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Article

4-(Pyrazol-4-yl)-pyrimidines as Selective Inhibitors of Cyclin-Dependent Kinase 4/6

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Identification and structure-guided optimization of a series of 4-(pyrazol-4-yl)-pyrimidines as selective CDK4/6 inhibitors is reported herein. Several potency and selectivity determinants were established based on the X-ray crystallographic analysis of representative compounds bound to monomeric CDK6. Significant selectivity for CDK4/6 over CDK1 and CDK2 was demonstrated with several compounds in both enzymatic and cellular assays.

Introduction

Cyclin-dependent kinases (CDKs[a]) 4 and 6 are highly homologous proline-dependent serine/threonine kinases that belong to the CDK enzyme family.[1] CDK family members such as CDK1, 2, and 4/6 function as regulators of cell cycle progression and check points, whereas CDK8 and 9 are involved in transcriptional regulation.[2] Each CDK enzyme is activated by binding to a specific cyclin, whose expression is often tied to a particular phase of the cell cycle. The CDK4/6|D-cyclin enzyme complex is responsible for the deactivation of retinoblastoma protein (pRb) via phosphorylation of pRb. This in turn leads to the release of the E2F transcription factor and activation of genes required for G1 phase to S phase transition.[3]

Alteration of the pRb pathway to favor cell proliferation is one of the hallmarks of a transformed cell phenotype and is universally observed in cancers. Loss of pRb function that results in unchecked E2F activity can be achieved either by loss of pRb itself or by aberrations in other parts of the pRb pathway that lead to deactivation of the protein (80% of cancers maintain a functional pRb protein but display genetic alterations elsewhere).[2a] Some examples of the latter include: translocation of D-cyclins in mantle-cell lymphoma and multiple myeloma, amplification of cyclin D1 in squamous cell esophageal cancer and breast cancer, amplifications of CDK4 in liposarcoma, and suppression of p16 in melanoma, nonsmall-cell lung cancer, and pancreatic cancer.[4] In addition to these direct genetic defects, CDK4/6 kinase activity can also be hyperactivated by mitogen pathways with activating mutations of their own.[5] These mutations are expected to increase cell cycle progression via increasing D-cyclin expression. Taken together, many different cancers spanning various tissue origins appear to contain activating aberrations of the CDK4/6 pathway.

On the basis of clear evidence that numerous cancers hyperactivate CDK4/6 kinase activity to achieve unchecked proliferation, suppression of CDK4/6 kinase activity has been proposed as an effective way to treat human neoplasia. Indeed, inhibition of CDK4/6 kinase activity stops the progression of tumors in various in vivo and in vitro models.[6] Furthermore, genetic knockout experiments involving CDK4/6 have demonstrated that the inhibition of these kinases in fibroblast cells was well tolerated due to compensation by CDK1, while CDK1 inhibition led to lethality in all cell systems investigated.[7] This indicates that selective CDK4/6 inhibitors may have a larger therapeutic window as compared to pan-CDK inhibitors.

While there are several pan-CDK inhibitors in clinical trials,[8] a variety of CDK4/6-selective inhibitors are emerging in the literature.[2d,9] Among those, **1** (PD-0332991, Figure 1)[10] is noteworthy, with selectivity achieved over a broad panel of protein kinases including CDK1 and 2, oral efficacy in several xenograft models, and advancement into clinical trials.[11] Recently, we embarked on efforts toward identification of CDK4/6-selective and potent inhibitors. Herein, we describe our structure-based optimization of 4-(pyrazol-4-yl)-pyrimidines (**A**),[12] a hit series identified via high-throughput screening.

Chemistry

The compounds described in this report were prepared via two different coupling reactions: (1) displacement of a sulfone

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[a] Abbreviations: CDK, cyclin-dependent kinase; pRb, retinoblastoma protein; S_NAr, nucleophilic aromatic substitution; dba, dibenzylideneacetone; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; XANTPHOS, 4,5-bis(diphenylphosphino)-9,9′-dimethylzanthene; SEM, 2-(trimethylsilyl)-ethoxymethyl; LDA, lithium diisopropylamide; LHMDS, lithium bis(trimethylsilyl)amide; mCPBA, *meta*-chloroperbenzoic acid; NCS, *N*-chlorosuccinimide; DMF, dimethylformamide; NBS, *N*-bromosuccinimide; DDQ, 2,3-dichloro-5,6-dicyanobenzoquinone; TBAI, tetrabutylammonium iodide; Boc, *t*-butoxycarbonyl; THF, tetrahydrofuran; TFAA, trifluoroacetic anhydride; AIBN, 2,2′-azo bisisobutyronitrile; ATP, adenosine-5′-triphosphate; PSA, polar surface area; SAR, structure–activity relationship; ELISA, enzyme-linked immunosorbent assay; FACS, fluorescence-activated cell sorting; ALK, anaplastic lymphoma kinase; ERK2, extracellular signal-related kinase 2; FGFR-4, fibroblast growth factor receptor-4; GSK 3β, glycogen synthase kinase 3β; JAK1, janus kinase 1; MAPK2, mitogen-activated protein kinase 2; MAPK 5, mitogen-activated protein kinase 5; PDGFRα, platelet-derived growth factor receptor α; PDK1, 3-phosphoinositide dependent kinase 1; PKA, protein kinase A; PKB α, protein kinase B α; SYK, spleen tyrosine kinase; cMET, mesenchymal-epithelial transition factor.

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at the *C*2 position of the pyrimidine core with an amine side chain,(2) palladium-mediated amination reaction of the 2-chloro-pyrimidine (Scheme 1). These reactions were followed by removal of protecting groups where necessary.

The general synthetic routes to **B** and **C** are described in Scheme 2.[13] Acylation of 4-methyl-2-(methylthio)pyrimidine **2** with various esters afforded the ketones **3a−f**. The ketones were then treated with dimethylformamide dimethyl acetal, and the resulting product was condensed with hydrazine to provide the pyrazoles **4a−f**. Subsequent oxidation of **4a−f** gave the sulfones **5a−f**. **5b** was further converted to 2-chloro-pyrimidine **6** upon treatment with sulfuryl chloride in acetic acid at 60 °C. Protection of the pyrazole **6** with a 2-(trimethylsilyl)ethoxymethyl (SEM) group followed by chlorination with *N*-chlorosuccinimide afforded bischloro 4-(pyrazol-4-yl)-pyrimidine **7**.

Exploration of other substitutions on the pyrazole is summarized in Schemes 3 and 4. Regioselective bromination of **4b** and **5b** to yield **8** and **9**, respectively, was disclosed previously.[13] Oxidation of **8** with *m*-chloroperbenzoic acid provided **10**, which was converted to **11** via subsequent Stille reaction. The same Stille reaction conditions were applied to **9** to obtain **12** in 69% yield. 3-Trifluoromethylpyrazole **13**[14] was protected with a *N*,*N*-dimethylsulfamoyl group and installed on the pyrimidine ring following the procedure developed by Strekowski et al.[15] to give **14** (Scheme 4).

Scheme 5 describes a general synthetic route to pyridin-2-ylamines.[10a,16] Displacement of bromine with various piperazine derivatives or 4-(dimethylamino)piperidine was followed by reduction of the nitro group to afford **16−22**. Insertion of a methylene between the pyridine and the piperazine was achieved by following the reaction steps described in Scheme 6. Conversion of 5-methyl-pyridin-2-ylamine **23** to its 2,2,2-trifluoroacetamide and subsequent bromination of the methyl group[17] provided *N*-(5-bromomethyl-pyridin-2-yl)-2,2,2-trifluoro-acetamide, which was then reacted with substituted piperazine derivatives. Methanolysis of the resulting products gave **24** and **25**. A Boc-protected piperidine was installed via Suzuki reaction of **26** and **27**,[18] followed by hydrogenation to give **28** in 42% yield over two steps (Scheme 7). 6-Chloro-pyridazine **29**[19] and 5-bromo-pyrazine **30**[20] were subjected to palladium-catalyzed cross-coupling with benzophenone imine, an ammonia synthon,[21] and subsequently deprotected to yield **31** and **32** (Scheme 8).

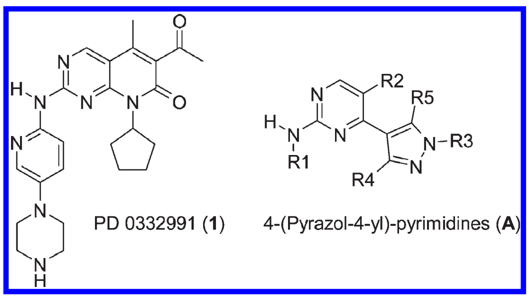
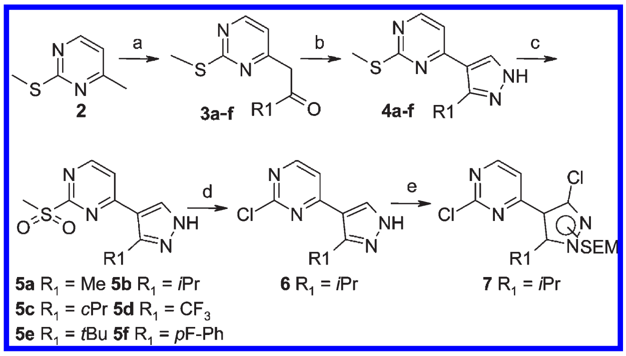


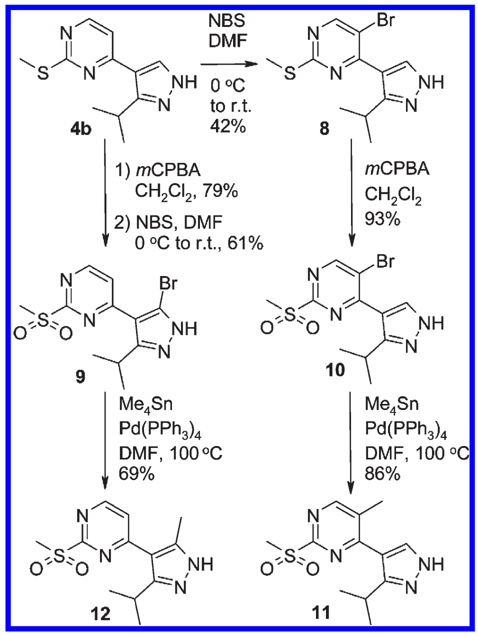
Figure 1. Selective CDK4/6 inhibitor **1** and general structure of 4-(pyrazol-4-yl)-pyrimidines (**A**).

Scheme 2[a]

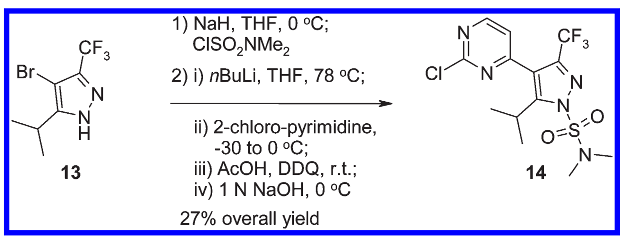


[a] Reagents and conditions: (a) LDA or LHMDS, THF, 0 °C; R_1CO_2Me, 0 °C to room temperature; (b) (i) dimethylformamide dimethyl acetal, (ii) $H_2NNH_2 \cdot H_2O$, MeOH; (c) *m*CPBA, CH_2Cl_2 or oxone, DMF, 90 °C; (d) SO_2Cl_2, AcOH, 60 °C, 43%; (e) (i) Cs_2CO_3, SEMCl, DMF, 73%, (ii) NCS, DMF, 40 °C, 62%.

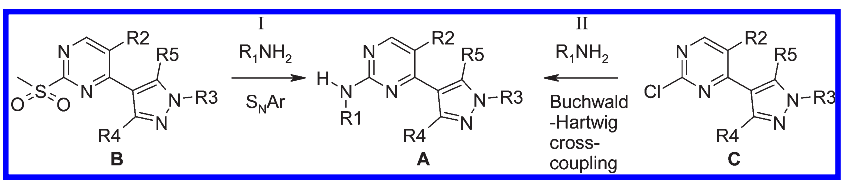
Scheme 3



Scheme 4

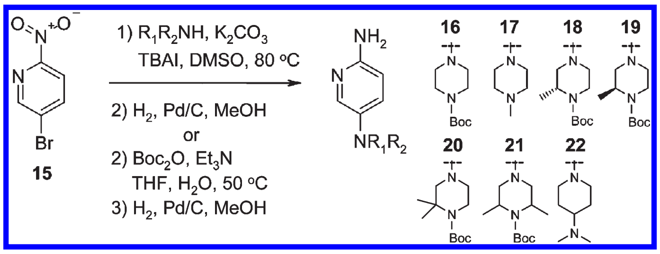


Scheme 1[a]

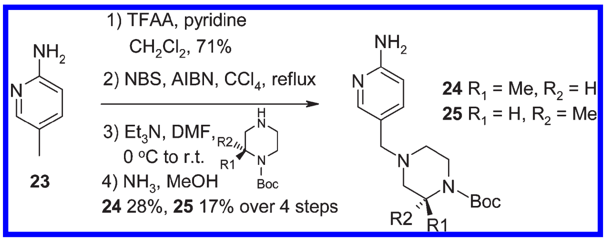


[a] Reagents and conditions: (I) R_1NH_2, heating; (II) R_1NH_2, $Pd_2(dba)_3$, BINAP or XANTPHOS, NaO*t*Bu or Cs_2CO_3, dioxane, heating.

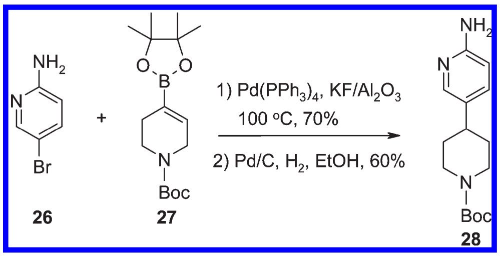
Scheme 5



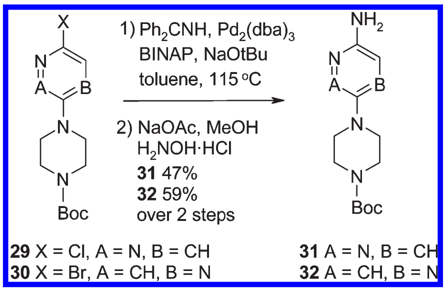
Scheme 6



Scheme 7



Scheme 8

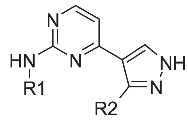


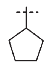
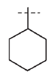
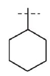
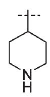
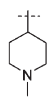
Results and Discussion

High-throughput screening of the Novartis compound collection against the CDK4 enzyme identified a pyrazolyl-pyrimidine derivative **33** as a promising hit for optimization (Table 1). Competition binding experiments confirmed that **33** binds competitively and reversibly to the ATP binding site of CDK4 (data not shown). This compound also demonstrated selectivity against other non-CDK kinases despite the fact that it contains an aminopyrimidine moiety, a common element in many ATP-competitive kinase inhibitors. However, similar activity against CDK1 and 2 alerted us a potential hurdle of achieving selectivity within the CDK family. The low molecular weight (MW 243) and calculated properties (cLogP 2.36, polar surface area (PSA) 66) made compound **33** attractive as a starting point for a medicinal chemistry campaign.

During the early hit-to-lead optimization, the rapid synthesis of the core allowed us to quickly explore the structure−activity relationship (SAR) at the *C*2 position of the pyrimidine as well as substitution on the pyrazole moiety. Substitution on the

Table 1. IC_{50} Values for Compounds in the CDK Enzyme Assays[a,b]



compd	R1	R2	IC_{50} (μM) CDK4/ Cyclin D1	IC_{50} (μM) CDK1/ Cyclin B	IC_{50} (μM) CDK2/ Cyclin A
33		Me	0.936±0.180	2.722±0.150	1.833±0.077
34		Me	0.676±0.005	3.303±0.246	3.478±0.367
35		*i*Pr	0.022±0.000	0.035±0.002	0.039±0.002
36		*i*Pr	0.023±0.001	0.492±0.063	0.828±0.061
37		*i*Pr	0.012±0.001	0.338±0.035	0.517±0.032

[a] See Experimental Section for detailed descriptions of each assay. [b] Results are expressed as the mean ± standard deviation of one to two IC_{50} determinations. For each determination, concentration−inhibition curves were obtained in duplicate and then averaged to afford a single IC_{50} curve with a ≥95% confidence interval.

pyrazole with an isopropyl group (**35**) led to an improvement in the overall potency against CDKs as compared to methyl derivative **34**. Subsequent incorporation of a basic amine into the cyclohexyl ring at the *C*2 side chain, as exemplified by compounds **36** and **37**, resulted in the enhancement in selectivity for CDK4 over CDK1 and CDK2. In addition to slight improvement in CDK4 binding affinity, *N*-methylation of the piperidine also improved the cellular potency (vide infra) of **37** (non-normalized IC_{50} 0.300 μM, normalized IC_{50} 0.640 μM) relative to **36** (non-normalized IC_{50} 0.944 μM, normalized IC_{50} 1.615 μM).[22]

With a potent and modestly selective compound **37** in hand, we next probed the binding mode of 4-(pyrazol-4-yl)-pyrimidines to the enzyme. To this end, an X-ray crystal structure of **37** bound to inactive monomeric CDK6 was obtained (Figure 2).[23] CDK6 shares approximately 70% homology with CDK4 and demonstrates a comparable SAR profile with reduced potency (Table 2). The X-ray structure reveals that **37** binds to the CDK6 ATP binding pocket in a compact conformation in which the pyrimidine and the pyrazole are coplanar and the piperazine moiety packs against the isopropyl group of the pyrazole. Two hydrogen-bonding interactions are indicated in the CDK6 hinge region, one between the pyrimidine *N*1 and the backbone NH of Val101 and the other between the 2-amino NH and the Val101 backbone carbonyl. The pyrazole N and NH form additional polar interactions with the side chains of Lys43 and Asp163, respectively. An edge-to-face aromatic−aromatic contact is observed between the pyrazole and the kinase gatekeeper residue, Phe80. The isopropyl substituent has complementary packing and hydrophobic interactions with Val27,

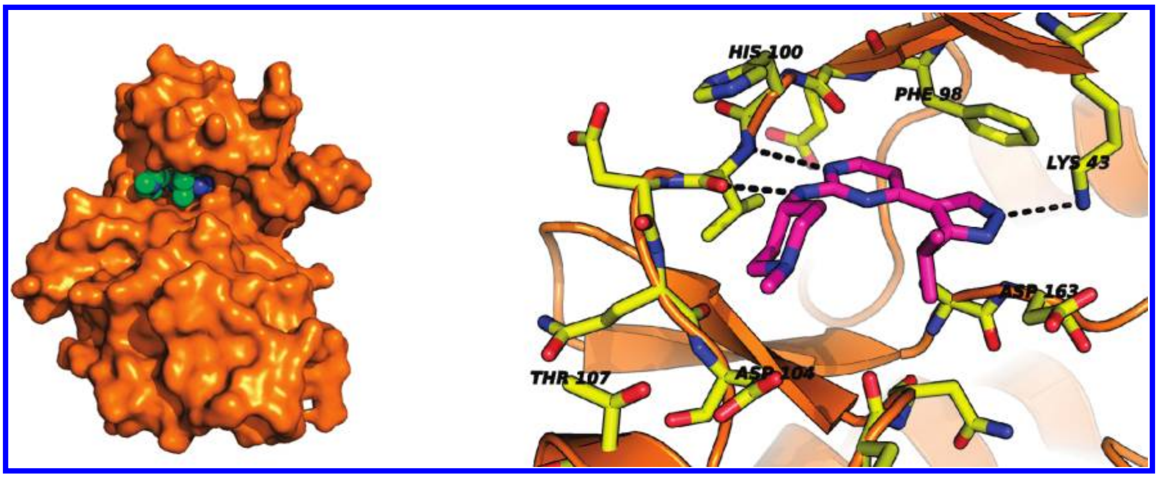
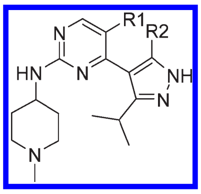


Figure 2. X-ray structure of compound **37** bound to CDK6.

Table 2. IC_{50} Values for Compounds in the CDK Enzyme Assays[a,b]



compd	R1	R2	IC_{50} (μM) CDK4/cyclin D1	CDK6/cyclin D3	CDK1/cyclin B	CDK2/cyclin A
38	Me	H	0.130 ± 0.020	NA[c]	3.028 ± 0.035	4.187 ± 0.251
39	H	Me	1.979 ± 0.549	7.769 ± 0.910	> 15	> 15
40	Br	H	0.540 ± 0.018	0.737 ± 0.058	2.507 ± 0.364	1.965 ± 0.135
41	H	Br	0.076 ± 0.009	0.231 ± 0.018	1.722 ± 0.214	1.037 ± 0.124

[a] See Experimental Section for detailed descriptions of each assay. [b] Results are expressed as the mean ± standard deviation of one to two IC_{50} determinations. For each determination, concentration−inhibition curves were obtained in duplicate and then averaged to afford a single IC_{50} curve with a ≥95% confidence interval. [c] NA: not available

Gly20, Leu152, Ala162, and the hydrophobic residue of the Asn150 side chain. The piperidinyl group sits in a solvent exposed cleft which is mainly hydrophobic but lined with several polar residues at the edge (Thr107, Asp104, Asp102, Gln/Glu149).

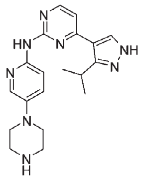
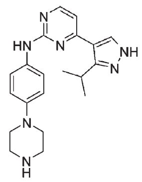
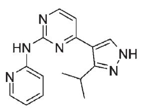
The overlay of X-ray structures of compounds **37** and **1** bound to CDK6 suggests space available for substitution on the pyrimidine and the pyrazole for a tighter binding in the gatekeeper area defined by Phe98 (data not shown). Indeed, exploiting substitutions at *C*5 and *C*6 of the pyridopyrimidine series resulted in a potent and selective compound (**1**).[9f,10a] To probe this region with the 4-(pyrazol-4-yl)-pyrimidines, we prepared compounds which contain methyl or bromine at the *C*5 of the pyrimidine or the *C*3 of the pyrazole. This exercise resulted in reduced potency compared to **37** (Table 2).

Next, we turned our attention to the *C*2 side chain of the pyrimidine to further improve enzyme potency and selectivity. Analysis of reported SAR around **1**[9f,10] and X-ray structure of compound **37** bound to CDK6, as well as molecular modeling studies, suggested that additional selectivity could be obtained by replacing the piperidinylamine with a piperazine-substituted pyridinylamine. Introduction of the pyridine could enhance selectivity over other kinases via interactions with the side-chain of hinge residue His 100. An analysis of the sequence alignment of over 400 kinases (data not shown) indicates that this His residue is conserved in only a few kinases. The distal amine of the piperazine could reach into a more polar and solvent exposed region of CDK4/6, composed of residues Asp96(CDK4)/Asp104(CDK6) and Thr99(CDK4)/Thr107-(CDK6). As previously noted,[24] this “selectivity” pocket has a divergent charge profile due, in part, to the residues Thr99/107 in CDK4/6 and Lys89 in CDK1/2. A basic substituent approaching this space could introduce unfavorable electrostatic repulsion in CDK1/2, thereby boosting selectivity over these closely related kinases.

Compound **42** indeed demonstrated improved selectivity profile over **37**, although CDK4 enzyme potency remained similar (Table 3). The aniline counterpart of **42** proved to be a less selective CDK inhibitor, as shown with compound **43**.[10a] Removal of the piperazine (**44**) resulted in reduction in potency, selectivity, and solubility (**42** 0.9105 mM at pH 6.8, **44** 0.0851 mM at pH 6.8). The piperazine moiety proved to be not only a solubilizing group but also an important selectivity determinant by reason of deleterious interactions unique to CDK1/2. A crystal structure of CDK6 in complex with compound **42** confirmed that the key hydrogen-bonding interactions with the hinge region are maintained, and the core of the pyrazole-pyrimidine scaffold is essentially identical in its interactions (data not shown).

To explore pyrazole substituents, we prepared a small set of closely related analogues (Table 4). Although the selectivity for CDK4 appeared to be retained, any change in size of the substituent R_1 (R_2 = H) diminished the potency for CDK4. This pattern of substitution was also observed in a series of

Table 3. IC_{50} Values for Compounds in the CDK Enzyme Assays[a,b]

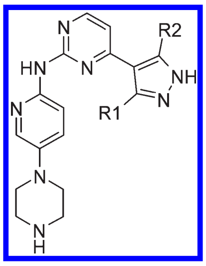
compd	structure	IC_{50} (μM)		
		CDK4/ Cyclin D1	CDK1/ Cyclin B	CDK2/ Cyclin A
42		0.025±0.001	5.576±0.804	6.498±0.980
43		<0.005	0.071±0.009	0.040±0.021
44		0.193±0.008	1.069±0.172	0.672±0.201

[a] See Experimental Section for detailed descriptions of each assay. [b] Results are expressed as the mean ± standard deviation of one to two IC_{50} determinations. For each determination, concentration−inhibition curves were obtained in duplicate and then averaged to afford a single IC_{50} curve with a ≥95% confidence interval.

imidazole pyrimidine amides where isopropyl was found to be optimal for hydrophobic interactions with CDKs.[25] Introduction of chloride atom at R_2 (**50**) led to a modest improvement in the CDK4 inhibitory activity. A crystal structure of compound **50** bound to CDK6 (Figure 3) revealed that the planes of the pyrimidine and the pyrazole are tilted relative to each other, with an interplanar angle of ca 25°. The chlorine substituent of the pyrazole is projected toward the aromatic plane of Phe80, possibly forming a favorable Cl−π interaction.[26] Chlorination of the pyrazole also resulted in improved metabolic stability in rat liver microsomes (hepatic extraction ratio 67% for **42** and 36% for **50**). As seen earlier, 3-isopropyl-5-methyl-pyrazole of **51** led to a reduction in potency in CDK4, suggesting that replacement of a hydrogen with a methyl may interrupt a favorable edge-to-face aromatic−aromatic interaction observed in the compound **42**.

With the pyrazole substituents fixed as R_1 = isopropyl and R_2 = chloride, different heteroaromatic rings and various basic solubilizing groups were applied to the pyrimidine *C*2 side chain in an attempt to further improve selectivity over CDK1 and 2 (Table 5). Pyridazine (**52**) and pyrazine (**53**) were not equivalent to pyridine in terms of CDK4 potency and selectivity. Replacement of a piperazine with a piperidine (**54**) and substitution on the terminal amine of the piperazine (**55** and **56**) was well tolerated; however, no impact on selectivity was seen. Compounds in which steric bulk was introduced around the terminal amine (**57**−**60**) demonstrated only a slight loss in CDK1/2 activity. When the piperazine moiety was further extended into the solvent-exposed region, overall loss of CDK activities was observed, as shown with compounds **61** and **62**. The best potency and selectivity profile was demonstrated with compound **63**, wherein the 4-(dimethylamino)piperidine moiety is speculated to make a favorable polar interaction with Thr107 of CDK4/6 and an unfavorable electrostatic repulsion with Lys89 in CDK1/2. Finally, we tested whether a trifluoromethyl group could act as a surrogate for Cl on the

Table 4. IC_{50} Values for Compounds in the CDK Enzyme Assays[a,b]



compd	R1	R2	IC_{50} (μM) CDK4/ cyclin D1	CDK1/ cyclin B	CDK2/ cyclin A
45	Me	H	0.532 ± 0.001	> 15	> 15
46	CF_3	H	0.037 ± 0.008	5.422 ± 0.175	10.065 ± 1.134
47	*c*Pr	H	0.089 ± 0.003	15.031 ± 3.621	15.634 ± 4.455
48	*t*Bu	H	0.187 ± 0.012	> 15	> 15
49	*p*-F-Ph	H	0.742 ± 0.019	> 15	> 15
50	*i*Pr	Cl	0.011 ± 0.000	6.325 ± 0.549	1.435 ± 0.036
51	*i*Pr	Me	0.274 ± 0.034	> 15	> 15

[a] See Experimental Section for detailed descriptions of each assay. [b] Results are expressed as the mean ± standard deviation of one to two IC_{50} determinations. For each determination, concentration−inhibition curves were obtained in duplicate and then averaged to afford a single IC_{50} curve with a ≥95% confidence interval.

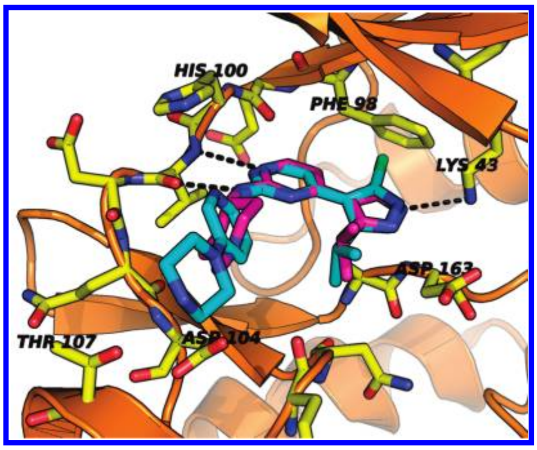
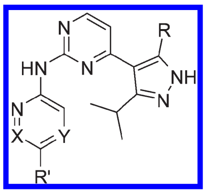


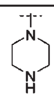
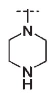
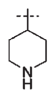
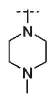
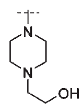
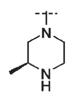
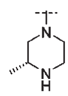
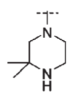
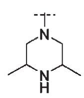
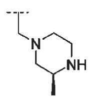
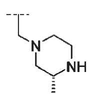
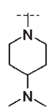
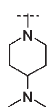
Figure 3. Overlay of compounds **50** (carbon atoms, cyan; chlorine, green) and **37** (carbon atoms, purple) bound to the active site of CDK6 (carbon atoms, yellow).

pyrazole ring. Compound **64** showed an 8-fold decrease of CDK4 potency as compared to **63**; however, this decrease was less dramatic than that observed in the case of compounds **51** vs **50**, which suggests that the CF_3-substituted pyrazole holds some advantage relative to the methyl-substituted in terms of its interaction with CDK4.

Five representive compounds with a range of potency and selectivity for CDK4/6, as well as structural diversity, were chosen for evaluation in a cell-based assay measuring phosphorylation levels of pRb at the Ser780 site using an enzyme-linked immunosorbent assay (ELISA) method (Table 6). Jeko-1, a mantle-cell lymphoma cell line, was selected for use in this assay due to its known translocation and subsequent overexpression of cyclin D1.[4a] Percent inhibition was calculated at each compound concentration by comparing phosphorylation levels against the level seen in the vehicle control, and these inhibitions were used to determine non-normalized IC_{50}s. A separate ELISA assay was conducted to quantitate

Table 5. IC_{50} Values for Compounds in the CDK Enzyme Assays[a,b]



compd	X	Y	R	R'	IC_{50} (μM) CDK4/ Cyclin D1	CDK1/ Cyclin B	CDK2/ Cyclin A
52	N	CH	Cl		0.022±0.001	3.484±0.543	1.546±0.043
53	CH	N	Cl		0.058±0.004	3.165±0.184	1.081±0.244
54	CH	CH	Cl		0.012±0.006	7.020±4.028	2.384±0.569
55	CH	CH	Cl		0.009±0.003	3.073±0.295	0.949±0.053
56	CH	CH	Cl		0.017±0.005	8.799±1.584	2.179±0.086
57	CH	CH	Cl		0.013±0.000	10.961±3.408	1.939±0.028
58	CH	CH	Cl		0.011±0.000	8.258±1.685	1.662±0.076
59	CH	CH	Cl		0.016±0.001	10.256±0.267	2.787±0.044
60	CH	CH	Cl		0.013±0.001	14.072±2.468	3.625±0.879
61	CH	CH	Cl		0.040±0.005	>15	3.862±0.136
62	CH	CH	Cl		0.039±0.012	>15	4.142±0.410
63	CH	CH	Cl		0.010±0.000	>15	5.265±1.921
64	CH	CH	CF_3		0.079±0.000	>15	13.964±3.127

[a] See Experimental Section for detailed descriptions of each assay. [b] Results are expressed as the mean ± standard deviation of one to two IC_{50} determinations. For each determination, concentration−inhibition curves were obtained in duplicate and then averaged to afford a single IC_{50} curve with a ≥95% confidence interval.

total pRb levels at each compound concentration and to compensate for the reduced signal due to the loss of total pRb protein. The numbers incorporating the results from this second ELISA are reported as normalized IC_{50}s.

Table 6. IC_{50} Values for Compounds in the CDK4 Cellular Assays[a,b]

	IC_{50} (μM)	
compd	non-normalized	normalized
42	0.451 ± 0.052	0.591 ± 0.068
50	0.223 ± 0.016	0.467 ± 0.033
54	0.134 ± 0.024	0.383 ± 0.069
63	0.324 ± 0.061	0.365 ± 0.068
64	0.468 ± 0.107	0.557 ± 0.127

[a] See Experimental Section for detailed descriptions of each assay. [b] Results are expressed as the mean ± standard deviation of single IC_{50} determinations. For each determination, concentration−inhibition curves were obtained in triplicate and then averaged to afford a single IC_{50} curve with a ≥95% confidence interval.

The same set of compounds was then tested for their ability to affect individual phases of the cell cycle. To this end, a flow cytometry analysis was performed, where it was expected that selective CDK4 inhibitors would afford an exclusive G1 arrest by inhibition of pRb phosphorylation and subsequent blocking of S phase transition (Figure 4). Jeko-1 cells were treated with compound and then sorted based on their DNA content using fluorescence-activated cell sorting (FACS). In each case, a dose-related increase in G1 arrest was observed with increasing concentrations of compound. Compound **42** demonstrated a clean G1 block at 1 μM. However, at 3.3 μM, we started to see blocks in non-G1 phases of the cell cycle, suggesting that the ca 200-fold CDK4 vs CDK1/2 selectivity seen in enzymatic assays with **42** is insufficient for achieving a comparable cellular selectivity to that of compound **1**.[10] Compounds **50**, **54**, and **63** imposed a G1 block on cells at 0.37 μM, a lower concentration than achieved with **42**, thereby corroborating the data from the pRb phosphorylation studies, which showed lower IC_{50}s for these compounds. Exclusive G1 arrest was maintained over a wider range of concentrations with these compounds as compared to **42**, which we attribute to their improved enzyme selectivity for CDK4. A shift of the clean G1 arrest concentration window to higher concentrations with compound **64** was in agreement with its less potent enzymatic and cellular IC_{50}s. Compounds **63** and **64** exhibited the most sustained G1 arrest among five compounds and were tested further against a selection of serine−threonine and tyrosine kinases and proved to be selective for CDK4/6 over 35 other kinases. Several representative data are shown in Table 7.

Conclusions

A series of substituted 4-(pyrazol-4-yl)-pyrimidines were identified as selective inhibitors of CDK4/6. X-ray crystallographic studies demonstrated a general binding mode of the compounds bound to CDK6 and guided further optimization efforts in the series. Our SAR agreed with that of previously reported CDK inhibitors,[10,25] wherein a substituted pyridinylamine side-chain off of the pyrimidine *C*2 position introduced both potency and selectivity and an isopropyl-substituted pyrazole at *C*3 afforded further improvements in potency. Additional substitution of the pyrazole with chlorine was found to enhance potency and selectivity in both enzymatic and cellular settings. A robust G1 cell cycle block of Jeko-1 cells was demonstrated with several compounds, suggesting that the enzymatic selectivity of CDK4 over CDK1/2 could be translated to a specific cellular phenotype that mirrored the genetic inhibition of CDK4/6. Selective compounds in the cell cycle flow cytometry analyses, **63** and **64**, were evaluated against a panel of protein kinases and exhibited broad selectivity. Further studies on these compounds will be reported in due course.

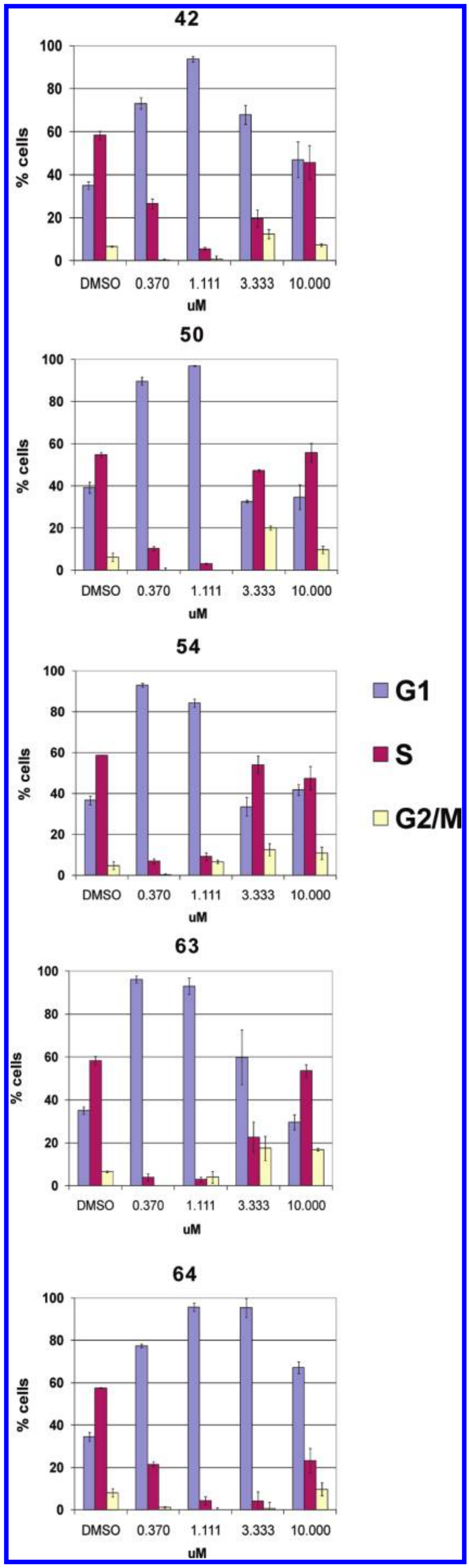


Figure 4. Cell cycle flow cytometry analyses.

Table 7. Selected Inhibitory Activity of Compounds **63** and **64** against a Panel of Kinases[a]

protein kinase	IC_{50} (μM) 63	64
anaplastic lymphoma kinase (ALK)	>10	>10
extracellular signal-related kinase 2 (ERK2)	>10	>10
fibroblast growth factor receptor-4 (FGFR-4)	>10	>10
glycogen synthase kinase (GSK3β)	9.6	>10
janus kinase 1 (JAK1)	>10	>10
mitogen-activated protein kinase 2 (MAPK2)	>10	>10
mitogen-activated protein kinase 5 (MAPK5)	>10	>10
platelet-derived growth factor receptor α (PDGFRα)	>10	>10
3-phosphoinositide dependent kinase 1 (PDK1)	>10	>10
protein kinase A (PKA)	6.8	>10
protein kinase B (PKBα)	>10	>10
spleen tyrosine kinase (SYK)	>10	>10
mesenchymal-epithelial transition factor (cMET)	>10	>10

[a] Results are from single IC_{50} determinations. For each determination, concentration−inhibition curves were obtained in triplicate and then averaged to afford a single IC_{50} curve with a ≥95% confidence interval.

Experimental Section

CDK Enzyme Assays. Human CDK4/cyclin D1 was expressed in Sf21 cells via baculovirus infection. An assay for monitoring CDK4/cyclin D1-catalyzed phosphorylation of pRb at the Ser780 site was performed using TR-FRET in a 384-well format and was used for IC_{50} determination and kinetic analysis. The reaction was carried out in a 30 μL volume containing 0.25 nM CDK4/cyclin D1, 150 nM biotin-pRb (773−924), 3 μM ATP, and 1.3% DMSO (or compound in DMSO) in the assay buffer (50 mM HEPES-Na, pH 7.5; 5 mM $MgCl_2$, 1 mM DTT, 0.02% Tween-20, and 0.05% BSA). Three μM ATP was added last to initiate the reaction. The reaction was quenched with 10 μL of 240 mM EDTA-Na (pH 8.0) after 60 min incubation at 22 °C. The signal was developed by the addition of 40 μL of detection solution containing 40 nM SA-APC, 143 ng/mL antiphospho-pRb (S780) antibody, and 2 nM Eu-W1024 antirabbit IgG antibody in the detection buffer (50 mM HEPES-Na, pH 7.5, 60 mM EDTA-Na, pH 8.0, 0.05% BSA, and 0.1% Triton X-100). After 60 min incubation in the dark, the plate was read on Envision (Perkin-Elmer 2102−0010).

Human CDK6/cyclin D3 was purchased from Carna Biosciences Inc. (catalog no. 04-107). An assay for monitoring CDK6/cyclin D3-catalyzed phosphorylation of pRb at the Ser780 site was performed using TR-FRET in a 384-well format and was used for IC_{50} determination and kinetic analysis. The reaction was carried out in a 30 μL volume containing 0.20 nM CDK6/cyclin D3, 200 nM biotin-pRb (773−924), 3 μM ATP, and 1.3% DMSO (or compound in DMSO) in the assay buffer (50 mM HEPES-Na, pH 7.5; 5 mM $MgCl_2$, 1 mM DTT, 0.02% Tween-20, and 0.05% BSA). Three μM ATP was added last to initiate the reaction. The reaction was quenched with 10 μL of 120 mM EDTA-Na (pH 8.0) after 120 min incubation at 22 °C. The signal was developed by the addition of 40 μL of detection solution containing 40 nM SA-APC, 143 ng/mL antiphospho-pRb (S780) antibody, and 2 nM Eu-W1024 antirabbit IgG antibody in the detection buffer (50 mM HEPES-Na, pH 7.5, 60 mM EDTA-Na, pH 8.0, 0.05% BSA, and 0.1% Triton X-100). After 60 min incubation in the dark, the plate was read on Envision (Perkin-Elmer 2102−0010).

The inhibition of human CDK1/cyclin B and human CDK2/cyclin A (catalog no. 14-450 and 14-448, respectively, Millipore) was monitored using IMAP-FP assays (Molecular Devices, CA) by following the phosphorylation of Tamra-Histone H1-derived peptide (catalog no. R7385, Molecular Devices). The final reaction volume was 20 μL and contained 0.25 nM CDK1/cyclin B or 0.3 nM CDK2/cyclin A, 100 nM Tamra-H1, and 20 μM ATP in 1× reaction buffer (R8139, Molecular Devices). The reactions were run for 2 h at 22 °C. Quenching and detection was carried out following the protocols for the peptide substrate provided by the vendor.

CDK4 Cellular Assays. The pRb expressing Jeko-1 mantle cell lymphoma cell line was grown in complete media consisting of RPMI1640 (Gibco catalog no. 22400-071), 20% FBS (Gibco catalog no. 10082-131), 2 mM L-glutamine (Gibco catalog no. 25030-081), and 1% penicillin/streptomycin (Gibco catalog no. 15140-133). Jeko-1 cells were seeded in Biocoat Cell Environment poly-D-lysine 96-well tissue culture plates (Becton Dickinson catalog no. 356461) at 20000 cells/well in 100 μL final volume of complete media. Cells were allowed to adhere overnight. Compounds were prepared as 10 mM stock solution in DMSO and diluted to a concentration of 110 μM in complete media in a 96-well tissue culture plate and then serially diluted 4-fold, allowing a titration curve of 7 points with a final concentration of 26 nM. Ten μL of the dilution were then transferred to the cell culture plate, resulting in a final concentration range of 10 μM to 2 nM. The incubation was carried out at 37 °C with 5% CO_2. All compounds were tested in triplicates at each concentration. Following compound incubation, the media was removed and the cells were lysed in 35 μL of lysis buffer, consisting of 50 mM Tris.Cl, pH 7.2, 120 mM NaCl, 1 mM EDTA, 6 mM EGTA, 1% NP-40, complete protease inhibitor cocktail (Roche, catalog no. 11836170001) and a protease inhibitor cocktail from Calbiochem (catalog no. 524525). The plates were placed at 4 °C with vigorous shaking for 5 min to lyse the cells. The resulting lysates contained approximately 1 μg/μL of protein.

The 4H1 total pRb antibody from Cell Signaling Technology (catalog no. 9309) was added to clear MaxiSorp plates (Nunc catalog no. 442404) at a concentration of 50 ng per well in 50 μL of Dulbecco's phosphate buffered saline (DPBS) (Gibco catalog no. 14190-144). Plates were incubated overnight at 4 °C with rocking. After a 250 μL wash with TBST (Teknova catalog no. T9501) and blot-drying, 250 μL Superblock (Pierce catalog no. 37535) was added to each well. After shaking for 10 min, the Superblock solution was replaced with fresh Superblock and plates were incubated on a shaker for an additional 50 min. After blocking, 30 μL of Jeko-1 cell lysate, containing approximately 10 μg of total protein, were added to wells in triplicate. Twenty μL of PBS (Gibco catalog no. 10010-023) containing 10% Superblock (Pierce catalog no. 37535) were added to each well for a final reaction volume of 50 μL. Plates were then sealed with Uniseal plate sealers (Whatman catalog no. 7704-0007) and incubated for 2 h at room temperature on a shaker. Plates were washed with 3 × 250 μL TBST. Fifty μL of a 1:1000 dilution of antiphospho Rb Ser^{780} from Cell Signaling (catalog no. 9307) in PBS/10% Superblock were added, and the plate was incubated on a shaker for 1 h at room temperature. For all incubation steps, plates were covered with Uniseal plate sealers. Following incubation, plates were washed with 3 × 250 μL TBST. Next, 50 μL of a 1:2500 dilution of donkey-antirabbit HRP (Promega catalog no. W401B) in PBS/10% Superblock were added, and plates were incubated for 30 min at room temperature on a shaker. Plates were again washed as described above. Finally, 50 μL of Ultra TMB ELISA (Pierce catalog no. 34028) were added and plates incubated, unsealed, 5−15 min in the dark, until blue color developed. After incubation, 50 μL of 2 M sulfuric acid were added to plates to top the reaction, and absorbance was determined on a SpectraMax (Molecular Devices, Sunnydale, CA) within 15 min at 450 nm. All washes were performed using a Bio-Tek plate washer.

The Total Rb ELISA kit (Invitrogen catalog no. KHO0011) was used to determine the levels of total pRb. This kit uses wells precoated with a proprietary total pRb antibody for capture. All reagents listed, with the exception of cell lysate, were included in the kit. The nature of the antibodies used for capture and detection was labeled as proprietary and not disclosed. Ten μg of cell lysate was loaded into the wells and volume adjusted to 50 μL with standard dilution buffer. Plates were sealed with film included in the kit and incubated for 2 h at room temperature on a shaker. Plates are then manually washed three times with 250 μL wash buffer. Fifty μL of proprietary primary antibody (preconjugated to biotin) was added to wells and incubated for 1 h at room temperature on a shaker. Then plates were again washed as noted above. The secondary antibody (HRP preconjugated to Streptavidin) was diluted 1:100 in streptavidin-HRP diluent buffer, and 50 μL was added to each well. Plates were then incubated for 30 min. Afterward, plates were washed four times with buffer as outlined above. Finally, 50 μL of stabilized Chromogen was added per well and plates were incubated for 15 min, at which point, 50 μL of stop solution was added. Plates were then read on a Spectramax at 450 nm.

Upon quantitation of the pRb phosphorylation (p-pRb) levels, % inhibition values were derived for each concentration tested and used to determine 50% inhibitory concentrations (IC_{50}) for a particular compound (non-normalized). The total pRb levels were then used to adjust the p-pRb % inhibition values to account for any loss of signal due to the absence of the pRb protein itself, and the IC_{50} values obtained from the adjusted % inhibitions represent normalized cellular p-pRb IC_{50}.

Fluorescence Activated Cell Sorting (FACS). Analysis of cellular DNA content by propidium iodide (PI) staining was used to determine cells that were in G_0/G_1, S, or G_2/M phase. The media containing Jeko-1 cells was transferred to a fresh V-bottom 96-well polypropylene plate (Nunc catalog no. 249944). Next, cells were spun at 1000*g* for 10 min and the media was gently removed using pipet. Then 100 μL of a hypotonic lysis buffer (0.1% sodium citrate (Sigma catalog no. S-4641), 0.1% Triton X-100 (MP Biomedicals catalog no. 807423), 25 μg/mL PI (MP Biomedicals catalog no. 195458), and 10 μg/mL RNase (Roche catalog no. 1 579 681) were added to the cells, and the whole cocktail was incubated at room temperature in the dark for 1 h. If necessary, cells were stored at this step overnight at 4 °C. Finally, the cells were subjected to DNA content analysis using the BD LSR II System and FACSDiva, version 5.0.1 (BD biosciences, Franklin Lakes, NJ, USA). The data was analyzed using the ModFit LT 3.1.

Crystallography. An equimolar complex of a compound and CDK6 at 5 mg/mL in buffer (25 mM Tris, 300 mM NaCl, 1 mM TCEP, pH 7.5, 20% glycerol) was crystallized using the hanging-drop vapor diffusion method. The well contained 100 mM MES pH 6.0, 25−50 mM NH_4NO_3, and 6−16% PEG3350. Crystals were frozen using glycerol as a cryoprotectant, and data were collected at beamline 17ID of the Argonne Photo Source (Chicago, IL) using an ADSC-Q210 detector. Data were processed using the HKL200 package.[27] Using CDK2 as the start model, structures were solved employing the software suites from CCP4[28] and CNX[29] and deposited to the PDB (PDB ID: 3NUP, 3NUX).

Chemistry. All solvents employed were commercially available "anhydrous" grade, and reagents were used as received unless otherwise noted. A Biotage Initiator Sixty system was used for microwave heating. Flash column chromatography was performed on either an Analogix Intelliflash 280 using Si 50 columns (32−63 μm, 230−400 mesh, 60 Å) or on a Biotage SP1 system (32−63 μm particle size, KP-Sil, 60 Å pore size). Preparative high pressure liquid chromatography (HPLC) was performed using a Waters 2525 pump with 2487 dual wavelength detector and 2767 Sample manager. Columns were Waters C18 OBD 5 μm, either 50 mm × 100 mm Xbridge or 30 mm × 100 mm Sunfire. Systems were run with either a 5−95% or 10−90% ACN/H_2O gradient with either a 0.1% TFA or 0.1% NH_4OH modifier. NMR spectra were recorded on Bruker AV400 (Avance 400 MHz) or AV500 (Avance 500 MHz) instruments. Analytical LC−MS was conducted using an Agilent 1100 series with UV detection at 214 and 254 nm and an electrospray mode (ESI) coupled with a Waters ZQ single quad mass detector. One of two methods was used: method A, 5−95% ACN/H_2O with 5 mM ammonium formate with a 2 min run, 3 μL injection through an Inertisil C8 3 cm × 5 mm × 3 μm; method B, 20−95% ACN/H_2O with 10 mM ammonium formate with a 2 min run, 3 μL injection through an Inertisil C8 3 cm × 5 mm × 3 μm.

All tested compounds were ≥95% purity as determined by an Agilent 1100 HPLC system and one of the following methods, unless explicitly noted. Method 1 (at both 214 and 254 nm): used an Inertisil ODS3 3 μm 3.0 mm × 100 mm C18 column at the flow rate of 1.0 mL/min, with a gradient of 5−95% acetonitrile/water 5 mM ammonia formate over 7.75 min. Method 2 (at both 214 and 254 nm): used an Inertisil ODS3 3 μm 3.0 mm × 100 mm C18 column at the flow rate of 1.0 mL/min, with a gradient of 5−95% acetonitrile/water with 0.1% TFA over 7.75 min. Method 3 (at 214 nm): used an Inertsil ODS3 3 μm 3.0 mmm × 100 mm C18 column at the flow rate of 1.5 mL/min, with a gradient of 10−95% acetonitrile/water with 0.1% TFA over 15 min. Method 4 (at both 215 and 254 nm): used a Nova-Pak 4 μm 3.9 mm × 150 mm C18 column at the flow rate of 2.0 mL/min, with a gradient of 10−90% acetonitrile/water with 0.1% TFA over 5.0 min. Method 5 (at both 214 and 254 nm): used an Inertisil ODS3 100 mm × 3 mm C18 column at the flow rate of 1.0 mL/min, with a gradient of 5−95% acetonitrile/water with 0.1% formic acid over 7.75 min. LC/ESI-MS data were recorded using a Waters LCT Premier mass spectrometer with dual electrospray ionization source and Agilent 1100 liquid chromatograph. The resolution of the MS system was approximately 12000 (fwhm definition). HPLC separation was performed at 1.0 mL/min flow rate with the gradient from 10% to 95% in 2.5 min. Ammonia formate (10 mM) was used as the modifier additive in the Aqueous phase. Sulfadimethoxine (Sigma; protonated molecule *m/z* 311.0814) was used as a reference and acquired through the LockSpray channel every third scan.

3-Methyl-1-(2-methylsulfanyl-pyrimidin-4-yl)-butan-2-one (3b). To a cooled (−20 °C) solution of diisopropylamine (1746 g, 2.0 equiv) in THF (10 L) was added a solution of *n*BuLi in THF (1.6 M, 8 L, 1.5 equiv) dropwise over 3 h. The reaction mixture was warmed to 0 °C and treated with a solution of 4-methyl-2-methylsulfanyl-pyrimidine (**2**, 1211 g, 8.63 mol) in THF (1 L) dropwise. The resulting solution was stirred for 15 min and treated with a solution of isobutyric acid methyl ester (1038 mL, 1.05 equiv) in DMF-THF (5 L, 4:1 = v/v) dropwise. The resulting mixture was warmed to room temperature and stirred overnight. The reaction mixture was treated with 1 N aqueous solution of HCl (17 L) and extracted with *tert*-butyl methyl ether (TBME) (3 × 10 L). The combined organics were washed with water (3 × 5 L), brine (5 L), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (18 kg silica) with hexane/ethylacetate 12:1 gave 993 g (4.66 mol, 54%) of 3-methyl-1-(2-methylsulfanyl-pyrimidin-4-yl)-butan-2-one (**3b**). ^{1}H NMR (600 MHz, DMSO-d_6, a 4:1 mixture of keto- and enol form) δ ppm 13.84 (br s, 0.2 H), 8.54 (d, *J* = 5.06 Hz, 1.6 H), 8.38 (d, *J* = 5.10 Hz, 0.2 H), 7.08 (d, *J* = 5.06 Hz, 1.6 H), 6.85 (d, *J* = 5.10 Hz, 0.2 H), 5.49 (s, 0.2 H), 3.99 (s, 1.6 H), 2.58−2.80 (m, 0.8 H), 2.31−2.56 (m, 3.2 H), 1.13 (d, *J* = 7.00 Hz, 1.6 H), 1.05 (d, *J* = 7.00 Hz, 4.8 H). MS *m/z* 211.3 $(M + H)^+$.

1-Cyclopropyl-2-(2-methylsulfanyl-pyrimidin-4-yl)-ethanone (3c). To a cooled (0 °C) solution of lithium hexamethyldisilazane (1 M, 14.2 mL, 2 equiv) was added neat 4-methyl-2-methylsulfanyl-pyrimidine (**2**, 1 mL, 7.1 mmol), and the resulting mixture was stirred for 5 min and then treated with cyclopropylcarboxylate methyl ester (0.72 mL, 3 equiv). The reaction mixture was stirred at room temperature for 30 min, treated with water (25 mL) and extracted into CH_2Cl_2 (3 × 50 mL). Combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography (EtOAc/heptanes 10 to 60%) gave 1-cyclopropyl-2-(2-methylsulfanyl-pyrimidin-4-yl)-ethanone (**3c**, 1.47 g) in quantitative yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (d, *J* = 5.05 Hz, 1 H), 7.13 (d, *J* = 5.05 Hz, 1 H), 4.05 (s, 2 H), 2.49 (s, 3 H), 2.43 (m, 1 H), 0.92 (m, 4 H). MS *m/z* 209.3 $(M + H)^+$.

1,1,1-Trifluoro-3-(2-methylsulfanyl-pyrimidin-4-yl)-propan-2-one (3d). Prepared from 4-methyl-2-methylsulfanyl-pyrimidine (**2**) and methyltrifluoroacetate following the procedure described for **3c** in 60% yield. MS *m/z* 237.1 $(M + H)^+$.

3,3-Dimethyl-1-(2-methylsulfanyl-pyrimidin-4-yl)-butan-2-one (3e). Prepared from 4-methyl-2-methylsulfanyl-pyrimidine (**2**) and trimethylacetylchloride following the procedure described for **3c** in quantitative yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, J = 5.05 Hz, 1 H), 7.07 (d, J = 5.05 Hz, 1 H), 4.05 (s, 2H), 2.48 (s, 3H), 1.16 (s, 9H). MS m/z 225.3 $(M + H)^+$.

1-(4-Fluoro-phenyl)-2-(2-methylsulfanyl-pyrimidin-4-yl)-ethanone (3f). Prepared from 4-methyl-2-methylsulfanyl-pyrimidine (**2**) and methyl 4-fluorobenzoate following the procedure described for **3c** and used as a crude mixture for the next reaction. MS m/z 263.2 $(M + H)^+$.

4-(3-Methyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (4a). To a cooled (0 °C) solution of lithium hexamethyldisilazane (1 M, 14.2 mL, 2 euiv) was added neat 4-methyl-2-methylsulfanyl-pyrimidine (1 mL, 7.1 mmol), and the resulting mixture was stirred for 5 min and then treated with anhydrous ethyl acetate (10 mL). The reaction mixture was stirred for 30 min at room temperature and concentrated in vacuo. The residue was dissolved in methanol (2 mL) and treated with dimethylformamide dimethylacetal (10 mL). The resulting mixture was heated at 100 °C for 1 h and cooled to room temperature. The mixture was then treated with 55% hydrazine hydrate (2 mL) and stirred for 18 h. The reaction mixture was concentrated in vacuo, and the residue was redissolved in CH_2Cl_2 (50 mL), washed with saturated aqueous sodium bicarbonate (2 × 20 mL), water (2 × 20 mL), and brine (30 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. Column chromatography (EtOAc/heptanes 10 to 60%) gave 4-(3-methyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (**4a**, 126 mg) in 19% yield over three steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13 (broad doublet tautomers, 1 H), 8.47 (d, J = 5.43 Hz, 1 H), 7.39 (d, J = 5.43 Hz, 1 H), 3.31 (s, 3 H), 2.53 (s, 3 H). MS m/z 207.3 $(M + H)^+$.

4-(3-Isopropyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (4b). A mixture of dimethylformamide dimethylacetal (1.15 L, 2.0 equiv) and 3-methyl-1-(2-methylsulfanyl-pyrimidin-4-yl)-butan-2-one (**3b**, 890 g, 4.23 mol) in DMF (1 L) was heated at 90 °C for 2 h. The reaction mixture was then concentrated in vacuo and dried under high vacuum overnight. The residue was triturated with 100 mL of hexane. The solid was collected and dried under high-vacuum to provide 1-dimethylamino-4-methyl-2-(2-methylsulfanyl-pyrimidin-4-yl)-pent-1-en-3-one (583 g) in 52% yield as red crystals. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 8.38 (d, J = 5.23 Hz, 1 H), 7.66 (s, 1 H), 6.99 (d, J = 5.23 Hz, 1 H), 2.92−3.12 (sept, J = 6.80 Hz 1 H), 2.55−2.95 (br s, 6H), 2.42 (s, 3 H), 0.95 (d, J = 6.80 Hz, 6 H). MS m/z 266.2 $(M + H)^+$.

To 1-dimethylamino-4-methyl-2-(2-methylsulfanyl-pyrimidin-4-yl)-pent-1-en-3-one (580 g, 2.18 mol) in a 10 L reactor was added aqueous hydrazine hydrate (24%, 2.5 L, 5.5 equiv) at 0 °C. The resulting yellow suspension was slowly warmed to room temperature and stirred for 1 h. The reaction mixture was extracted EtOAc (3 × 2.5 L). Organics were washed with water (2 × 1 L), brine (0.5 L), dried over $MgSO_4$, filtered, and concentrated to give 4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (**4b**, 511 g) in quantitative yield as red crystals. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 13.03 (br s, 1H), 8.44 (d, J = 5.47 Hz, 1 H), 7.38 (d, J = 5.47 Hz, 1 H), 3.95 (br s, 1 H), 2.48 (s, 3 H), 1.25 (br s, 6 H). MS m/z 235.3 $(M + H)^+$.

4-(3-Cyclopropyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (4c). A mixture of 1-cyclopropyl-2-(2-methylsulfanyl-pyrimidin-4-yl)-ethanone (**3c**, 1.47 g, 7.1 mmol) and dimethylformamide dimethylacetal (10 mL) in methanol (2 mL) was heated at 100 °C for 1.5 h. After cooling to room temperature, the reation mixture was treated with 55% hydrazine hydrate (3 mL) and stirred for 18 h. The mixture was concentrated, and the residue was dissolved in CH_2Cl_2 (50 mL), washed with saturated aqueous sodium bicarbonate (2 × 20 mL), water (2 × 20 mL), and brine (30 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. Column chromatography (EtOAc/heptanes 10−60%) provided 4-(3-cyclopropyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (**4c**, 1.2 g) in 73% yield. MS m/z 233.3 $(M + H)^+$.

2-Methylsulfanyl-4-(3-trifluoromethyl-1*H*-pyrazol-4-yl)-pyrimidine (4d). A mixture of 1,1,1-trifluoro-3-(2-methylsulfanyl-pyrimidin-4-yl)-propan-2-one (**3d**, 1.13 g, 4.8 mmol), dimethylformamide dimethylacetal (2.3 mL, 2 equiv), and acetic acid (600 μL, 2 equiv) in THF (15 mL) was stirred at room temperature for 18 h and treated with 55% hydrazine hydrate (40 mL). After stirring additional 4 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL), washed with saturated aqueous sodium bicarbonate (2 × 20 mL), water (2 × 20 mL), and brine (30 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. Column chromatography (EtOAc/heptanes 10−60%) gave 2-methylsulfanyl-4-(3-trifluoromethyl-*1H*-pyrazol-4-yl)-pyrimidine (**4d**, 450 mg) in 40% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1 H), 8.61 (d, J = 5.18 Hz, 1 H), 7.47 (d, J = 5.18 Hz, 1 H), 2.53 (s, 3H). MS m/z 261.2 $(M + H)^+$.

4-(3-*tert*-Butyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (4e). Prepared from 3,3-dimethyl-1-(2-methylsulfanyl-pyrimidin-4-yl)-butan-2-one (**3e**) following the procedure described for **4c** in 42% yield. MS m/z 249.3 $(M + H)^+$.

4-[3-(4-Fluoro-phenyl)-1*H*-pyrazol-4-yl]-2-methylsulfanyl-pyrimidine (4f). Prepared from 1-(4-fluoro-phenyl)-2-(2-methylsulfanyl-pyrimidin-4-yl)-ethanone (**3f**) following the procedure described for **4c** in 56% yield over three steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.47 (br d tautomers, 1 H), 8.5 (br s tautomer 1, 0.5 H), 8.45 (d, J = 5.31 Hz, 1 H), 8.19 (br s tautomer 2, 0.5 H), 7.56 (br s, 2 H), 7.32 (m, 1 H), 7.25 (m, 1 H), 7.14 (m, 1 H), 2.23 (s, 3 H). MS m/z 287.3 $(M + H)^+$.

2-Methanesulfonyl-4-(3-methyl-1*H*-pyrazol-4-yl)-pyrimidine (5a). To a solution of 4-(3-methyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (**4a**) (110 mg, 0.5 mmol) in DMF (6 mL) was added solid oxone (770 mg, 2.5 equiv), and the resulting mixture was heated at 90 °C for 1 h. After cooling to room temperature, the reaction mixture was treated with water (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). Combined organics were washed with brine, dried over Na_2SO_4, filtered, concentrated, and used for the next reaction without purification. MS m/z 239.3 $(M + H)^+$.

4-(3-Isopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (5b). To a cooled (0 °C) solution of 4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (**4b**, 530 g, 2.26 mol) in CH_2Cl_2 (5 L) was added *m*CPBA (70%, 1.4 kg, 2.5 equiv) in 100 g portions to keep the internal temperature below 10 °C. The suspension was then slowly warmed to room temperature and stirred for another 2 h. The reaction mixture was treated with saturated aqueous $NaHCO_3$ solution (1.1 L), and the phases were separated. The aqueous phase was extracted CH_2Cl_2 (3 × 2 L). The combined organics were washed with water (1 L), brine (0.5 L), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (1.5 kg silica) with hexane/ethylacetate 2:3 gave 375 g (1.4 mol, 62%) of 4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**5b**) as beige crystals. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.23 (br s, 1H), 8.86 (d, J = 5.41 Hz, 1 H), 7.99 (d, J = 5.41 Hz, 1 H), 3.89 (br s, 1 H), 3.40 (s, 3 H), 1.29 (br s, 6 H). MS m/z 267.1 $(M + H)^+$.

4-(3-Cyclopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (5c). Prepared from 4-(3-cyclopropyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (**4c**) following the procedure described for **5a**: MS m/z 265.3 $(M + H)^+$.

2-Methanesulfonyl-4-(3-trifluoromethyl-1*H*-pyrazol-4-yl)-pyrimidine (5d). Prepared from 2-methylsulfanyl-4-(3-trifluoromethyl-1*H*-pyrazol-4-yl)-pyrimidine (**4d**) following the procedure described for **5a** in 71% yield: MS m/z 293.1 $(M + H)^+$.

4-(3-*tert*-Butyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (5e). Prepared from 4-(3-*tert*-butyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (**4e**) following the procedure described for **5a**: MS m/z 281.3 $(M + H)^+$.

4-[3-(4-Fluoro-phenyl)-1*H*-pyrazol-4-yl]-2-methanesulfonyl-pyrimidine (5f). Prepared from 4-[3-(4-fluoro-phenyl)-1*H*-pyrazol-4-yl]-2-methylsulfanyl-pyrimidine (**4f**) following the procedure described for **5a**: MS m/z 319.2 $(M + H)^+$.

2-Chloro-4-(3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidine (6). To a suspension of 4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**5b**, 15.2 g, 56.9 mmol) in acetic acid (15 mL) was added sulfuryl chloride (20 mL, 4.2 equiv), and the resulting mixture was heated at 60 °C for 7 h. After cooling to room temperature, the reaction mixture was concentrated to remove acetic acid. The residue was diluted with EtOAc (300 mL) and washed with water (100 mL), 20% aqueous $Na_2S_2O_3$ (100 mL), and saturated aqueous $NaHCO_3$ (2 × 100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (EtOAc/heptanes 10−60%) gave 2-chloro-4-(3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidine (**6**, 5.5 g) in 43% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (d, J = 6.0 Hz, 1 H), 8.04 (s, 1 H), 7.48 (d, J = 6.0 Hz, 1 H), 3.82 (q, J = 7.0 Hz, 1 H), 1.24 (d, J = 7.0 Hz, 6 H). MS m/z 223.3 $(M + H)^+$.

A Mixture of 2-Chloro-4-[5-chloro-3-isopropyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-pyrimidine and 2-Chloro-4-[3-chloro-5-isopropyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-pyrimidine (7). To a solution of 2-chloro-4-(3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidine (**6**, 4.3 g, 19 mmol) in DMF (28 mL) was added Cs_2CO_3 (13.99 g, 2.2 equiv), and the resulting mixture was stirred for 45 min at room temperature. The reaction mixture was treated with SEMCl (8.0 mL, 2.3 equiv) and stirred at room temperature for 90 min. The reaction mixture was diluted with EtOAc (150 mL), washed with 4% aqueous NaCl (150 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (EtOAc/heptanes 5−30%) gave a mixture of 2-chloro-4-[3-isopropyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-pyrimidine and 2-chloro-4-[5-isopropyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-pyrimidine (5.0 g) in 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ∼9:1 mixture of tautomers, only major peaks analyzed) δ 8.51 (d, J = 5.3 Hz, 1 H), 8.13 (s, 1 H), 7.31 (d, J = 5.3 Hz, 1 H), 5.42 (s, 2 H), 3.64 (t, J = 8.3 Hz, 2 H), 3.61 (m, 1H), 1.37 (d, J = 6.8 Hz, 6 H), 0.94 (t, J = 8.2 Hz, 2 H). 0.00 (s, 9 H). MS m/z 353.3 $(M + H)^+$.

To a solution of a mixture of 2-chloro-4-[3-isopropyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-pyrimidine and 2-chloro-4-[5-isopropyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-pyrimidine (3.1 g, 8.7 mmol) in DMF (15 mL) was added *N*-chlorosuccinicimide (3.53 g, 3.0 equiv), and the resulting mixture was stirred at 40 °C for 3 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (400 mL), washed with 20% aqueous $Na_2S_2O_3$ (80 mL), saturated aqueous $NaHCO_3$ (80 mL), and 4% aqueous NaCl (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (EtOAc/heptanes 5−30%) gave a mixture of 2-chloro-4-[5-chloro-3-isopropyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-pyrimidine and 2-chloro-4-[3-chloro-5-isopropyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-pyrimidine (**7**, 2.1 g) in 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ∼19:1 mixture of tautomers, only major peaks analyzed) δ 8.61 (d, J = 5.3 Hz, 1 H), 7.62 (d, J = 5.3 Hz, 1 H), 5.50 (s, 2 H), 3.68 (m, 2 H), 3.64 (m, 1 H), 1.30 (d, J = 6.9 Hz, 6 H), 0.94 (m, 2 H), 0.01 (s, 9 H). MS m/z 387.4 $(M + H)^+$.

5-Bromo-4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (8). To a solution of 4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (**4b**, 0.50 g, 2.1 mmol) in DMF (5 mL) was added *N*-bromosuccinicimide (0.37 g, 1.0 equiv) at 0 °C. The mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with 20% $Na_2S_2O_3$ aqueous solution. The mixture was stirred for several min and then basified with saturated $NaHCO_3$ aqueous solution. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc/pet. ether) to give 5-bromo-4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (**8**, 0.28 g) as a yellow solid in 42% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1 H), 8.24 (s, 1 H), 3.59−3.75 (m, 1 H), 2.49 (s, 3 H), 1.29 (d, J = 7.03 Hz, 6 H). MS m/z 315.3 $(M + H)^+$.

4-(5-Bromo-3-isopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (9). To a solution of 4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**5b**, 3.0 g, 11 mmol) in DMF (90 mL) was added *N*-bromosuccinimide (2.0 g, 1 equiv) at 0 °C. The mixture was stirred at room temperature for 2 d. The mixture was treated with water and extracted with EtOAc. The organic extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (32% EtOAc/pet. ether) to give 4-(5-bromo-3-isopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**9**, 2.4 g) as a white solid in 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 5.5 Hz, 1 H), 8.09 (d, J = 5.5 Hz, 1 H), 3.81 (m, 1 H), 3.31 (s, 3 H), 1.31 (d, J = 7.0 Hz, 6 H). MS m/z 347.3 $(M + H)^+$.

5-Bromo-4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (10). To a solution of 5-bromo-4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (**8**, 157 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) was added *m*CPBA (336 mg, 77%, 0.54 mmol) 0 °C. The mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with 20% $Na_2S_2O_3$ aqueous solution. The mixture was stirred for several minutes and then basified with saturated $NaHCO_3$ aqueous solution. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc:heptane = 10:90 to 100:0) to give 5-bromo-4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**10**, 160 mg) as a light-yellow solid in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1 H), 8.55 (s, 1 H), 3.86 (ddd, J = 13.68, 7.03, 6.90 Hz, 1 H), 3.37 (s, 3 H), 1.42 (d, J = 7.03 Hz, 6 H). MS m/z 346.8 $(M + H)^+$.

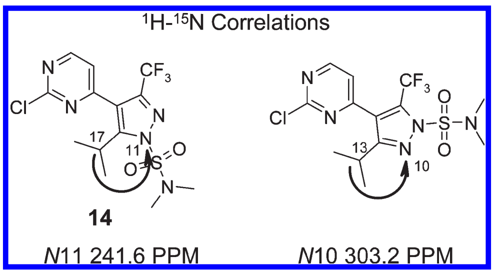
4-(3-Isopropyl-1*H*-pyrazol-4-yl)-5-methyl-2-methylsulfonyl-pyrimidine (11). To a degassed solution of 5-bromo-4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (**10**, 100 mg, 0.29 mmol) and $Pd(PPh_3)_4$ (66.9 mg, 0.058 mmol) in DMF (2 mL) was added tetramethyltin (155 mg, 0.87 mmol) by syringe at room temperature. The mixture was heated at 100 °C for 16 h. After cooling to room temperature, the mixture was filtered through a pad of Celite and rinsed with CH_2Cl_2. The filtrate was washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography ($MeOH:CH_2Cl_2$ = 1:99 to 8:92) to give 4-(3-isopropyl-1*H*-pyrazol-4-yl)-5-methyl-2-methylsulfonyl-pyrimidine (**11**, 70 mg) as a white solid in 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1 H), 7.94 (s, 1 H), 3.81 (q, J = 7.07, 1 H), 3.33 (s, 3 H), 2.54 (s, 3 H), 1.37 (d, J = 7.07 Hz, 6 H). MS m/z 281.3 $(M + H)^+$.

4-(3-Isopropyl-1*H*-pyrazol-4-yl)-5-methyl-2-methylsulfonyl-pyrimidine (12). To a degassed solution of 5-bromo-4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methylsulfonyl-pyrimidine (**9**, 100 mg, 0.29 mmol) and $Pd(PPh_3)_4$ (66.9 mg, 0.058 mmol) in DMF (2 mL) was added tetramethyltin (0.11 mL, 0.78 mmol) by syringe at room temperature. The mixture was heated at 100 °C for 16 h. After cooling to room temperature, the mixture was filtered through a pad of Celite and rinsed with EtOAc. The filtrate was washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc:heptane = 10:90 to 100:0) to give 4-(3-isopropyl-1*H*-pyrazol-4-yl)-5-methyl-2-methylsulfonyl-pyrimidine as a light-yellow solid (**12**, 56 mg) in 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 5.05 Hz, 1 H), 7.55 (d, J = 5.05 Hz, 1 H), 3.69 (ddd, J = 13.77, 7.07, 6.96 Hz 1 H), 3.39 (s, 3 H), 2.58 (s, 3 H), 1.39 (d, J = 7.07 Hz, 6 H). MS m/z 281.1 $(M + H)^+$.

4-(2-Chloro-pyrimidin-4-yl)-5-isopropyl-3-trifluoromethyl-pyrazole-1-sulfonic Acid Dimethylamide (14). To a cooled (0 °C) solution of 4-bromo-5-isopropyl-3-trifluoromethyl-1*H*-pyrazole (**13**, 1.52 g, 5.91 mmol) in THF (40 mL) was added NaH (60%, 0.478 g, 4.0 equiv) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was treated with *N*,*N*-dimethylsulfamoyl chloride (1.2 mL, 3.9 equiv) and stirred at room temperature for 20 h. The reaction mixture was diluted with EtOAc

(150 mL), washed with saturated aqueous NaCl (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (EtOAc/heptanes 0 to 8%) gave a mixture of 4-bromo-5-isopropyl-3-trifluoromethyl-pyrazole-1-sulfonic acid dimethylamide and 4-bromo-3-isopropyl-5-trifluoromethyl-pyrazole-1-sulfonic acid dimethylamide (1.04 g) in 48% yield: MS *m*/*z* 366.0 $(M + H)^+$.

A solution of a mixture of 4-bromo-5-isopropyl-3-trifluoromethyl-pyrazole-1-sulfonic acid dimethylamide and 4-bromo-3-isopropyl-5-trifluoromethyl-pyrazole-1-sulfonic acid dimethylamide (1.04 g, 2.84 mmol) in THF (10 mL) was added to a cooled (−78 °C) solution of *n*BuLi (2.5 M, 1.5 mL, 1.3 equiv) in THF (5 mL) over 5 min. The resulting mixture was treated with a suspension of 2-chloropyrimidine (0.348 g, 1.07 equiv) in THF (2 mL) quickly and stirred at −30 °C for 40 min and 0 °C for 20 min. The reaction mixture was quenched with a solution of acetic acid (0.17 mL, 1.04 equiv) and water (0.02 mL, 0.39 equiv) in THF (0.5 mL) and treated with DDQ (0.681 g, 1.05 equiv). The resulting mixture was stirred at room temperature for 5 min, cooled to 0 °C, treated with a cold aqueous solution of NaOH (1 N, 3.2 mL, 1.1 equiv), and stirred at 0 °C for 5 min. The reaction mixture was diluted with EtOAc (150 mL), washed with saturated aqueous $NaHCO_3$ (70 mL) and brine (70 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (EtOAc/heptanes 3 to 20%) gave 4-(2-chloro-pyrimidin-4-yl)-5-isopropyl-3-trifluoromethyl-pyrazole-1-sulfonic acid dimethylamide (**14**, 0.686 g) in 57% yield and 4-(2-chloro-pyrimidin-4-yl)-3-isopropyl-5-trifluoromethyl-pyrazole-1-sulfonic acid dimethylamide (0.093 mg) in 8% yield. ^{1}H NMR (400 MHz, CD_3OD, **14** only) δ 8.78 (d, *J* = 5.0 Hz, 1 H), 7.50 (d, *J* = 5.0 Hz, 1 H), 3.78 (m, 1 H), 3.19 (s, 6 H), 1.24 (d, *J* = 7.2 Hz, 6 H). MS *m*/*z* 398.1 $(M + H)^+$. The structure was determined by 2D NMR analysis including HSQC and HMBC.



5-(4-Methyl-piperazin-1-yl)-pyridin-2-ylamine (17). To a solution of 5-bromo-2-nitro-pyridine (**15**, 15.0 g, 73.9 mmol) in DMSO (150 mL) were added 1-methyl-piperazine (12.7 g, 126.1 mmol), tetrabutylammonium iodide (1.6 g, 4.3 mmol), and potassium carbonate (15.3 g, 110.7 mmol). The reaction mixture was heated at 80 °C for 5 h. The reaction mixture was poured into ice−water and then extracted with EtOAc. The combined extracts were washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (1:9 methanol/chloroform) gave 1-methyl-4-(6-nitro-pyridin-3-yl)-piperazine (16.2 g, 98.6%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, *J*=4.0 Hz, 1 H), 8.14 (d, *J*= 8.0 Hz, 1 H), 7.47 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.48 (t, *J* = 4.0 Hz, 4 H), 2.43 (t, *J* = 4.0 Hz, 4 H), 2.20 (s, 3 H). MS *m*/*z* 222.9 $(M + H)^+$.

A solution of 1-methyl-4-(6-nitro-pyridin-3-yl)-piperazine (2.0 g, 9.0 mmol) in methanol (100 mL) was hydrogenated in the presence of 10% Pd/C (0.2 g) using an H_2 balloon. After 16 h, the reaction mixture was filtered through a pad of Celite and rinsed with methanol (2 × 15 mL). The filtrate was concentrated and purified by column chromatography (1:9 methanol/chloroform) to afford the title compound (**17**, 1.5 g, 87%) as a solid. ^{1}H NMR (400 MHz, D_2O) δ 7.64 (dd, *J* = 9.5, 2.8 Hz, 1 H), 7.40 (d, *J* = 2.8 Hz, 1 H), 6.83 (d, *J* = 9.5 Hz, 1 H), 3.50 (br s, 4 H), 3.11−3.05 (m, 4 H), 2.82 (s, 3 H). MS *m*/*z* 192.9 $(M + H)^+$.

(*R*)-4-(6-Amino-pyridin-3-yl)-2-methyl-piperazine-1-carboxylic Acid *tert*-Butyl Ester (18). To a solution of 5-bromo-2-nitropyridine (**15**, 4.0 g, 19.7 mmol) in DMSO (40 mL) were added *R*-(−)-2-methyl-piperazine (3.0 g, 29.8 mmol), tetrabutylammonium iodide (0.42 g, 1.2 mmol), and potassium carbonate (4.1 g, 29.7 mmol). The reaction mixture was heated at 80 °C for 16 h. The reaction mixture was poured into ice−water (150 mL) and then extracted with chloroform. The extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography (1:9 methanol/chloroform) gave (*R*)-3-methyl-1-(6-nitro-pyridin-3-yl)-piperazine (4.3 g, 98%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 9.2 Hz, 1 H), 8.13 (d, *J* = 3.1 Hz, 1 H), 7.20 (dd, *J* = 9.2, 3.1 Hz, 1 H), 3.78−3.74 (m, 2 H), 3.15 (m, 1 H), 3.04−3.00 (m, 3 H), 2.68 (m, 1 H), 1.19 (d, *J* = 6.3 Hz, 3 H). MS *m*/*z* 222.8 $(M + H)^+$.

To a solution of (*R*)-3-methyl-1-(6-nitro-pyridin-3-yl)-piperazine (2.4 g, 10.8 mmol) in CH_2Cl_2 (30 mL) were added di-*tert*-butyl dicarbonate (2.8 g, 12.9 mmol) and triethylamine (3.0 mL, 21.6 mmol). The reaction mixture was heated to reflux for 4 h and concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL). The solution was washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (1:9 methanol/chloroform) gave (*R*)-2-methyl-4-(6-nitro-pyridin-3-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (2.5 g, 71.8%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 12.4 Hz, 1 H), 8.10 (d, *J* = 4.0 Hz, 1 H), 7.16 (dd, *J* = 12.4 Hz, 4.0 Hz, 1 H), 4.40 (br s, 1 H), 3.99 (m, 1 H), 3.75 (m, 1 H), 3.63 (m, 1 H), 3.43−3.34 (m, 2 H), 3.25 (m, 1 H), 1.49 (s, 9 H), 1.25 (d, *J* = 4.0 Hz, 3 H). MS *m*/*z* 323.0 $(M + H)^+$.

A solution of (*R*)-2-methyl-4-(6-nitro-pyridin-3-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (2.5 g, 7.7 mmol) in methanol (100 mL) was hydrogenated in the presence of 10% Pd/C (0.2 g) using an H_2 balloon. After 16 h, the reaction mixture was filtered through a pad of Celite and rinsed with methanol (2 × 15 mL). The filtrate was concentrated and purified by column chromatography (1:9 methanol/chloroform) to afford the title compound (**18**, 1.86 g, 82%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (d, *J* = 2.8 Hz, 1 H), 7.14 (dd, *J* = 8.8, 2.9 Hz, 1 H), 6.39 (d, *J* = 8.8 Hz, 1 H), 4.16 (br s, 1 H), 3.76 (m, 1 H), 3.23 (m, 1 H), 3.13−3.06 (m, 2 H), 2.60 (m, 1 H), 2.42 (m, 1 H); 1.40 (s, 9 H) 1.21 (d, *J* = 6.7 Hz, 3 H). MS *m*/*z* 293.5$(M + H)^+$.

(*S*)-4-(6-Amino-pyridin-3-yl)-2-methyl-piperazine-1-carboxylic Acid *tert*-Butyl Ester (19). Prepared from *S*-(+)-2-methyl-piperazine following the procedure for **18** in 50% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (d, *J* = 2.8 Hz, 1 H), 7.14 (dd, *J* = 8.8, 2.9 Hz, 1 H), 6.39 (d, *J* = 8.8 Hz, 1 H), 4.16 (br s, 1 H), 3.76 (m, 1 H), 3.23 (m, 1 H), 3.13−3.06 (m, 2 H), 2.60 (m, 1 H), 2.42 (m, 1 H); 1.40 (s, 9 H) 1.21 (d, *J* = 6.7 Hz, 3 H). MS *m*/*z* 293.0 $(M + H)^+$.

4-(6-Amino-pyridin-3-yl)-2,2-dimethyl-piperazine-1-carboxylic Acid *tert*-Butyl Ester (20). Prepared from 2,2-dimethyl-piperazine following the procedure for **18** in 51% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, *J* = 3.0 Hz, 1 H), 7.09 (dd, *J* = 8.8, 3.0 Hz, 1 H), 6.39 (d, *J* = 8.8 Hz, 1 H), 5.32 (br s, 2 H), 3.52−3.49 (m, 2 H), 3.01−2.98 (m, 2 H), 2.89 (s, 2 H), 1.40 (s, 9 H), 1.34 (s, 6 H). MS *m*/*z* 307.0 $(M + H)^+$.

4-(6-Amino-pyridin-3-yl)-2,6-dimethyl-piperazine-1-carboxylic Acid *tert*-Butyl Ester (21). Prepared from 2,6-dimethyl-piperazine following the procedure for **18** in 54% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 2.7 Hz, 1 H), 7.17 (dd, *J* = 8.7, 2.7 Hz, 1 H), 6.50 (d, *J* = 8.7 Hz, 1 H), 4.24−4.21 (m, 4 H), 3.10 (d, *J* = 11.6 Hz, 2 H), 2.81 (dd, *J* = 11.6, 4.2 Hz, 2 H), 1.50 (s, 9 H), 1.37 (d, *J* = 6.8 Hz, 6 H). MS *m*/*z* 307.0 $(M + H)^+$.

***N**4*,*N**4*-Dimethyl-3,4,5,6-tetrahydro-2*H*-[1,3′]bipyridinyl-4,6′-diamine (22).** To a solution of 5-bromo-2-nitropyridine (**15**, 5.10 g, 24.9 mmol) in MeCN (60 mL) were added 4-dimethylamino piperidine (3.64 g, 1.14 equiv) and *i*Pr_2NEt (4.75 mL, 1.09 equiv), and the resulting mixture was heated to reflux for 20 h. The reaction mixture was cooled to room temparature and concentrated.

Dimethyl-(6′-nitro-3,4,5,6-tetrahydro-2*H*-[1,3′]bipyridinyl-4-yl)-amine (4.89 g) was obtained by trituration in MeCN in 79% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (d, *J* = 6.0 Hz, 1 H), 8.21 (s, 1 H), 7.56 (dd, *J* = 9.3, 3.0 Hz, 1 H), 4.29 (dd, *J* = 16, 2.5 Hz, 2 H), 3.51 (m, 1 H), 3.12 (m, 2 H), 2.91 (s, 6 H), 2.13−2.37 (m, 2 H), 1.82 (dd, *J* = 12, 4.1 Hz, 2 H). MS *m*/*z* 251.2 $(M + H)^+$.

A mixture of dimethyl-(6′-nitro-3,4,5,6-tetrahydro-2*H*-[1,3′]-bipyridinyl-4-yl)-amine (3.44 g, 13.6 mmol) and 10% Pd/C (333 mg) in MeOH−H_2O (80 mL, v/v = 1:1) was stirred under H_2 (1 atm) for 24 h. The reaction mixture was filtered through a pad of Celite (rinsed with MeOH) and concentrated in vacuo. Trituration of the residue in MeCN gave *N**4*,*N**4*-dimethyl-3,4,5,6-tetrahydro-2*H*-[1,3′]bipyridinyl-4,6′-diamine (**22**, 2.554 g) in 85% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (d, *J* = 2.8 Hz, 1 H), 7.40 (dd, *J* = 9.1, 2.9 Hz, 1 H), 6.64 (d, *J* = 9.0 Hz, 1 H), 3.56 (dd, *J* = 10.3, 2.1 Hz, 2 H), 3.23 (m, 1 H), 2.87 (s, 6 H), 2.74 (m, 2 H), 2.17 (m, 2 H), 1.86 (m, 2 H). MS *m*/*z* 221.3 $(M + H)^+$.

(*S*)-4-(6-Amino-pyridin-3-ylmethyl)-2-methyl-piperazine-1-carboxylic Acid *tert*-Butyl Ester (24). Prepared following the procedure described for **25** (see below), substituting (*R*)-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester for (*S*)-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester in 28% yield. ^{1}H NMR (400 MHz, DMSO) δ 7.75 (s, 1 H), 7.27 (d, *J* = 8.4 Hz, 1 H), 6.39 (d, *J* = 8.4 Hz, 1 H), 5.80 (s, 2 H), 4.04 (br s, 1 H), 3.65 (m, 1 H), 3.29 (d, *J* = 13.0 Hz, 1 H), 3.18 (d, *J* = 13.0 Hz, 1 H), 2.93 (m, 1 H), 2.71 (m, 1 H), 2.51 (m, 1 H), 1.94 (m, 1 H), 1.81 (m, 1 H), 1.38 (s, 9 H), 1.17 (d, *J* = 7.3 Hz, 3 H). MS *m*/*z* 307.2 $(M + H)^+$.

(*R*)-4-(6-Amino-pyridin-3-ylmethyl)-2-methyl-piperazine-1-carboxylic Acid *tert*-Butyl Ester (25). To a cooled (0 °C) solution of 2-amino-5-methylpyridine (**23**, 25.0 g, 231.4 mmol) in CH_2Cl_2 (250 mL) were added pyridine (181.0 mL) and trifluoroacetic anhydride (35.7 mL, 254.6 mmol). The reaction mixture was stirred for 2 h, quenched with water, and extracted with CH_2Cl_2. The extract was washed with citric acid solution, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (3:7 EtOAc/pet. ether) gave 2,2,2-trifluoro-*N*-(5-methyl-pyridin-2-yl)-acetamide (37.0 g, 78%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (br s, 1 H), 8.17 (s, 1 H), 8.08 (d, *J* = 8.4 Hz, 1 H), 7.62 (dd, *J* = 8.4 Hz, 1 H), 2.53 (s, 3 H). MS *m*/*z* 204.7 $(M + H)^+$.

To a solution of 2,2,2-trifluoro-*N*-(5-methyl-pyridin-2-yl)-acetamide (37.0 g, 181.2 mmol) in carbon tetrachloride (500 mL) were added *N*-bromosuccinicimide (31.9 g, 179.4 mmol) and AIBN (3.27 g, 19.9 mmol). The reaction mixture was heated to reflux for 4 h. After cooling to room temperature, the mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give the crude bromide (50.0 g, ca 98%), which was used for the next step without further purification.

To a solution of the crude bromide (2.0 g, 10 mmol) in dimethylformamide (40 mL) were added (*R*)-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (4.7 g, 16.7 mmol) and triethylamine (1.4 mL, 10 mmol) at 0 °C. The reaction mixture was stirred for 36 h. The mixture was diluted with water (150 mL) and extracted with EtOAc (50 mL × 3). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (1:10 EtOAc/petroleum ether) to provide (*R*)-2-methyl-4-[6-(2,2,2-trifluoroacetylamino)-pyridin-3-ylmethyl]-piperazine-1-carboxylic acid *tert*-butyl ester (1.6 g, 40%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (br s, 1 H), 8.29 (d, *J* = 1.8 Hz, 1 H), 8.16 (d, *J* = 8.5 Hz, 1 H), 7.81 (dd, *J* = 8.5, 1.8 Hz, 1 H), 4.21 (br s, 1 H), 3.83 (m, 1 H), 3.55 (d, *J* = 13.6 Hz, 1 H), 3.42 (d, *J* = 13.6 Hz, 1 H), 3.11 (m, 1 H), 2.74 (d, *J* = 10.6 Hz, 1 H), 2.55 (d, *J* = 11.1 Hz, 1 H), 2.18 (dd, *J* = 11.1, 3.9 Hz, 1 H), 2.06 (m, 1 H), 1.48 (s, 9 H), 1.19 (d, *J* = 8.0 Hz, 3 H). MS *m*/*z* 403.2 $(M + H)^+$.

To a solution of ammonia in MeOH (ca 7 N, 150 mL) was added (*R*)-2-methyl-4-[6-(2,2,2-trifluoroacetylamino)-pyridin-3-ylmethyl]-piperazine-1-carboxylic acid *tert*-butyl ester (1.6 g, 4.0 mmol). The mixture was stirred for 24 h and concentrated under reduced pressure. The residue was purified by column chromatography (1:100 MeOH/chloroform) to give (*R*)-4-(6-amino-pyridin-3-ylmethyl)-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (**25**, 0.72 g, 56%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (s, 1 H), 7.27 (d, *J* = 8.4 Hz, 1 H), 6.39 (d, *J* = 8.4 Hz, 1 H), 5.80 (s, 2 H), 4.04 (br s, 1 H), 3.65 (m, 1 H), 3.29 (d, *J* = 13.0 Hz, 1 H), 3.18 (d, *J* = 13.0 Hz, 1 H), 2.93 (m, 1 H), 2.71 (m, 1 H), 2.51 (m, 1 H), 1.94 (m, 1 H), 1.81 (m, 1 H), 1.38 (s, 9 H), 1.17 (d, *J* = 7.3 Hz, 3 H). MS *m*/*z* 307.2 $(M + H)^+$.

6-Amino-3′,4′,5′,6′-tetrahydro-2′*H*-[3,4′]bipyridinyl-1′-carboxylic Acid *tert*-Butyl Ester (28). To a mixture of 5-bromo-2-amino-pyridine (**26**, 0.67 g, 3.9 mmol) and 4-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (**27**, 1.20 g, 3.9 mmol) were added $Pd(PPh_3)_4$ (0.45 g, 0.39 mmol) and KF/Al_2O_3 (3.6 g). The mixture was degassed for 0.5 h and then heated at 100 °C for 2 h. The reaction mixture was diluted with EtOAc (100 mL), filtered through a pad of Celite, and the filter cake was rinsed with EtOAc (2 × 50 mL). The combined filterates were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (1:2 EtOAc/petroleum ether) provided 6-nitro-3′,6′-dihydro-2′*H*-[3,4′]bipyridinyl-1′-carboxylic acid *tert*-butyl ester (0.75 g, 70%) as a brownish solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, *J* = 2.4 Hz, 1 H), 7.48 (dd, *J* = 8.7, 2.4 Hz, 1 H), 6.41 (d, *J* = 8.7 Hz, 1 H), 5.98 (s, 1 H), 5.93 (br s, 2 H), 3.94 (br s, 2 H), 3.51−3.48 (m, 2 H), 2.37 (br s, 2 H), 1.41 (s, 9 H). MS *m*/*z* 276.2 $(M + H)^+$.

A solution of 6-nitro-3′,6′-dihydro-2′*H*-[3,4′]bipyridinyl-1′-carboxylic acid *tert*-butyl ester (0.75 g, 2.7 mmol) in EtOH (20 mL) was hydrogenated in the presence of 10% Pd/C (0.2 g) using an H_2 balloon. After 16 h, the reaction mixture was filtered through a pad of Celite and rinsed with EtOH (2 × 10 mL). The filtrate was concentrated and purified by column chromatography to give 6-amino-3′,4′,5′,6′-tetrahydro-2′*H*-[3,4′]bipyridinyl-1′-carboxylic acid *tert*-butyl ester (**28**, 0.45 g, 60%) as a solid. ^{1}H NMR (400 MHz, MeOD) δ 7.76 (d, *J* = 2.3 Hz, 1 H), 7.38 (dd, *J* = 8.6, 2.3 Hz, 1 H), 6.56 (d, *J* = 8.6 Hz, 1 H), 4.21−4.18 (m, 2 H), 2.84 (br s, 2 H), 2.60 (m, 1 H), 1.78−1.75 (m, 2 H), 1.58−1.57(m, 2 H), 1.48 (s, 9 H). MS *m*/*z* 278.2 $(M + H)^+$.

4-(6-Amino-pyridazin-3-yl)-piperazine-1-carboxylic Acid *tert*-Butyl Ester (31). To a solution of 4-(6-chloro-pyridazin-3-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (**29**, 2.0 g, 6.7 mmol) in toluene (30 mL) were added benzophenone imine (1.3 g, 7.3 mmol), $Pd_2(dba)_3$ (0.18 g, 0.2 mmol), BINAP (0.37 g, 0.6 mmol), and sodium *tert*-butoxide (0.9 g, 0.9 mmol). The reaction mixture was degassed for 0.5 h and then heated at 115 °C for 14 h. The mixture was cooled to room temperature, diluted with water (200 mL), and extracted with EtOAc (200 mL × 3). The extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (3:7 EtOAc/petroleum ether) to afford 4-[6-(benzhydrylidene-amino)-pyridazin-3-yl]-piperazine-1-carboxylic acid *tert*-butyl ester (1.5 g, 51%) as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.76 (m, 2 H), 7.36−7.18 (m, 8 H), 6.82 (d, *J* = 9.5 Hz, 1 H), 6.73 (d, *J* = 9.5 Hz, 1 H), 3.53 (br s, 8 H), 1.49 (s, 9 H). MS *m*/*z* 444.2 $(M + H)^+$.

To a solution of 4-[6-(benzhydrylidene-amino)-pyridazin-3-yl]-piperazine-1-carboxylic acid *tert*-butyl ester (1.5 g, 3.4 mmol) in MeOH (14 mL) were added sodium acetate (0.56 g, 6.8 mmol) and hydroxyamine hydrochloride (0.43 g, 6.1 mmol). The reaction mixture was stirred for 0.5 h and then concentrated in vacuo. The residue was purified by column chromatography (1:9 MeOH/chloroform) to give 4-(6-amino-pyridazin-3-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (**31**, 0.87 g, 92%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD) δ 7.30 (d, *J* = 9.7 Hz, 1 H), 6.97 (dd, *J* = 9.7, 2.1 Hz, 1 H), 3.53−3.52 (m, 4 H), 3.37−3.35 (m, 4 H), 1.47 (s, 9 H). MS *m*/*z* 280.2 $(M + H)^+$.

5′-Amino-2,3,5,6-tetrahydro-[1,2′]bipyrazinyl-4-carboxylic Acid *tert*-Butyl Ester (32). Prepared from 5′-bromo-2,3,5,6-tetrahydro-[1,2′]bipyrazinyl-4-carboxylic acid *tert*-butyl ester (**30**) following the procedure described for **31** in 59% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, *J* = 1.4 Hz 1 H), 7.57 (d, *J* = 1.4 Hz, 1 H), 5.61 (s, 2 H), 3.42−3.40 (m, 4 H), 3.19−3.16 (m, 4 H) 1.41 (s, 9 H). MS *m*/*z* 280.2 $(M + H)^+$.

Cyclopentyl-[4-(3-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-amine (33). Synthesized from 4-(3-methyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**5a**) and cyclopentylamine following the procedure described for **37** (see below) in 46.7% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (br s, 1 H), 8.16 (d, J = 5.56 Hz, 1 H), 7.34 (s, 1 H), 6.88 (d, J = 5.56 Hz, 1 H), 4.21 (br s, 1 H), 2.57 (s, 3 H), 1.93 (d, J = 6.06 Hz, 2 H), 1.78−1.61 (m, 2 H), 1.61−1.44 (m, 4 H). Anal. RP-HPLC t_R = 6.20 min (method 2, purity 96.30%/90.40%). HR-MS *m*/*z* $(M + H)^+$: measured 244.1567, calcd 244.1562.

Cyclohexyl-[4-(3-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-amine (34). Synthesized from 4-(3-methyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**5a**) and cyclohexylamine following the procedure described for **37** (see below) in 32.4% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.84 (br s, 1 H), 8.15 (d, J = 6 Hz, 1 H), 7.96 (s, 1 H), 6.78 (d, J = 6 Hz, 1 H), 6.75 (br s, 1 H), 3.72 (m, 1 H), 2.58 (s, 3 H), 1.94 (m, 2 H), 1.71 (m, 2 H), 1.63 (m, 1 H), 1.30 (m, 5 H). Anal. RP-HPLC t_R = 7.25 min (method 2, purity 96.6%/100%). HR-MS *m*/*z* $(M + H)^+$: measured 258.1718, calcd 258.1719.

Cyclohexyl-[4-(3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-amine (35). Synthesized from 4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**5b**) and cyclohexylamine following the procedure described for **37** (see below) in 36.3% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (b. s, 1 H), 8.10 (d, J = 5.05 Hz, 1 H), 7.85 (s, 1 H), 6.61 (d, J = 5.05 Hz, 1 H), 5.08 (br s, 1 H), 3.93 (br s, 1 H), 3.77 (ddd, J = 14.40, 10.36, 4.04 Hz, 1 H), 2.00 (dd, J = 12.38, 3.28 Hz, 2 H), 1.71 (ddd, J = 13.26, 3.66, 3.28 Hz, 2 H), 1.58 (dd, J = 9.09, 4.04 Hz, 1 H), 1.30 (d, J = 7.07 Hz, 8 H), 1.24−1.09 (m, 3 H). Anal. RP-HPLC t_R = 7.87 min (method 2, purity 100.00%/100.00%). HR-MS *m*/*z* $(M + H)^+$: measured 286.2039, calcd 286.2032.

[4-(3-Isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-piperidin-4-yl-amine (36). Synthesized from 4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**5b**) and piperidin-4-ylamine following the procedure described for **37** (see below) in 38% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (d, J = 5.0 Hz, 1 H), 7.91 (s, 1 H), 6.76, (d, J = 5.0 Hz, 1 H), 3.95 (m, 2 H), 3.29 (ddd, J = 12.8, 3.8, 3.7 Hz, 2 H), 2.93−2.87 (m, 2 H), 2.10 (dd, J = 13.9 Hz, 3.3 Hz, 2 H), 1.65 (q, J = 10.6 Hz, 2 H), 1.26 (d, J = 7.1 Hz, 6 H). Anal. RP-HPLC t_R = 9.58 min (method 1, purity 100.00%/100.00%). HR-MS *m*/*z* $(M + H)^+$: measured 287.1985, calcd 287.1984.

[4-(3-Isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(1-methyl-piperidin-4-yl)-amine (37). The mixture of 4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**5b**, 30 mg, 0.11 mmol) and 1-methyl-piperidin-4-ylamine (63 mg, 0.55 mmol) in DMSO (0.5 mL) was heated at 130 °C for 1 h. The crude product was purified by prep-HPLC with a gradient of 5−90% acetonitrile/water with 3% *n*-propanol to give [4-(3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(1-methyl-piperidin-4-yl)-amine (**37**, 10.9 mg) in 33% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (d, J = 5.6 Hz, 1 H), 8.01 (s, 1 H), 6.84 (d, J = 5.6 Hz, 1 H), 4.11 (s, 1 H), 3.88, (dd, J = 14.6, 6.6 Hz, 1 H), 2.94 (d, J = 12.1 Hz, 2 H), 2.34 (s, 3 H), 2.22 (t, J = 11.4 Hz, 2 H), 2.06 (d, J = 10.6 Hz, 2 H), 1.66 (q, J = 9.6 Hz, 2 H), 1.37 (d, J = 6.6 Hz, 6 H); Anal. RP-HPLC t_R = 5.16 min (method 1, purity 97.4%/97.8%). HR-MS *m*/*z* $(M + H)^+$: measured 301.2142, calcd 301.2141.

[4-(3-Isopropyl-1*H*-pyrazol-4-yl)-5-methyl-pyrimidin-2-yl]-(1-methyl-piperidin-4-yl)-amine (38). Synthesized from 4-(3-isopropyl-1*H*-pyrazol-4-yl)-5-methyl-2-methylsulfonyl-pyrimidine (**11**) and 1-methyl-piperidin-4-ylamine following the procedure described for **37** in 26.4% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1 H), 7.77 (br s, 1 H), 3.85 (dd, J = 14.9, 6.3 Hz, 1 H), 3.66 (br s, 1 H), 2.95 (d, J = 12.1 Hz, 2 H), 2.36 (s, 3 H), 2.28 (t, J = 11.4 Hz, 2 H), 2.18 (s, 3 H), 2.03 (d, J = 10.6 Hz, 2 H), 1.63 (d, J = 10.6 Hz, 2 H), 1.29 (d, J = 7.1 Hz, 6 H). Anal. RP-HPLC t_R = 5.72 min (method 1, purity 100.0%/100.0%). HR-MS *m*/*z* $(M + H)^+$: measured 315.2287, calcd 315.2297.

4-(3-Isopropyl-5-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(1-methyl-piperidin-4-yl)-amine (39). Synthesized from 4-(3-isopropyl-1*H*-pyrazol-4-yl)-5-methyl-2-methylsulfonyl-pyrimidine (**12**) and 1-methyl-piperidin-4-ylamine following the procedure described for **37** in 53.2% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (d, J = 5.0 Hz, 1 H), 6.67 (d, J = 5.0 Hz, 1 H), 3.88 (dd, J = 14.6, 6.6 Hz, 1 H), 3.67 (s, 1 H), 2.90 (d, J = 11.6 Hz, 2 H), 2.42 (s, 3H), 2.31 (s, 3H), 2.19 (t, J = 11.1 Hz, 2 H), 2.04 (d, J = 11.1 Hz, 2 H), 1.64 (d, J = 9.6 Hz, 2 H), 1.31 (d, J = 6.6 Hz, 6 H). Anal. RP-HPLC t_R = 5.71 min (method 1, purity 98.2%/95.1%). HR-MS *m*/*z* $(M + H)^+$: measured 315.2285, calcd 315.2297.

[5-Bromo-4-(3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(1-methyl-piperidin-4-yl)-amine (40). Synthesized from 5-bromo-4-(3-isopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**10**) and 1-methyl-piperidin-4-ylamine following the procedure described for **37** in 11.3% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (s, 1 H), 8.00 (s, 1 H), 3.70 (dd, J = 15.4, 6.3 Hz, 1 H), 3.61 (d, J = 6.6 Hz, 1 H), 2.79 (d, J = 11.6 Hz, 2 H), 2.19 (s, 3H), 2.06 (t, J = 12.1 Hz, 2 H), 1.90 (d, J = 11.6 Hz, 2 H), 1.52 (d, J = 9.1 Hz, 2 H), 1.21 (d, J = 7.1 Hz, 6 H). Anal. RP-HPLC t_R = 5.71 min (method 1, purity 88.8%/93.3%). HR-MS *m*/*z* $(M + H)^+$: measured 379.1250, calcd 379.1246.

[4-(5-Bromo-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(1-methyl-piperidin-4-yl)-amine (41). Synthesized from 4-(5-bromo-3-isopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**9**) and 1-methyl-piperidin-4-ylamine following the procedure described for **37** in 66.7% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (d, J = 5.0 Hz, 1 H), 7.00 (d, J = 5.0 Hz, 1 H), 3.88 (dd, J = 15.2, 6.6 Hz, 1 H), 3.77 (dt, J = 14.2, 7.1 Hz, 1 H), 2.93 (d, J = 12.1 Hz, 2 H), 2.33 (s, 3H), 2.22 (t, J = 11.4 Hz, 2 H), 2.05 (d, J = 10.1 Hz, 2 H), 1.66 (d, J = 9.6 Hz, 2 H), 1.33 (d, J = 7.1 Hz, 6 H). Anal. RP-HPLC t_R = 5.79 min (Method 1, purity 98%/95.2%). HR-MS *m*/*z* $(M + H)^+$: measured 379.1245, calcd 379.1246.

4-(3-Isopropyl-1*H*-pyrazol-4-yl)-*N*-(5-(piperazin-1-yl)pyridin-2-yl)pyrimidin-2-amine (42). To a solution of 2-chloro-4-[3-isopropyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-pyrimidine and 2-chloro-4-[5-isopropyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-pyrimidine (a mixture of intermediates from **6** to **7**, 40 mg, 0.113 mmol) in 1,4-dioxane (3 mL) in a sealed tube were added *tert*-butyl 4-(6-aminopyridin-3-yl)piperazine-1-carboxylate (**16**, 32.2 mg, 1.02 equiv), BINAP (6.97 mg, 0.1 equiv), NaO*t*Bu (16.3 mg, 1.5 equiv), and $Pd_2(dba)_2$ (5.20 mg, 0.05 equiv). Nitrogen was bubbled into the resulting mixture for 3 min to degas. The mixture was sealed and heated at 110 °C for 3.5 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite (rinsed with EtOAc). The filtrate was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (EtOAc/heptanes 0 to 50%) and subsequent HPLC purification gave *tert*-butyl 4-(6-(4-(3-isopropyl-1-((2-silylethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)-pyridin-3-yl)piperazine-1-carboxylate (25 mg) in 37% yield. ^{1}HNMR (400 MHz, CD_3OD) δ 8.38 (d, J = 5.3 Hz, 1 H), 8.34 (s, 1 H), 8.11 (d, J = 9.1 Hz, 1 H), 8.01 (d, J = 2.9 Hz, 1 H), 7.51 (dd, J = 9.2, 3.0 Hz, 1 H), 7.07 (d, J = 5.3 Hz, 1 H), 5.44 (s, 2 H), 3.86 (q, J = 6.9 Hz, 1 H), 3.71−3.58 (m, 5 H), 3.52 (t, J = 6.7 Hz, 1 H), 3.19−3.01 (m, 4 H), 1.51 (s, 9 H), 1.31 (d, J = 7.0 Hz, 6 H), 0.98−0.86 (m, 2 H), 0.0 (s, 9 H). MS *m*/*z* 595.6 $(M + H)^+$.

To a solution of *tert*-butyl 4-(6-(4-(3-isopropyl-1-((2-silylethoxy)-methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)piperazine-1-carboxylate (25 mg, 0.042 mmol) in 1,4-dioxane (1.0 mL) was added 4 M HCl in dioxane (1.0 mL, 100 equiv). The mixture was stirred at room temperature for 5 h. The yellow solid was collected by filtration, washed with cold dioxane (5 mL) and then ether (10 mL), and dried under high vacuum overnight to give 4-(3-isopropyl-1*H*-pyrazol-4-yl)-*N*-(5-(piperazin-1-yl)pyridin-2-yl)pyrimidin-2-amine as a hydrochloride salt (23 mg) in 91% yield. ^{1}HNMR (600 MHz, CD_3OD) δ 8.49 (d, J = 6.0 Hz, 1 H), 8.28 (s, 1 H), 8.04−7.97 (m, 2 H), 7.48 (d, J = 6.0 Hz, 1 H), 7.45 (d, J = 9.9 Hz, 1 H), 4.16 (m, 1 H), 3.51−3.47 (m, 4 H), 3.43−3.40 (m, 4 H), 1.36 (d, J = 6.8 Hz, 6 H). Anal. RP-HPLC t_R = 3.30 min (method 5, 100.00%/100%). HR-MS *m*/*z* $(M + H)^+$: measured 364.2238, calcd 364.2250.

[4-(3-Isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(4-piperazin-1-yl-phenyl)-amine (43). To a solution of 2-chloro-4-(3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidine (**6**, 55 mg, 0.247 mmol) in 1,4-dioxane (3 mL) in a microwave vial were added 4-(4-aminophenyl)piperazine-1-carboxylic acid *t*-butyl ester (75.4 mg, 1.1 equiv), XANTPHOS (14.3 mg, 0.1 equiv), Cs_2CO_3 (86.9 mg, 2.0 equiv), and $Pd_2(dba)_2$ (11.3 mg, 0.05 equiv). Nitrogen was bubbled into the resulting mixture for 3 min to degas. The mixture was sealed and heated in a microwave reactor at 150 °C for 40 min. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite (rinsed with EtOAc) and washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (EtOAc/heptanes 0−50%) and subsequent HPLC purification gave *tert*-butyl 4-(4-(4-(3-isopropyl-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)phenyl)piperazine-1-carboxylate (13.2 mg) in 11% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (s, 1 H), 8.15 (d, J = 6.3 Hz, 1 H), 7.42 (d, J = 8.8 Hz, 2 H), 7.18 (d, J = 6.2 Hz, 1 H), 7.10 (d, J = 9.0 Hz, 2 H), 3.97 (m, 1 H), 3.63 (br s, 4 H), 3.13−3.26 (m, 4 H), 1.51 (s, 9 H), 1.24 (d, J = 7.0 Hz, 6H). MS m/z 464.5 $(M + H)^+$.

[4-(3-Isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(4-piperazin-1-yl-phenyl)-amine (**43**) was prepared from *tert*-butyl 4-(4-(4-(3-isopropyl-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)phenyl)piperazine-1-carboxylate following the procedure described for the deprotection reaction of **42** as a hydrochloride salt in quantitative yield. ^{1}H NMR (600 MHz, CD_3OD) δ 8.39 (s, 1 H), 8.05 (br s., 1 H), 7.39−7.21 (m, 3 H), 7.13 (d, J = 8.7 Hz, 2 H), 3.79 (br s, 1 H), 3.50−3.41 (m, 4 H), 3.41−3.30 (m, 4 H), 2.58 (s, 6 H). Anal. RP-HPLC t_R = 3.30 min (method 5, 100%/100%). HR-MS m/z $(M + H)^+$: measured 364.2238, calcd 364.2250.

4-(3-Isopropyl-1*H*-pyrazol-4-yl)-N-(pyridin-2-yl)pyrimidin-2-amine (44). To a solution of 2-chloro-4-(3-isopropyl-1*H*-pyrazol-4-yl)pyrimidine (**6**, 100 mg, 0.45 mmol) and pyridine-2-amine (54.4 mg, 0.49 mmol) in 1,4-dioxane (5 mL) in a sealed tube were added Xantphos (26 mg, 0.1 equiv), LHMDS 1 M solution (670 uL, 1.5 equiv), and $Pd_2(dba)_2$ (21 mg, 0.05 equiv). Nitrogen was bubbled into the resulting mixture for 3 min to degas. The mixture was sealed and heated at 110 °C for 3.5 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite (rinsed with EtOAc). The filtrate was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (EtOAc/heptanes 0−50%) and subsequent HPLC purification gave 4-(3-isopropyl-1*H*-pyrazol-4-yl)-*N*-(pyridin-2-yl)pyrimidin-2-amine (**44**, 15 mg) in 12% yield. ^{1}HNMR (400 MHz, CD_3OD) δ 8.50 (d, J = 5.6 Hz, 1 H), 8.33 (d, J = 5.4 Hz,1 H), 8.15 (br s,1 H), 7.99 (br m, 2 H), 7.32 (d, J = 5.4 Hz, 1 H), 7.19 (d, J = 2.4 Hz, 1 H), 1.69−1.45 (m, 2 H), 1.38 (d, J = 7.0 Hz, 6 H). Anal. RP-HPLC t_R = 2.70 min (method 5, 100%/100%). HR-MS m/z $(M + H)^+$: measured 281.1511, calcd 281.1515.

4-{6-[4-(3-Methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-pyridin-3-yl}-piperazine-1-carboxylic Acid *tert*-Butyl Ester (45). A mixture of 2-methanesulfonyl-4-(3-methyl-1*H*-pyrazol-4-yl)-pyrimidine (**5a**, 120 mg, 0.5 mmol) and 4-(6-amino-pyridin-3-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (**16**, 211 mg, 1.5 equiv) in toluene (6 mL) was heated at 120 °C for 16 h, allowing the solvent to boil off to yield a melt. After cooling to room temperature, the residue was dissolved in CH_2Cl_2 (10 mL) and treated with trifluoroacetic acid (2 mL). After 1 h, the reaction mixture was concentrated and purified by HPLC. A trifluoroacetic acid salt was then neutralized using polymer-linked carbonate resin (Stratospheres SPE PL-HCO_3 MP 500 mg cartridges) to yield 5 mg of 4-{6-[4-(3-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-pyridin-3-yl}-piperazine-1-carboxylic acid *tert*-butyl ester (**45**) in 3% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (br s, 1 H), 9.19 (s, 1 H), 8.37 (d, J = 5.31 Hz, 1 H), 8.08 (d, J = 8.97 Hz, 1 H), 7.96 (d, J = 3.03 Hz, 1 H), 7.41 (dd, J = 8.97, 3.03 Hz, 1 H), 7.06 (d, J = 5.31 Hz, 1 H), 3.01 (m, 4 H), 2.84 (m, 4 H), 2.56 (2.56, 3 H). Anal. RP-HPLC t_R = 1.89 min (method 3, purity 94%/88%). HR-MS m/z $(M + H)^+$: measured 337.1895, calcd 337.1889.

(5-Piperazin-1-yl-pyridin-2-yl)-[4-(3-trifluoromethyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-amine (46). Prepared from 2-methanesulfonyl-4-(3-trifluoromethyl-1*H*-pyrazol-4-yl)-pyrimidine (**5d**) and 4-(6-amino-pyridin-3-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (**16**) following the procedure described for **45** in < 1% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1 H), 8.34 (d, J = 5.31, 1 H), 8.24 (s, 1 H), 8.19 (d, J = 8.97 Hz, 1 H), 7.94 (d, J = 2.78 Hz, 1 H), 7.39 (dd, J = 8.97, 2.78 Hz, 1 H), 6.92 (d, J = 5.31 Hz, 1 H), 3.01 (m, 4 H), 2.84 (m, 4 H). Anal. RP-HPLC t_R = 3.36 min (method 4, 94%, 89%). HR-MS m/z $(M + H)^+$: measured 391.1618, calcd 391.1607.

[4-(3-Cyclopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(5-piperazin-1-yl-pyridin-2-yl) amine (47). Prepared from 4-(3-cyclopropyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**5c**) and 4-(6-amino-pyridin-3-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (**16**) following the procedure described for **45**, except neutralization, in 3% yield as a trifluoroacetic acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (br s, 1 H), 8.93 (s, 2 H), 8.50 (d, J = 5.31 Hz, 1 H), 8.30 (s, 1 H), 8.02 (s, 1 H), 7.84 (d, J = 8.72 Hz, 1 H), 7.76 (d, J = 8.72 Hz, 1 H), 7.43 (d, J = 5.31 Hz, 1 H), 3.37 (m, 4 H), 3.29 (m, 4 H), 2.88 (m, 1H), 1.02 (m, 2 H), 0.91 (m, 2 H). Anal. RP-HPLC t_R = 3.10 min (method 5, 87%,87%). HR-MS m/z $(M + H)^+$: measured 363.2060, calcd 363.2046.

[4-(3-*tert*-Butyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(5-piperazin-1-yl-pyridin-2-yl)-amine (48). Prepared from 4-(3-*tert*-butyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**5e**) and 4-(6-amino-pyridin-3-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (**16**) following the procedure described for **45**, except neutralization, as a trifluoroacetic acid salt in 7% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1 H), 8.81 (bs, 1 H), 8.48 (d, J = 5.56 Hz, 1 H), 8.07 (s, 1 H), 8.01 (s, 1 H), 7.85 (d, J = 9.22 Hz, 1 H), 7.78 (d, J = 9.22 Hz, 1 H), 7.24 (d, J = 5.43 Hz, 1 H), 3.36 (m, 4 H), 3.28 (m, 4 H), 1.42 (s, 9 H). Anal. RP-HPLC t_R = 3.36 min (method 5, 91%/90%). HR-MS m/z $(M + H)^+$: measured 379.2365, calcd 379.2359.

{4-[3-(4-Fluoro-phenyl)-1*H*-pyrazol-4-yl]-pyrimidin-2-yl}-(5-piperazin-1-yl-pyridin-2-yl)-amine (49). Prepared from 4-[3-(4-fluorophenyl)-1*H*-pyrazol-4-yl]-2-methanesulfonyl-pyrimidine (**5f**) and 4-(6-amino-pyridin-3-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (**16**) following the procedure described for **45** in < 1% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1 H), 8.34 (d, J = 5.18 Hz, 1 H), 8.24 (s, 1 H), 7.91 (d, J = 2.91 Hz, 1 H), 7.59 (dd, J = 8.84, 8.84 Hz, 2 H), 7.57 (d, J = 2.91 Hz, 1 H), 7.25 (dd, J = 8.84, 8.84 Hz, 2 H), 7.02 (dd, J = 8.84, 2.91 Hz, 1 H), 6.81 (d, J = 5.18 Hz, 1 H), 2.97 (m, 4 H); 2.84 (m, 4 H). Anal. RP-HPLC t_R = 2.20 min (method 4, purity 97%/93%. HR-MS m/z $(M + H)^+$: measured 417.1965, calcd 417.1951.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(5-piperazin-1-yl-pyridin-2-yl)-amine (50). *tert*-Butyl 4-(6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)piperazine-1-carboxylate was prepared from **7** and 4-(6-amino-pyridin-3-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (**16**) following the procedure described for the coupling reaction of **42** in 10.4% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (d, J = 5.2 Hz, 1 H), 8.15 (d, J = 9.1 Hz, 1 H), 8.01 (d, J = 2.9 Hz, 1 H), 7.48 (dd, J = 9.2 Hz, 1 H), 7.13 (d, J = 5.2 Hz, 1 H), 5.52 (s, 2 H), 3.71 (m, 2 H), 3.19−3.07 (m, 5 H), 3.13(m, 4 H), 1.50 (s, 9 H), 1.25 (d, J = 6.9 Hz, 6 H), 0.93 (m, 2 H), 0.00 (s, 9 H). MS m/z 629.6 $(M + H)^+$.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(5-piperazin-1-yl-pyridin-2-yl)-amine (**50**) was prepared from *tert*-butyl 4-(6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)-methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)piperazine-1-carboxylate following the procedure described for the deprotection reaction of **42** as a hydrochloride salt in 65% yield. ^{1}HNMR (400 MHz, CD_3OD) δ 8.59 (d, J = 5.7 Hz, 1 H), 8.07 (dd, J = 9.5, 3.0 Hz, 1 H), 7.86 (d, J = 2.6 Hz, 1 H), 7.56 (d, J = 5.7 Hz, 1 H), 7.44 (d, J = 9.5 Hz, 1 H), 3.97−3.73 (m, 1 H), 3.47−3.39 (m, 4 H), 3.38−3.30 (m, 4 H), 1.25 (d, J = 7.1 Hz, 6 H). Anal. RP-HPLC

t_R = 3.45 min (method 5, purity 93.38%/95.94%). HR-MS m/z $(M + H)^+$: measured 339.1821, calcd 399.1812.

[4-(5-Isopropyl-3-methyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(5-piperazin-1-yl-pyridin-2-yl)-amine (51). Prepared from 4-(5-isopropyl-3-methyl-1*H*-pyrazol-4-yl)-2-methanesulfonyl-pyrimidine (**12**) and 4-(6-amino-pyridin-3-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (**16**) following the procedure described for **45** in 3% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1 H), 8.40 (d, J = 5.18 Hz, 1 H), 8.02 (d, J = 9.22, 1 H), 7.96 (d, J = 2.78 Hz, 1 H), 7.37 (dd, J = 9.22, 2.78 Hz, 1 H), 6.84 (d, J = 5.18 Hz, 1 H), 3.59 (dd, J = 8.84, 8.84 Hz, 2 H), 7.02 (dd, J = 8.84, 2.91 Hz, 1 H), 6.84 (d, J = 5.18 Hz, 1H), 3.59 (m, 1 H), 3.01 (m, 4 H), 2.84 (m, 4 H), 1.20 (d, J = 6.95, 6 H). Anal. RP-HPLC t_R = 3.27 min (method 2, purity 98%/95%). HR-MS m/z $(M + H)^+$: measured 379.2371, calcd 379.2359.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(6-piperazin-1-yl-pyridazin-3-yl)-amine (52). *tert*-Butyl 4-(6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridazin-3-yl)piperazine-1-carboxylate was prepared from **7** and 4-(6-amino-pyridazin-3-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (**31**) following the procedure described for the coupling reaction of **42** in 16% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (d, J = 5.0 Hz, 1 H), 8.35 (d, J = 9.5 Hz, 1 H), 7.39 (d, J = 10.0 Hz, 1 H), 7.18 (d, J = 5.0 Hz, 1 H), 5.52 (s, 2H), 3.76−3.66 (m, 2 H), 3.66−3.53 (m, 10 H), 1.51 (s, 9 H), 1.24 (d, J = 7.0 Hz, 6 H), 0.93 (t, J = 8.0 Hz, 2H), 0.00 (s, 9 H). MS m/z 630.5 $(M + H)^+$.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(6-piperazin-1-yl-pyridazin-3-yl)-amine (**52**) was prepared from *tert*-butyl 4-(6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)-methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridazin-3-yl)-piperazine-1-carboxylate following the procedure described for the deprotection reaction of **42** as a hydrochloride salt in 63% yield. ^{1}HNMR (400 MHz, CD_3OD) δ 8.79 (d, J = 5.6 Hz, 1 H), 8.14 (d, J = 10.1 Hz, 1 H), 7.90 (d, J = 10.0 Hz, 1 H), 7.69 (d, J = 5.4 Hz, 1 H), 4.02−3.80 (m, 5 H), 3.47−3.39 (m, 4 H), 1.38 (d, J = 7.1 Hz, 6 H). Anal. RP-HPLC t_R = 3.33 min (method 5, purity 100.00%/100.00%). HR-MS m/z $(M + H)^+$: measured 400.1771, calcd 400.1765.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(3,4,5,6-tetrahydro-2*H*-[1,2′]bipyrazinyl-5′-yl)-amine (53). *tert*-Butyl 4-(5-(4-(5-chloro-3-isopropyl-1-((2-(trimethyl-silyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyrazin-2-yl)piperazine-1-carboxylate was prepared from **7** and 5′-amino-2,3,5,6-tetrahydro-[1,2′]bipyrazinyl-4-carboxylic acid *tert*-butyl ester (**32**) following the procedure described for the coupling reaction of **55** (see below) in 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, J = 1.4 Hz, 1 H), 8.47 (d, J = 5.2 Hz, 1 H), 7.86 (d, J = 1.5 Hz, 1 H), 7.58 (s, 1 H), 7.06 (d, J = 5.2 Hz, 1 H), 5.49 (s, 2 H), 3.75−3.64 (m, 2 H), 3.64−3.44 (m, 9 H), 1.50 (s, 9 H), 1.27 (d, J = 7.0 Hz, 6 H), 1.01−0.89 (m, 2 H), 0.00 (s, 9 H). MS m/z 630.5 $(M + H)^+$.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(3,4,5,6-tetrahydro-2*H*-[1,2′]bipyrazinyl-5′-yl)-amine (**53**) was prepared from *tert*-butyl 4-(5-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyrazin-2-yl)piperazine-1-carboxylate following the procedure described for the deprotection reaction of **42** as a hydrochloride salt in 87% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (d, J = 6.9 Hz, 1 H), 8.37 (d, J = 1.4 Hz, 1 H), 8.23 (d, J = 1.3 Hz, 1 H), 7.87 (d, J = 6.8 Hz, 1 H), 4.16 (dt, J = 14.0, 6.9 Hz, 1 H), 3.98−3.86 (m, 4 H), 3.47−3.34 (m, 4 H), 1.40 (d, J = 7.1 Hz, 6 H). Anal. RP-HPLC t_R = 3.54 min (method 5, purity 100.00%/100.00%). HR-MS m/z $(M + H)^+$: measured 400.1765, calcd 400.1765.

4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-*N*-(5-(piperidin-4-yl)-pyridin-2-yl)pyrimidin-2-amine (54). *tert*-Butyl 4-(6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino)pyridin-3-yl)piperidine-1-carboxylate was prepared from **7** and 6-amino-3′,4′,5′,6′-tetrahydro-2′*H*-[3,4′]-bipyridinyl-1′-carboxylic acid *tert*-butyl ester (**28**) following the procedure described for the coupling reaction of **42** in 8% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 9.22 (d, J = 5.3 Hz, 1 H), 8.95 (d, J = 8.6 Hz, 1 H), 8.84 (d, J = 2.3 Hz, 1 H), 8.34 (dd, J = 8.7, 2.4 Hz, 1 H), 7.85 (d, J = 5.2 Hz, 1 H), 6.20 (s, 2 H), 4.91 (d, J = 13.01 Hz, 2 H), 4.46−4.25 (m, 3 H), 3.57 (br s, 2 H), 3.50−3.32 (m, 1 H), 2.51 (br s, 2 H), 2.37−2.21 (m, 2 H), 2.17 (s, 9 H), 1.93 (d, J = 6.8 Hz, 6 H), 1.61 (m, 2 H), 0.67 (s, 9 H). MS m/z 629.6 $(M + H)^+$.

4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-*N*-(5-(piperidin-4-yl)-pyridin-2-yl)pyrimidin-2-amine (**54**) was prepared from *tert*-butyl 4-(6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)piperidine-1-carboxylate following the procedure described for the deprotection reaction of **42** as a hydrochloride salt in quantitative yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.72 (d, J = 5.5 Hz, 1 H), 8.31 (s, 1 H), 8.21 (d, J = 8.5 Hz, 1 H), 7.76 (d, J = 9.03 Hz, 1 H), 7.65 (d, J = 5.5 Hz, 1 H), 3.98 (dt, J = 14.05, 7.03 Hz, 1 H), 3.58 (d, J = 13.0 Hz, 2 H), 3.28−3.09 (m, 3 H), 2.19 (d, J = 14.0 Hz, 2 H), 2.06−1.89 (m, 2 H), 1.37 (d, J = 7.03 Hz, 6 H). Anal. RP-HPLC t_R = 3.63 min (method 5, purity 96.73%/98.27%). HR-MS m/z $(M + H)^+$: measured 398.1842, calcd 398.1860.

{4-[5-Chloro-3-isopropyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-pyrimidin-2-yl}-[5-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-amine (55). To a solution of **7** (100 mg, 0.258 mmol) in 1,4-dioxane (4 mL) and water (100 μL) in a microwave vial were added 5-(4-methyl-piperazin-1-yl)-1-pyridin-2-ylamine (**17**, 49.6 mg, 1.0 equiv), BINAP (16.1 mg, 0.1 equiv), NaO*t*Bu (37.2 mg, 1.5 equiv), and $Pd_2(dba)_2$ (11.8 mg, 0.05 equiv). Nitrogen was bubbled into the resulting mixture for 3 min to degas. The mixture was sealed and heated at 140 °C for 6 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite (rinsed with EtOAc). The filtrate was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (EtOAc/heptanes 0−100%) yielded a solid, which was triturated with cold MeCN to give {4-[5-chloro-3-isopropyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-pyrimidin-2-yl}-[5-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-amine (33 mg) in 23.5% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 5.0 Hz, 1 H), 8.31 (d, J = 9.0 Hz, 1 H), 8.01 (d, J = 2.5 Hz, 1 H), 7.78 (s, 1 H), 7.32 (dd, J = 9.0, 3.0 Hz, 1 H), 7.05 (d, J = 5.5 Hz, 1 H), 5.50 (s, 2 H), 3.68 (m, 2 H), 3.66−3.55 (m, 1 H), 3.21 (br s, 4 H), 2.66 (br s, 4 H), 2.41 (br s, 3 H), 1.28 (d, J = 7.0 Hz, 6 H), 0.94 (m, 2 H), 0.00 (s, 9 H). MS m/z 543.6 $(M + H)^+$.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[5-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-amine (**55**) was prepared from {4-[5-chloro-3-isopropyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-pyrimidin-2-yl}-[5-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-amine following the procedure described for the deprotection reaction of **42** as a hydrochloride salt in 18.6% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (d, J = 6.0 Hz, 1 H), 8.08 (dd, J = 9.5, 3.0 Hz, 1 H), 7.86 (d, J = 3.0 Hz, 1 H), 7.57 (d, J = 5.5 Hz, 1 H), 7.44 (d, J = 9.5 Hz, 1 H), 3.97−3.75 (m, 3 H), 3.65−3.49 (m, 3 H), 3.30−3.06 (m, 3 H), 2.89 (s, 3 H), 1.25 (d, J = 7.0 Hz, 6 H). Anal. RP-HPLC t_R = 4.04 min (method 5, purity 100.00%/100.00%). HR-MS m/z $(M + H)^+$: measured 413.1960, calcd 413.1969.

2-(4-{6-[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-pyridin-3-yl}-piperazin-1-yl)-ethanol (56). To a solution of [4-(5-chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-(5-piperazin-1-yl-pyridin-2-yl)-amine hydrochloride (**50**, 50 mg, 0.125 mmol) in acetonitrile (5 mL) were added di-isopropylethylamine (44 μL, 2.0 equiv) and 2-bromoethanol (9.3 μL, 1.05 equiv). The reaction mixture was stirred at 40 °C for 24 h. The reaction mixture was diluted in EtOAc (10 mL) and washed with water (2 × 20 mL) and then with brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by HPLC to give 2-(4-{6-[4-(5-chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-ylamino]-pyridin-3-yl}-piperazin-1-yl)-ethanol (**56**, 9.5 mg) in 17% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 5.0 Hz, 1 H), 8.32 (d, J = 9.0 Hz, 1 H), 8.20 (br s, 1 H), 8.08 (d, J = 2.5 Hz, 1 H), 7.34 (dd, J = 9.5, 3.0 Hz, 1 H), 7.22 (d, J = 5.0 Hz, 1 H), 3.97−3.80 (m, 1 H), 3.75 (t, J = 5.3 Hz, 2 H), 3.64 (t, J = 6.8 Hz, 1 H), 3.25−3.13 (m, 4 H), 2.79 (br s, 4 H), 2.71 (t, J = 5.0 Hz, 1 H), 1.81−1.62 (m, 1 H), 1.34 (d, J = 7.0 Hz, 6 H), 0.96 (t, J = 7.3 Hz, 1 H). Anal. RP-HPLC t_R = 3.90 min (method 5, purity 94.44%/95.66%). HR-MS m/z $(M + H)^+$: measured 443.2079, calcd 443.2075.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[5-((*S*)-3-methyl-piperazin-1-yl)-pyridin-2-yl]-amine (57). (*S*)-*tert*-Butyl 4-(6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)-methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)-2-methylpiperazine-1-carboxylate was prepared from **7** and (*S*)-4-(6-amino-pyridin-3-yl)-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (**19**) following the procedure described for the coupling reaction of **55** in 51% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 9.7 Hz, 1 H), 8.58 (d, J = 5.3 Hz, 1 H), 7.76 (dd, J = 10.0, 3.0 Hz, 1 H), 7.54 (d, J = 2.8 Hz, 1 H), 7.32 (d, J = 5.3 Hz, 1 H), 5.50 (s, 2 H), 4.43 (br s, 1 H), 4.03 (d, J = 15.0 Hz, 1 H), 3.76−3.54 (m, 3 H), 3.43 (d, J = 12.4 Hz, 1 H), 3.33−3.22 (m, 2 H), 3.05 (d, J = 3.9 Hz, 1 H), 2.84 (br s, 1 H), 1.54−1.46 (m, 9 H), 1.38−1.24 (m, 9 H), 1.20 (d, J = 5.2 Hz, 1 H), 1.00−0.94 (m, 2 H), 0.00 (s, 9 H). MS m/z 643.6 $(M + H)^+$.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[5-((*S*)-3-methyl-piperazin-1-yl)-pyridin-2-yl]-amine (**57**) was prepared from (*S*)-*tert*-butyl 4-(6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)-2-methylpiperazine-1-carboxylate following the procedure described for the deprotection reaction of **42** as a hydrochloride salt in quantitative yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.68 (d, J = 5.8 Hz, 1 H), 8.17 (dd, J = 9.0, 2.8 Hz, 1 H), 7.96 (d, J = 2.8 Hz, 1 H), 7.65 (d, J = 5.8 Hz, 1 H), 7.53 (d, J = 9.6 Hz, 1 H), 3.96 (quin, J = 7.0 Hz, 1 H), 3.86 (dd, J = 19.9, 12.9 Hz, 2 H), 3.61−3.50 (m, 2 H), 3.40−3.31 (m, 1 H), 3.24−3.13 (m, 1 H), 2.95 (dd, J = 13.1,10.5 Hz, 1 H), 1.43 (d, J = 6.6 Hz, 3 H), 1.34 (d, J = 7.0 Hz, 6 H). Anal. RP-HPLC t_R = 3.75 min (method 5, purity 100.00%/100.00%). HR-MS m/z $(M + H)^+$: measured 413.1970, calcd 413.1969.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[5-((*R*)-3-methyl-piperazin-1-yl)-pyridin-2-yl]-amine (58). (*R*)-*tert*-Butyl 4-(6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)-methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)-2-methylpiperazine-1-carboxylate was prepared from **7** and (*R*)-4-(6-amino-pyridin-3-yl)-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (**18**) following the procedure described for the coupling reaction of **55** in 54% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 5.2 Hz, 1 H), 8.31 (d, J = 9.1 Hz, 1 H), 7.98 (d, J = 2.8 Hz, 1 H), 7.77 (s, 1 H), 7.29 (d, J = 3.0 Hz, 1 H), 7.05 (d, J = 5.2 Hz, 1 H), 5.49 (s, 2 H), 4.38 (br s, 1 H), 3.98 (d, J = 13.4 Hz, 1 H), 3.72−3.65 (m, 2 H), 3.61 (quin, J = 6.9 Hz, 1 H), 3.49 (q, J = 7.1 Hz, 1 H), 3.41 (d, J = 11.6 Hz, 1 H), 3.29−3.22 (m, 2 H), 2.93 (dd, J = 11.8, 3.8 Hz, 1 H), 2.75 (td, J = 11.7, 3.5 Hz, 1 H), 1.50 (s, 9 H), 1.34 (d, J = 6.8 Hz, 3 H), 1.28 (d, J = 7.0 Hz, 6 H), 1.22 (t, J = 7.0 Hz, 1 H), 0.91−0.98 (m, 2 H), 0.00 (s, 9 H). MS m/z 643.6 $(M + H)^+$.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[5-((*R*)-3-methyl-piperazin-1-yl)-pyridin-2-yl]-amine (**58**) was prepared from (*R*)-*tert*-butyl 4-(6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)-2-methylpiperazine-1-carboxylate following the procedure described for the deprotection reaction of **42** as a hydrochloride salt in quantitative yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (d, J = 5.5 Hz, 1 H), 8.10 (dd, J = 9.5, 3.0 Hz, 1 H), 7.87 (d, J = 3.0 Hz, 1 H), 7.56 (d, J = 5.5 Hz, 1 H), 7.45 (d, J = 9.5 Hz, 1H), 3.88 (dt, J = 14.0,7.0 Hz, 1 H), 3.84−3.70 (m, 2 H), 3.48 (d, J = 4.5 Hz, 2 H), 3.26 (td, J = 12.3, 3.0 Hz, 1 H), 3.15−3.04 (m, 1 H), 2.86 (dd, J = 13.0, 10.5 Hz, 1 H), 1.34 (d, J = 6.5 Hz, 3 H), 1.25 (d, J = 7.0 Hz, 6 H). Anal. RP-HPLC t_R = 3.70 min (method 5, purity 95.28%/97.72%). HR-MS m/z $(M + H)^+$: measured 413.1956, calcd 413.1969.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[5-(3,3-dimethyl-piperazin-1-yl)-pyridin-2-yl]-amine (59). *tert*-Butyl 4-(6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)-2,2-dimethylpiperazine-1-carboxylate was prepared from **7** and 4-(6-amino-pyridin-3-yl)-2,2-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester (**20**) following the procedure described for the coupling reaction of **55** in 42% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 5.2 Hz, 1 H), 8.26 (d, J = 9.1 Hz, 1 H), 7.84 (d, J = 2.8 Hz, 1 H), 7.69 (br s, 1 H), 7.13 (dd, J = 9.22, 2.8 Hz, 1 H), 7.03 (d, J = 5.2 Hz, 1 H), 5.49 (s, 2 H), 3.79 (t, J = 5.6 Hz, 2 H), 3.73−3.66 (m, 2 H), 3.61 (quin, J = 6.9 Hz, 1 H), 3.34 (t, J = 5.6 Hz, 2 H), 3.22 (s, 2 H), 1.56 (s, 6 H), 1.50 (s, 3 H), 1.45 (s, 6 H), 1.28 (d, J = 6.9 Hz, 6 H), 0.99−0.91 (m, 2 H), 0.00 (s, 9 H). MS m/z 657.4 $(M + H)^+$.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[5-(3,3-dimethyl-piperazin-1-yl)-pyridin-2-yl]-amine (**59**) was prepared from *tert*-butyl 4-(6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)-ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)-2,2-dimethylpiperazine-1-carboxylate following the procedure described for the deprotection reaction of **42** as a hydrochloride salt in 65% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.70 (d, J = 5.5 Hz, 1 H), 8.18 (dd, J = 9.8, 2.8 Hz, 1 H), 7.96 (d, J = 3.0 Hz, 1 H), 7.67 (d, J = 5.5 Hz, 1 H), 7.55 (d, J = 9.5 Hz, 1 H), 3.98 (dt, J = 14.0,7.0 Hz, 1 H), 3.49 (br s, 4 H), 3.35 (s, 2 H), 1.54 (s, 6 H), 1.35 (d, J = 7.0 Hz, 6 H). Anal. RP-HPLC t_R = 3.88 min (method 5, purity 100.00%/100.00%). HR-MS m/z $(M + H)^+$: measured 427.2122, calcd 427.2125.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[5-(3,5-dimethyl-piperazin-1-yl)-pyridin-2-yl]-amine (60). *tert*-Butyl 4-(6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)-2,6-dimethyl-piperazine-1-carboxylate was prepared from **7** and 4-(6-amino-pyridin-3-yl)-2,6-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester (**21**) following the procedure described for the coupling reaction of **55** in 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 5.2 Hz, 1 H), 8.35 (d, J = 9.1 Hz, 1 H), 7.97 (d, J = 2.5 Hz, 1 H), 7.33 (dd, J = 9.1, 2.5 Hz, 1 H), 7.06 (d, J = 5.2 Hz, 1 H), 5.50 (s, 2H), 4.32−4.21 (m, 2 H), 3.74−3.65 (m, 2 H), 3.61 (dt, J = 13.7, 6.8 Hz, 1 H), 3.26 (d, J = 11.7 Hz, 2 H), 2.9 (dd, J = 11.6, 4.2 Hz, 2 H), 1.50 (s, 10 H), 1.39 (d, J = 6.8 Hz, 6 H), 1.29 (d, J = 7.0 Hz, 6 H), 0.99−0.91 (m, 2 H), 0.00 (s, 9 H). MS m/z 657.4 $(M + H)^+$.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[5-(3,5-dimethyl-piperazin-1-yl)-pyridin-2-yl]-amine (**60**) was prepared from *tert*-butyl 4-(6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)-pyridin-3-yl)-2,6-dimethylpiperazine-1-carboxylate following the procedure described for the deprotection reaction of **42** as a hydrochloride salt in quantitative yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, J = 5.4 Hz, 1 H), 8.10 (d, J = 9.2 Hz, 1 H), 8.03 (d, J = 2.8 Hz, 1 H), 7.81 (d, J = 9.5 Hz, 1 H), 7.44 (d, J = 5.4 Hz, 1 H), 3.91−3.83 (m, 3 H), 3.78 (dt, J = 14.0, 6.9 Hz, 2 H), 3.40 (br s, 3 H), 2.88 (t, J = 12.1 Hz, 2 H), 1.35 (s, (d, J = 6.6 Hz, 6 H), 1.29 (d, J = 7.1 Hz, 6 H). Anal. RP-HPLC t_R = 3.77 min (method 5, purity 98.58%/100.00%). HR-MS m/z $(M + H)^+$: measured 427.2109, calcd 427.2125.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[5-((*S*)-3-methyl-piperazin-1-ylmethyl)-pyridin-2-yl]-amine (61). (*S*)-*tert*-Butyl 4-((6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)-ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)methyl)-2-methylpiperazine-1-carboxylate was prepared from **7** and (*S*)-4-(6-amino-pyridin-3-ylmethyl)-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (**24**) following the procedure described for the coupling reaction of **55** in 15% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d., J = 5.0 Hz, 1 H), 8.42 (d., J = 8.5 Hz, 1 H), 8.23 (s,1 H), 8.20 (br s, 1 H), 7.68 (dd, J = 8.5, 2.0 Hz, 1 H), 7.10 (d., J = 5.0 Hz, 1 H), 5.50 (s, 2 H), 4.20 (br s, 1 H), 3.82 (d, J = 12.0 Hz, 1 H), 3.74−3.66 (m, 2 H), 3.66−3.57 (m, 1 H), 3.54−3.46 (m, 1H), 3.41−3.33 (m, 1 H), 3.10 (td, J = 12.5, 3.0 Hz, 1 H), 2.78 (d., J = 11.0 Hz, 1 H), 2.59 (d, J = 11.5 Hz, 1 H), 2.14 (dd, J = 11.3, 3.8 Hz, 1 H), 2.08−1.97 (m, 1 H), 1.46 (s, 9 H), 1.28 (d, J = 6.5 Hz, 6 H), 1.22 (d, J = 6.5 Hz, 3 H), 0.99−0.91 (m, 2 H), 0.00 (s, 9 H). MS m/z 657.3 $(M + H)^+$.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[5-((*S*)-3-methyl-piperazin-1-ylmethyl)-pyridin-2-yl]-amine (**61**) was prepared from (*S*)-*tert*-butyl 4-((6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)methyl)-2-methylpiperazine-1-carboxylate following the procedure described for the deprotection reaction of **42** as a hydrochloride salt in 81% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (d, J = 6.0 Hz, 1 H), 8.55 (s, 1 H), 8.35 (dd, J = 9.0, 2.0 Hz, 1 H), 7.69 (d, J = 6.0 Hz, 1 H), 7.50 (d, J = 9.0 Hz, 1 H), 4.35 (br s, 2 H), 3.93 (dt, J = 14.0, 7.0 Hz, 1 H), 3.71 (br s, 1 H), 3.28 (br s, 1 H), 3.07 (br s, 1 H), 1.31 (d, J = 7.0 Hz, 3 H), 1.26 (d, J = 7.0 Hz, 6 H). Anal. RP-HPLC t_R = 3.84 min (method 5, purity 81.28%/94.42%). HR-MS m/z (M + H)$^+$: measured 427.2135, calcd 427.2125.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[5-((*R*)-3-methyl-piperazin-1-ylmethyl)-pyridin-2-yl]-amine (62). (*R*)-*tert*-Butyl 4-((6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)methyl)-2-methylpiperazine-1-carboxylate was prepared from **7** and (*R*)-4-(6-Amino-pyridin-3-ylmethyl)-2-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (**25**) following the procedure described for the coupling reaction of **55** in 32% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 5.0 Hz, 1 H), 8.42 (d, J = 8.6 Hz, 1 H), 8.22 (d, J = 1.5 Hz, 1 H), 7.97 (br s, 1 H), 7.70 (br s, 1 H), 7.11 (d., J = 5.0 Hz, 1 H), 5.50 (d, J = 8.6 Hz, 1 H), 4.21 (br s, 1 H), 3.83 (d, J = 12.1 Hz, 1 H), 3.75−3.57 (m, 3 H), 3.52 (d, J = 11.1 Hz, 1 H), 3.38 (d, J = 14.1 Hz, 1 H), 3.12 (br s, 1 H), 2.79 (br s, 1 H), 2.78 (d, J = 11.0 Hz, 1 H), 2.61 (d, J = 10.6 Hz, 1 H), 2.16 (br s, 1 H), 2.05 (br s, 1 H), 1.46 (s, 9 H), 1.29 (d, J = 7.1 Hz, 6 H), 1.24 (d, J = 6.6 Hz, 3 H), 0.99−0.91 (m, 2 H), 0.00 (s, 9 H). MS m/z 657.6 (M + H)$^+$.

[4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-[5-((*R*)-3-methyl-piperazin-1-ylmethyl)-pyridin-2-yl]-amine (**62**) was prepared from (*R*)-*tert*-butyl 4-((6-(4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)pyrimidin-2-ylamino)pyridin-3-yl)methyl)-2-methylpiperazine-1-carboxylate following the procedure described for the deprotection reaction of **42** as a hydrochloride salt in quantitative yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (d, J = 5.5 Hz, 1 H), 8.53 (br s, 1 H), 8.34 (d, J = 9.0 Hz, 1 H), 7.69 (d, J = 6.0 Hz, 1 H), 7.50 (d, J = 9.0 Hz, 1 H), 4.29 (br s, 3 H), 3.93 (m, 1 H), 3.68 (br s, 1 H), 3.30−3.51 (m, 3 H), 3.02 (br s, 1 H), 1.30 (d, J = 6.5 Hz, 3 H), 1.26 (d, J = 7.0 Hz, 6 H). Anal. RP-HPLC t_R = 3.85 min (method 5, purity 89.92%/100.00%). HR-MS m/z (M + H)$^+$: measured 427.2120, calcd 427.2125.

4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-*N*-(5-(4-(dimethylamino)piperidin-1-yl)pyridin-2-yl)pyrimidin-2-amine (63). 4-(5-Chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-*N*-(5-(4-(dimethylamino)piperidin-1-yl)pyridin-2-yl)pyrimidin-2-amine was prepared from **7** and *N**4*,*N**4*-dimethyl-3,4,5,6-tetrahydro-2*H*-[1,3′]bipyridinyl-4,6′-diamine (**22**) following the procedure described for the coupling reaction of **55** in 25% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 5.0 Hz, 1 H), 8.30 (d, J = 9.0 Hz, 1 H), 8.14 (s, 1 H), 8.04 (d, J = 3.0 Hz, 1 H), 7.33 (dd, J = 9.0, 3.0 Hz, 1 H), 7.04 (d, J = 5.0 Hz, 1H), 5.50 (s, 2 H), 3.76−3.55 (m, 5 H), 3.17 (br s, 1 H), 2.74 (td, J = 12.0, 2.0 Hz, 2 H), 2.37 (s, 6 H), 1.99 (d, J = 12.5 Hz, 2 H), 1.78−1.63 (m, 2 H), 1.28 (d, J = 6.5 Hz, 6 H), 0.99−0.90 (m, 2 H), 0.00 (s, 9 H). MS m/z 571.3 (M + H)$^+$.

4-(5-Chloro-3-isopropyl-1*H*-pyrazol-4-yl)-*N*-(5-(4-(dimethylamino)piperidin-1-yl)pyridin-2-yl)pyrimidin-2-amine (**63**) was prepared from 4-(5-chloro-3-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-*N*-(5-(4-(dimethylamino)piperidin-1-yl)pyridin-2-yl)pyrimidin-2-amine following the procedure described for the deprotection reaction of **42** as a hydrochloride salt in 71.8% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.68 (d, J = 5.7 Hz, 1 H), 8.17 (dd, J = 9.7, 3.0 Hz, 1 H), 7.90 (d, J = 2.8 Hz, 1 H), 7.63 (d, J = 5.7 Hz, 1 H), 7.51 (d, J = 9.7 Hz, 1 H), 3.84−4.05 (m, 3 H), 3.53−3.36 (m, 1 H), 2.98−2.95 (m, 2 H), 2.91 (s, 7 H), 2.25 (d, J = 13.0 Hz, 2 H), 1.91 (m, 2 H), 1.34 (d, J = 7.0 Hz, 6 H). Anal. RP-HPLC t_R = 3.84 min (method 5, purity 100.00%/100.00%). HR-MS m/z (M + H)$^+$: measured 441.2282, calcd 441.2282.

***N**6′*-[4-(5-Isopropyl-3-trifluoromethyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-*N**4*,*N**4*-dimethyl-3,4,5,6-tetrahydro-2*H*-[1,3′]-bipyridinyl-4,6′-diamine (64).** 4-[2-(4-Dimethylamino-3,4,5,6-tetrahydro-*2H*-[1,3′]bipyridinyl-6′-ylamino)-pyrimidin-4-yl]-5-isopropyl-3-trifluoromethyl-pyrazole-1-sulfonic acid dimethylamide was prepared from 4-(2-chloro-pyrimidin-4-yl)-5-isopropyl-3-trifluoromethyl-pyrazole-1-sulfonic acid dimethylamide (**14**) and *N**4*,*N**4*-dimethyl-3,4,5,6-tetrahydro-2*H*-[1,3′]bipyridinyl-4,6′-diamine (**22**) following the procedure described for the coupling reaction of **55** in 56% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (s, 1 H), 8.58 (d, J = 5.0 Hz, 1 H), 8.00 (d, J = 3.0 Hz, 1 H), 7.96, (d, J = 9.0 Hz, 1 H), 7.40 (dd, J = 9.0, 3.0 Hz, 1 H), 6.97 (d, J = 5.0 Hz, 1 H), 3.71−3.57 (m, 3 H), 3.14 (s, 6 H), 2.74−2.56 (m, 2 H), 2.18 (s, 6 H), 1.82 (d, J = 12 Hz, 2 H), 1.45 (m, 2 H), 1.18 (d, J = 7.0 Hz, 6 H). MS m/z 582.4 (M + H)$^+$.

To a suspension of 4-[2-(4-dimethylamino-3,4,5,6-tetrahydro-2*H*-[1,3′]bipyridinyl-6′-ylamino)-pyrimidin-4-yl]-5-isopropyl-3-trifluoromethyl-pyrazole-1-sulfonic acid dimethylamide (140 mg, 0.241 mmol) in MeOH (12 mL) was added a few drops of 37% HCl and the resulting solution was stirred at 40 °C for 16 h. The reaction mixture was concentrated and dissolved in MeOH (2 mL). The solution was filtered through PL-HCO_3 MP-Resin (StratoSpheres SPE, www.polymerlabs.com) and concentrated to give *N**6′*-[4-(5-Isopropyl-3-trifluoromethyl-1*H*-pyrazol-4-yl)-pyrimidin-2-yl]-*N**4*,*N**4*-dimethyl-3,4,5,6-tetrahydro-2*H*-[1,3′]-bipyridinyl-4,6′-diamine (**64**, 84.7 mg) in 74% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.75 (br s, 1 H), 9.52 (s, 1 H), 8.51 (d, J = 5.0 Hz, 1 H), 8.16−7.92 (m, 2 H), 7.37 (dd, J = 9.3, 2.8 Hz, 1 H), 6.84 (d, J = 5.0 Hz, 1 H), 3.63 (d, J = 12 Hz, 2 H), 3.41 (m, 1 H), 2.63 (t, J = 11 Hz, 2 H), 2.19 (s, 6 H), 1.83 (d, J = 12 Hz, 2 H), 1.48 (m, 2 H), 1.24 (d, J = 7.0 Hz, 6 H). Anal. RP-HPLC t_R = 3.91 min (method 1, purity 100.00%/100.00%). HR-MS m/z (M + H)$^+$: measured 475.2543, calcd 475.2546.

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