acetamide as a white solid (0.38 g, 26%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 9.34 (s, 1H), 8.95 (s, 2H), 6.25 (s, 1H), 6.03 (s, 1H), 2.11 (s, 3H). MS: calcd 181; found $[M + H]^+$ 182.

**(*S*)-*N*-(1-(5-Fluoropyrimidin-2-yl)ethyl)acetamide (27).** A solution of *N*-(1-(5-fluoropyrimidin-2-yl)vinyl)acetamide (compound **26**, 0.10 g, 0.55 mmol) in MeOH (5 mL) under $N_2$ was added (+)-1,2-bis((2*S*, 5*S*)-2,5-diethylphospholano)benzene (cyclooctadiene)rhodium(I)trifluoromethanesulfonate (0.04 g, 0.0055 mmol). The solution was transferred to a high pressure bomb and charged 150

psi $H_2$. The reaction stirred at room temperature for 4 h. The solvent was removed and the resulting residue was purified by flash column chromatography (EtOAc) to give (*S*)-*N*-(1-(5-fluoropyrimidin-2-yl)ethyl)acetamide as a white solid (0.096 g, 95%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.84 (d, $J = 0.8$ Hz, 2H), 8.34 (d, $J = 7.6$ Hz, 1H), 5.00 (m, 1H), 1.84 (s, 3H), 1.37 (d, $J = 6.8$ Hz, 3H). MS: calcd 183; found $[M + H]^+$ 184. Enantiomeric excess determined by HPLC (Chiralpak IA; 95:5 $CO_2$/MeOH), conditions similar to that for compound **22**; >99% ee.

**(*S*)-*tert*-Butyl-1-(5-Fluoropyrimidin-2-yl)ethylcarbamate (28).** A mixture of (*S*)-*N*-(1-(5-fluoropyrimidin-2-yl)ethyl)acetamide (compound **27**, 0.20 g, 1.09 mmol), DMAP (0.027 g, 0.22 mmol), and $Boc_2O$ (0.60 g, 2.73 mmol) in THF (10 mL) was stirred at 50 °C for 40 h. After cooling to room temperature, lithium hydroxide monohydrate (0.094 g, 2.24 mmol) and water (10 mL) was added. The reaction mixture was stirred at room temperature for 9 h. Ether (30 mL) was added and the organic layer was separated, washed with brine (20 mL), and dried over sodium sulfate. After removal of solvent, the resulting residue was purified by flash column chromatography (hexanes:EtOAc = 5:1) to give (*S*)-*tert*-butyl-1-(5-fluoropyrimidin-2-yl)ethylcarbamate as a pale-yellow oil (0.21 g, 80%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.84 (s, 2H), 7.24 (d, $J = 7.6$ Hz, 1H), 4.74 (m, 1H), 1.35 (s, 12H). MS: calcd 241; found $[M + H]^+$ 242.

**(*S*)-1-(5-Fluoropyrimidin-2-yl)ethanamine HCl salt (*S*)-9b (HCl Salt).** To a solution of (*S*)-*tert*-butyl-1-(5-fluoropyrimidin-2-yl)ethylcarbamate (compound **28**, 0.21 g, 0.87 mmol) in DCM (5 mL) was added HCl (1.3 mL, 5.2 mmol) in dioxane. The reaction mixture was stirred at room temperature for 3 h. The solvent was removed to give (*S*)-1-(5-fluoropyrimidin-2-yl)ethanamine as HCl salt as white solid (quantitative). MS: calcd 141; found $[M + H]^+$ 142.

**Microsome Stability Assay.** This primary in vitro test assesses the propensity of a compound to be metabolized by human liver microsomal enzymes. The time-dependent disappearance of compound (2 $\mu$M initial concentration) incubated with microsomes was measured by LC-MS/MS. Results are reported as intrinsic clearance of compound (CLint, in $\mu$L/min/mg protein).

**Aqueous Equilibrium Solubility Assay.** This primary in vitro test assesses the equilibrium solubility of a compound in pH 7.4 phosphate buffer. Solid compound was prepared by evaporation of a DMSO solution. Dried compound was incubated for 24 h with agitation in buffer. Undissolved compound was removed by filtration and the concentration of test compound in the filtrate was measured by HPLC-UV with MS confirmation. The upper and lower limits of the assay are typically 1 mM and ~1 $\mu$M, respectively.

**Plasma Protein Binding Assay.** This primary in vitro test assesses the extent of binding of a compound to plasma proteins using equilibrium dialysis to separate free from bound compound. The amount of compound in plasma (10 $\mu$M initial concentration) and in dialysis buffer (pH 7.4 phosphate buffer) is measured by LC-MS/MS after equilibration in a dialysis chamber. The fraction unbound (fu) is reported.

**Acknowledgment.** We thank the Analytical Chemistry group for providing HRMS and chiral HPLC data, Zhaiwei Lin and Jeremy Disch for experimental contributions, Ken Mattes for HTS analysis, Andy Thomas for helpful suggestions, and Julie Tucker from Global Structural Chemistry for the CDK2-**5** crystal structure.

**Supporting Information Available:** Elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM800343J