Journal of Medicinal Chemistry Article

J. Med. Chem. **2010,** *53,* 3973–4001 **3973**
DOI: 10.1021/jm901870q

Discovery of GSK1070916, a Potent and Selective Inhibitor of Aurora B/C Kinase

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Received December 18, 2009

The Aurora kinases play critical roles in the regulation of mitosis and are frequently overexpressed or amplified in human tumors. Selective inhibitors may provide a new therapy for the treatment of tumors with Aurora kinase amplification. Herein we describe our lead optimization efforts within a 7-azaindole-based series culminating in the identification of GSK1070916 (**17k**). Key to the advancement of the series was the introduction of a 2-aryl group containing a basic amine onto the azaindole leading to significantly improved cellular activity. Compound **17k** is a potent and selective ATP-competitive inhibitor of Aurora B and C with K_i* values of 0.38 ± 0.29 and 1.5 ± 0.4 nM, respectively, and is >250-fold selective over Aurora A. Biochemical characterization revealed that compound **17k** has an extremely slow dissociation half-life from Aurora B (>480 min), distinguishing it from clinical compounds **1** and **2**. In vitro treatment of A549 human lung cancer cells with compound **17k** results in a potent antiproliferative effect ($EC_{50} = 7$ nM). Intraperitoneal administration of **17k** in mice bearing human tumor xenografts leads to inhibition of histone H3 phosphorylation at serine 10 in human colon cancer (Colo205) and tumor regression in human leukemia (HL-60). Compound **17k** is being progressed to human clinical trials.

Introduction

The mammalian Aurora kinases (A, B, and C) are a family of Ser/Thr protein kinases that play key roles in regulating cell cycle progression through mitosis.[1−5] Along with its cellular binding partner TPX2[a], Aurora A plays an essential role in bipolar spindle assembly, including centrosome separation and maturation.[6−8] Small molecule inhibition of Aurora A kinase activity causes defects in centrosome separation, with the formation of characteristic monopolar spindles.[9] Aurora B is a chromosomal passenger protein that functions together with its binding partners INCENP, survivin, and borealin, to ensure proper kinetochore-microtubule attachments.[10−13] During mitosis, Aurora B is required for phosphorylation of histone H3 at serine 10 prior to chromosome condensation and plays a key role in chromosome segregation and cytokinesis.[14−16] Inhibition of Aurora B kinase activity with small molecules leads to failure in cytokinesis and abnormal exit from mitosis, resulting in endoreduplication, polyploid cells, and ultimately apoptosis.[17,18] Aurora C has a more restricted expression profile with low levels in most somatic tissues and high levels in the testis, and although its function is not as well understood, recent studies suggest that it has overlapping functions and similar localization patterns to Aurora B.[19−22]

A number of small molecule inhibitors of Aurora kinases have been progressed to clinical development.[3,23,24,25] VX-680/MK-0457 (**1**, Vertex/Merck) inhibits all three Aurora kinase isoforms with approximately equal potency and was the first inhibitor to show the potential for in vivo activity (Figure 1).[26] Examples of Aurora isoform selective agents include AZD-1152 (**2**, AstraZeneca, Aurora B/C selective),[27] MLN8054 (**3**, Millenium, Aurora A selective),[28] and most recently MK-5108 (Merck, Aurora A selective).[29] Although it is not clear whether inhibition of all three Aurora isoforms is necessary for optimal antitumor efficacy, in cell culture most of the reported pan-Aurora inhibitors induce an Aurora B inhibition phenotype, i.e., chromosomal endoreduplication abnormalities. This observation suggests that Aurora B inhibition alone may be sufficient for antitumor activity. In this report, we describe our efforts to improve the activity and selectivity profile of a 7-azaindole-based lead series culminating in the identification of GSK-1070916 (**17k**),[30] a potent and selective ATP-competitive inhibitor of Aurora B and C with >250-fold selectivity over Aurora A.

Lead Profile. Screening of small molecules for Aurora kinase inhibitors and subsequent SAR refinement identified compound **12c** as a lead with good Aurora B potency and selectivity over Aurora A (Figure 2). Although **12c** also displayed potent antiproliferative activity vs A549 lung cancer cells, other properties (activity vs non-Aurora kinases, high in vivo blood clearance

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[a] Abbreviations: TPX2, target protein of *Xenopus* kinesin-like protein 2; INCENP, inner centromere protein; DNAUC, dose normalized area under the curve.

Published on Web 04/26/2010

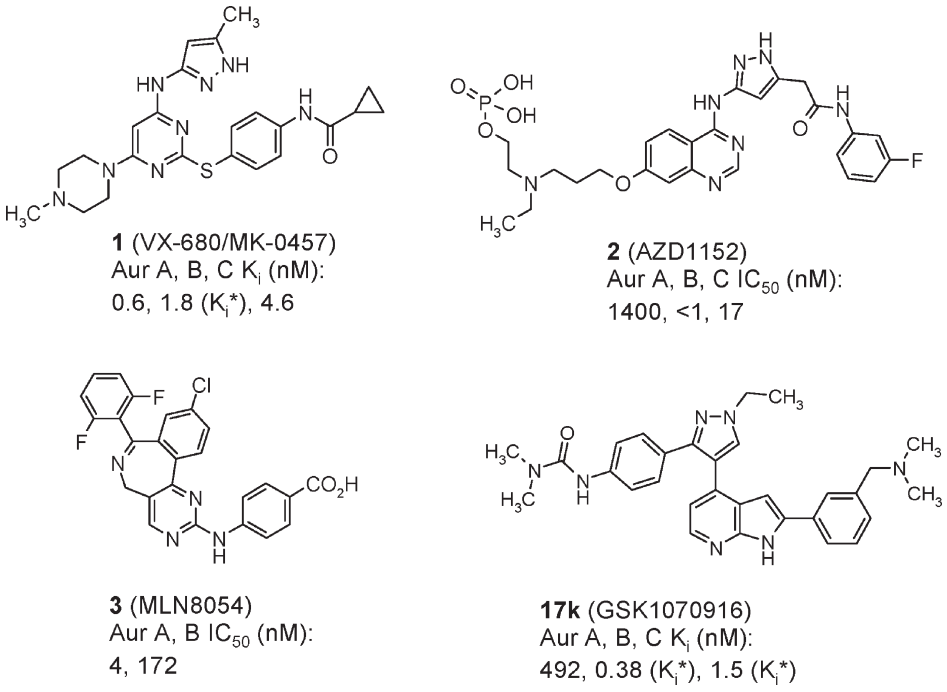


Figure 1. Structures and activities of lead Aurora inhibitors.

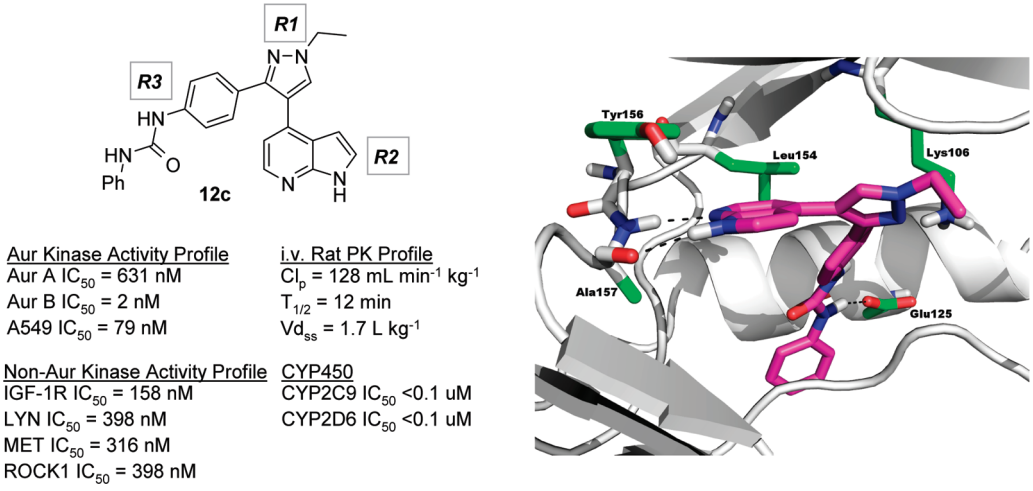


Figure 2. Biological profile and putative binding mode of inhibitor **12c** in an Aurora B homology model.

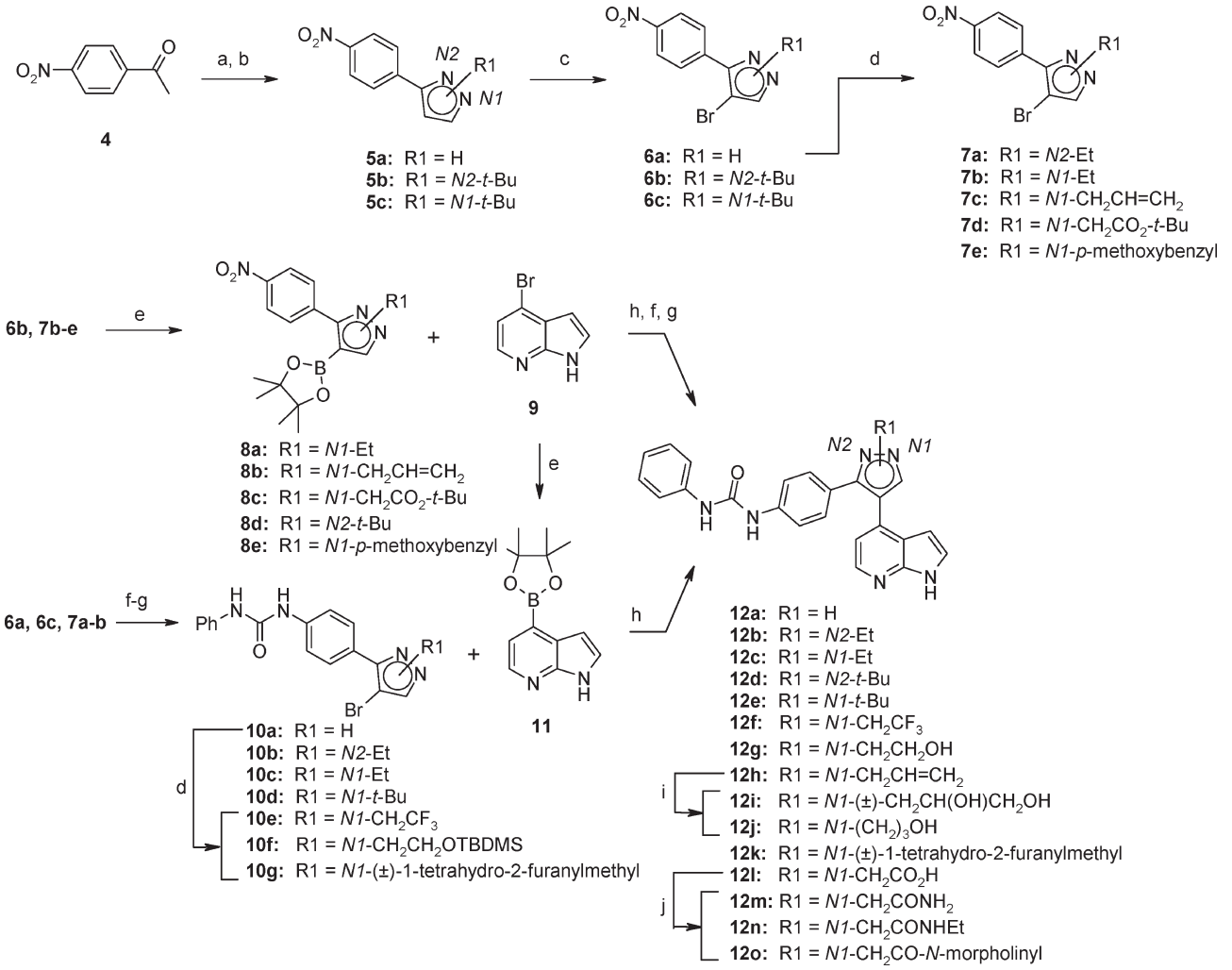
in rodents, and potent CYP2C9 and CYP2D6 inhibition) were pharmaceutically unattractive. A putative binding mode of compound **12c** in an Aurora B homology model is shown in Figure 2.[31] Compound **12c** is proposed to reside in the ATP-binding pocket with the azaindole interacting with the hinge region and the phenylurea occupying a hydrophobic pocket (back pocket). Relative to Aurora B/INCENP, Aurora A/TPX2 has a smaller and less accessible hydrophobic pocket where the urea moiety is proposed to reside, and this structural difference potentially explains the isoform selectivity of **12c** and related compounds.[7] The pyrazole ring occupies the ATP sugar pocket and the azaindole 2-position points toward the solvent accessible surface. Guided by this putative binding mode, our medicinal chemistry strategy consisted of exploring the SAR around three main areas of the molecule, the pyrazole ring (R1), the 2-position of the 7-azaindole ring (R2), and the phenylurea (R3), in a concerted effort to maintain Aurora B inhibitory activity and address the shortcomings of the lead.

Recent reports highlighting the use of drug-target residence time (i.e., dissociation half-life) as an additional parameter for compound optimization prompted us to evaluate compounds of interest for time dependence.[32,33] Accordingly, compound **12c** was tested for time dependent inhibition against Aurora B/INCENP with rapid dilution experiments and found to have a short residence time (7.7 ± 0.8 min), indicating the formation of a rapidly reversible, short-lived enzyme−inhibitor complex.[34] Aurora B/INCENP dissociation half-lives of < 30 min were also reported for clinical compounds **1** and **2**.[34]

Results and Discussion

Chemistry. The synthesis of derivatives **12a**−**o** which modify the pyrazole group (R1) commenced with the preparation of pyrazoles **5a**−**c** by reaction of 1-(4-nitrophenyl)ethanone with *N*,*N*-dimethylformamide dimethylacetal, followed by treatment with the appropriate hydrazine in ethanol (Scheme 1). Bromination with *N*-bromosuccinimide

Scheme 1. Synthesis of R1 Substituted Azaindole Derivatives[a]



[a] Reagents and conditions: (a) DMF·DMA, DMF, 80 °C; (b) hydrazine monohydrate or *t*-butylhydrazine·hydrochloride, EtOH, 70 °C; (c) NBS, DMF, rt; (d) R1-Br, NaH, DMF, 0 °C to rt; (e) bis(pinacolato)diboron, KOAc, $PdCl_2(PPh_3)_2$, 1,4-dioxane, 100 °C; (f) Sn(0), 6N HCl, EtOH, 70 °C or Zn, AcOH, rt; (g) PhNCO, pyr, rt; (h) $Pd(PPh_3)_4$, DMF, $NaHCO_3$ (aq), 100 °C; (i) **12i**: OsO_4, NMO, *t*-BuOH, H_2O, acetone, rt; **12j**: 9-BBN, 6N NaOH, 30% H_2O_2 (aq), THF, H_2O, 0 °C to rt; (j) **12m**: ethyl chloroformate, NH_4OH, TEA, THF, 0 °C to rt; **12n**: NH_2Et, EDCI, DMAP, DMF, rt; **12o**: morpholine, CDI, DMF, rt .

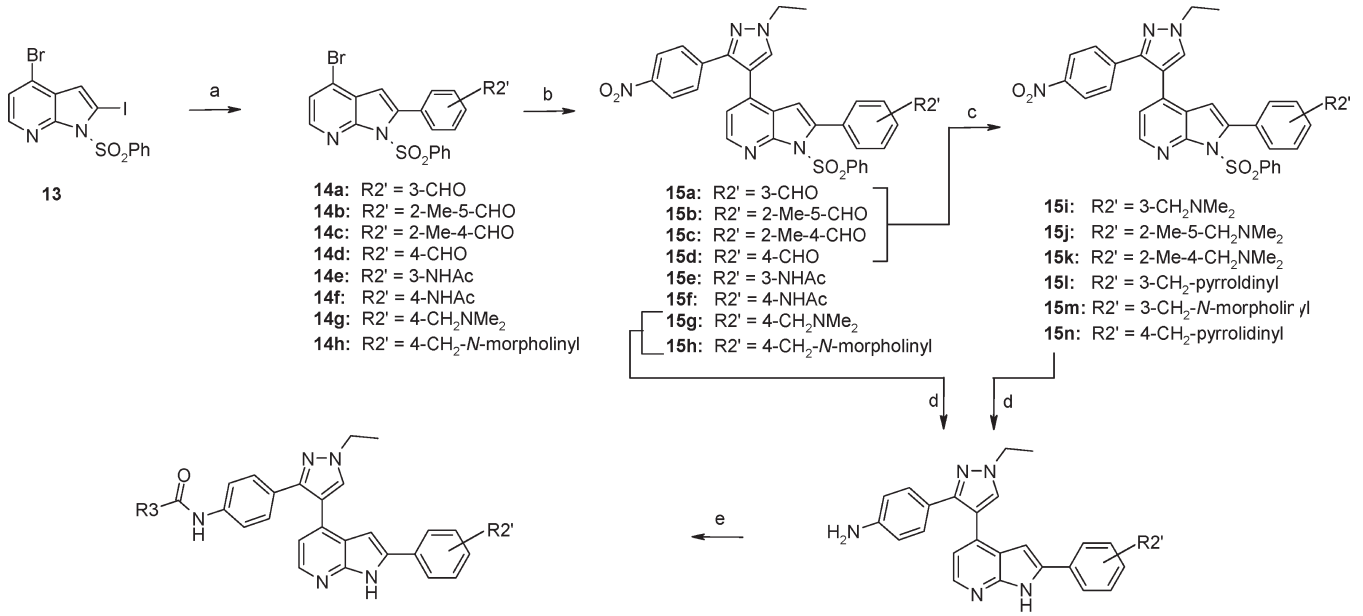
provided intermediate bromides **6a**−**c**. Alkylation of pyrazole **6a** under basic conditions provided regioisomeric mixtures which were readily separable by chromatographic methods to give **7a**−**e**. Bromides **7a**−**e** were used as is or converted to their corresponding boronates for the final palladium catalyzed Suzuki cross-coupling step with their azaindole counterparts. Synthesis of pyrazole bromides incorporating the phenylurea R3 group were prepared through Sn(0) or Zn(0) mediated reduction of the nitrophenyl derivatives **6a**, **6c**, or **7a**−**b** to their corresponding anilines and subsequent conversion to the phenylurea with phenyl isocyanate. These intermediates were either used as is or converted to their corresponding boronates for the subsequent Suzuki cross-coupling reactions with the requisite azaindole fragment.

Synthesis of compounds **17a**−**u** where R2 and R3 are functionalized is outlined in Scheme 2. Sequential Suzuki cross-coupling of 4-bromo-2-iodo-1-(phenylsulfonyl)-1*H*-pyrrolo-[2,3-*b*]pyridine (**13**)[35] with the appropriate phenyl boronic acids followed by pyrazole boronic acid **8a** provided intermediates **15a**−**h**. Aldehyde intermediates **15a**−**d** underwent reductive amination reactions to provide amines **15i**−**n**. With the pyrazole-azaindole core in place, the 4-nitrophenyl derivatives **15g**−**n** were reduced to their corresponding anilines, deprotected under basic conditions, and capped with appropriate R3-group, thereby providing target molecules **17c**−**u**.

A synthesis of compounds **22a**−**c**, where R2 is an amide group, is outlined in Scheme 3. Regioselective bromination of ethyl 1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate 7-oxide (**18**)[36] provided bromide **19**, which underwent Suzuki coupling with boronate **8a**. The Suzuki conditions also served to hydrolyze the ester, providing acid **20** from which the amide was installed via EDC or 1,1-carbonyldiimidazole mediated couplings. The phenyl urea was introduced along the lines described in Scheme 2 to provide the target compounds.

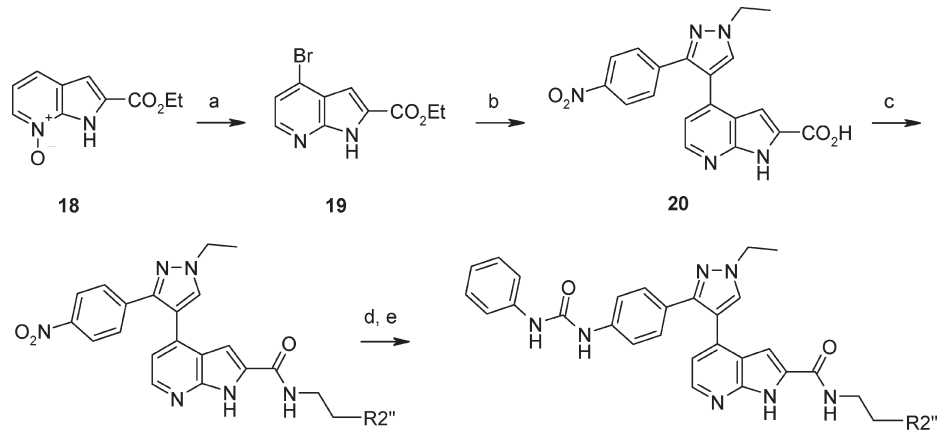
Derivatives which incorporate a substituted methylamino moiety at R2 (**28a**−**f**) were prepared using 2-formyl intermediate **24**, synthesized by phenylsulfonyl-directed metalation of **23** with LDA and trapping of the resulting anion with DMF (Scheme 4). Reductive amination of aldehydes **24** or **26** with an amine in the presence of sodium triacetoxyborohydride afforded the desired aminomethyl

Scheme 2. Synthesis of R2 and R3 Substituted Azaindole Derivatives[a]



[a] Reagents and conditions: (a) R2-Ph-B(OH)$_2$, Pd(PPh$_3$)$_4$, DMF, NaHCO$_3$ (aq), 100 °C; (b) **8a**, Pd(PPh$_3$)$_4$, DMF, NaHCO$_3$ (aq), 100 °C; (c) amine, NaBH(OAc)$_3$, THF, rt; (d) Sn(0), 6N HCl, EtOH, 70 °C or Zn, AcOH, rt; then 6N NaOH (aq), MeOH, 70 °C; (e) PhNCO or EtNCO, pyr, rt (or TEA, THF, rt), or 4-nitrophenyl chloroformate, TEA, THF, rt, HNMe$_2$. *Compounds **17a** and **17b** were prepared from **15e** and **15f**, respectively, through reduction of the nitro group with palladium hydroxide/hydrogen, urea formation with PhNCO and subsequent deprotection of the phenylsulfonyl group with 6N NaOH (aq); see the Experimental Section for details.

Scheme 3. Synthesis of R2 Amide Azaindole Derivatives[a]

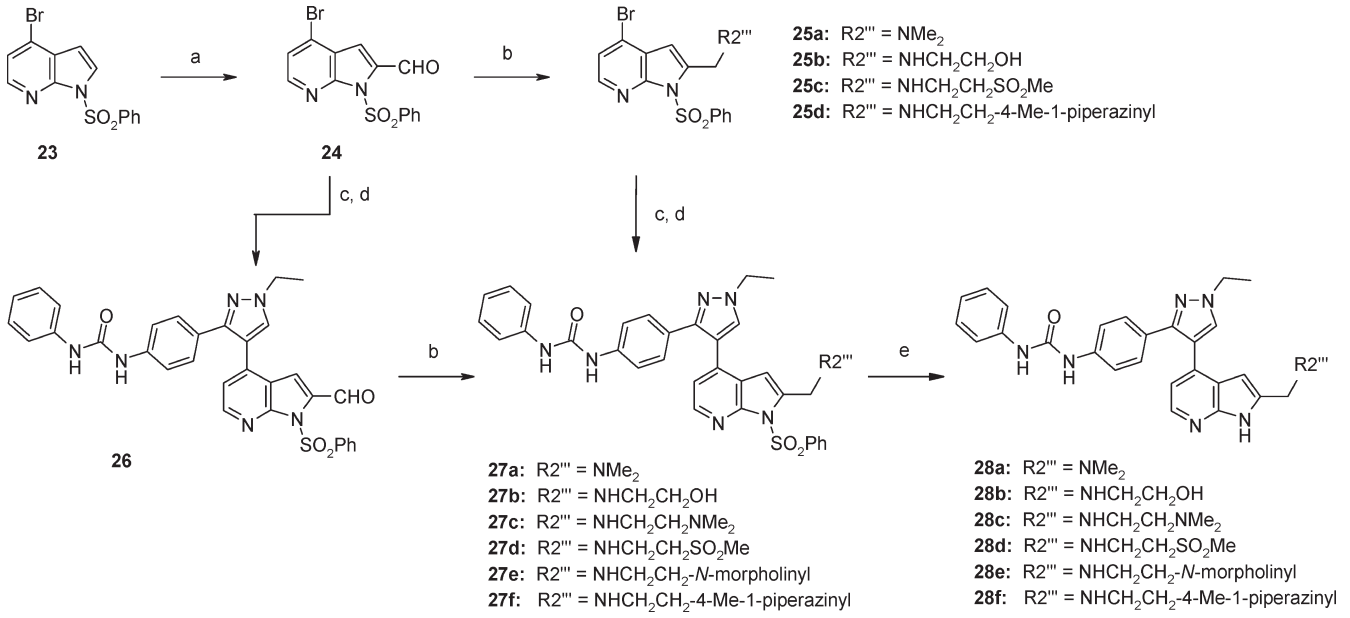


[a] Reagents and conditions: (a) Me$_4$NBr, (MeSO$_2$)$_2$O, DME; (b) **8a**, Pd(PPh$_3$)$_4$, 2 M K$_2$CO$_3$ (aq), dioxane, 100 °C; (c) EDC or 1,1-carbonyldiimidazole, NH$_2$CH$_2$CH$_2$R2'', DMF, rt; (d) Sn(0), 6N HCl, EtOH, 70 °C; (e) PhNCO, pyr, rt.

intermediates, which were then converted to final compounds **27a**−**f** through a similar sequence described in Scheme 2.

Biological Evaluation of Inhibitors. The ability of azaindole derivatives to inhibit Aurora B/INCENP and Aurora A/TPX2 protein kinase activity was determined using a

Scheme 4. Synthesis of R2 Methylamino Azaindole Derivatives[a]



[a] Reagents and conditions: (a) (i) LDA, THF, hexanes, −78 °C, (ii) DMF; (b) HNR''', $NaBH(OAc)_3$, CH_2Cl_2:AcOH (4:1); (c) bis(pinacolato)diboron, KOAc, $PdCl_2(dppf)\cdot CH_2Cl_2$, 1,4-dioxane, 90 °C; (d) **10c**, $Pd(PPh_3)_4$, satd aq $NaHCO_3$, DMF, 100 °C; (e) 6N NaOH, MeOH, 70 °C.

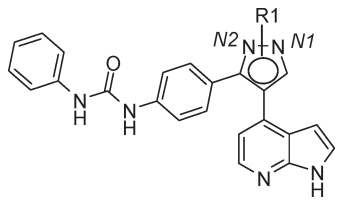
LEADSeeker (Amersham Biosciences) scintillation proximity assay (SPA) format as previously described.[30,34] Compounds were assayed for their antiproliferative activity against the human lung cancer cell line A549 using Promega CellTiter-Glo reagents as previously described.[30,37]

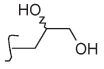
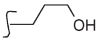
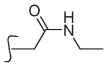
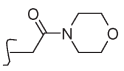
We first investigated the regiochemical preference for the pyrazole substituent (depicted as *N1* and *N2* in Table 1) while maintaining the phenyl urea at R3. Transposition of the ethyl group from the *N1*-position to the N2-position led to a 12-fold decrease in Aurora B inhibitory activity and concomitant loss in antiproliferative activity (cf. compound **12c** vs **12b**). Deleting the ethyl group of **12c** to give unsubstitued pyrazole **12a** resulted in ~15-fold lower potency against Aurora B and a concomitant loss in cellular potency. Initial structure−activity relationship (SAR) studies also established that modification of the phenyl urea, such as substituting the phenyl ring with electron withdrawing and/or donating groups, replacement of the phenyl group with alkyl groups, or replacement of the urea moiety with amides, sulfonamides, or carbamates, did not lead to substantial improvement in activity relative to **12c** (data not shown). Transposing the *para*-phenyl urea (**12c**) to the *meta* position led to significant loss in Aurora B inhibitory potency, presumably due to the *para*-substituent having a more favorable trajectory to access the hydrophobic back pocket region adjacent to the ATP binding site. Taken together, these data suggested that the enzyme preferred a bulky lipophilic *para*-R3 group albeit in combination with the unsubstituted azaindole core (R2 = H).

With the pyrazole *N1*-position identified as the preferred position for Aurora B enzymatic and cellular activity, our SAR efforts focused on exploring different pyrazole R1 substituents with a goal of further improving the cellular potency of this series. On the basis of the putative binding mode (vida supra), the pyrazole ring occupies the sugar pocket region of the ATP-binding site. Therefore we incorporated polar hydrogen bond donating groups in an effort to enhance potency. Indeed, incorporation of ethanol (**12g**), propanol (**12j**), or 1,2-propanediol (**12i**) moieties resulted in the identification of compounds with high Aurora B inhibitory activity but with significant erosion in antiproliferative activity. The attenuated cellular activity of alcohols **12g**, **12j**, and **12i** is potentially due to their reduced cell permeability (artificial membrane permeability 27, 3, and 41 nm s^{-1}, respectively) relative to **12c** (artificial membrane permeability = 170 nm s^{-1}).[38] Substitution of the pyrazole with various substituted acetamides (compounds **12m**−**o**) was also not fruitful. Taken together, small R1-alkyl groups were the substituents of choice during the course of further SAR investigations.

Although an inhibitor bound Aurora B cocrystal structure was not available during these investigations, our putative binding mode revealed a solvent accessible area toward the front pocket of the Aurora B ATP-binding pocket and could potentially accommodate a wide variety of functionality (vide supra).[27] We reasoned that incorporation of an appropriately substituted aryl group adjacent to the presumed hinge binding moiety would allow for access to the solvent accessible area of the enzyme without interfering with hinge binding and also enable modulation of physicochemical properties. A number of such compounds were prepared and evaluated in the A549 cell proliferation assay in the presence and absence of 70% human serum in order to assess the effect of inhibitor binding to serum proteins on their antiproliferative activity (Table 2). A comparable 10−20-fold decrease in cellular potency in the presence of 70% human serum was noted for this set of derivatives (data not shown). Incorporation of a 3-*N*-acetylaniline at R2 (**17a**) led to a 20-fold attenuation in the in vitro Aurora B inhibitory activity relative to unsubstituted azaindole **12c**; surprisingly, however, cellular activity was not diminished (Table 2). Compound **17a** has much slower Aurora B/INCENP dissociation half-life (320 ± 120 min) relative to **12c** (7.7 ± 0.8 min), and it is possible that its true potency is underestimated in our in vitro biochemical assay even with a 30 min enzyme−inhibitor preincubation.[34] This could potentially explain the level of cellular activity for compound **17a**.

Table 1. Biochemical and Cellular Data for Substituted Pyrazole Derivatives (R1)



Cmpd	R1	R1 position	IC_{50} (nM)		A549 EC_{50} (nM)[a]
			Aur B	Aur A	
12a	H	—	32	3848	12762
12b	Et	*N2*	25	5600	1586
12c	Et	*N1*	2	631	79
12d	*t*-Bu	*N2*	40	5770	890
12e	*t*-Bu	*N1*	50	8156	476
12f		*N1*	16	2150	326
12g		*N1*	3	792	2626
12i		*N1*	1	377	9609
12j		*N1*	2	969	779
12k		*N1*	97	6195	NT
12m		*N1*	64	5676	>20000
12n		*N1*	64	3392	>20000
12o		*N1*	85	6810	>20000

[a] NT = not tested.

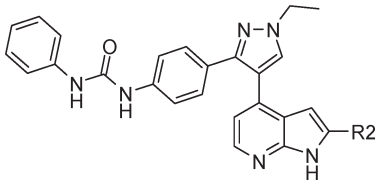
Incorporation of a *meta*-dimethlyaminomethyl-phenyl R2 group (**17c**) resulted in a further improvement in antiproliferative activity in A549 cells (EC_{50} = 14 nM). Interestingly, however, selectivity over Aurora A was diminished (cf. **12c**, 315-fold vs 3-fold). Reasons for the diminished Aurora A selectivity of compound **17c** and related compounds (e.g., **17a**, **17b**, **17e**) relative to **12c** are not clear, but a potential explanation is that the substituted phenyl group (R2) plays a role in orienting the phenylurea in the lipophilic back pocket, which is smaller and less accessible in Aurora A/TPX2.[7] In general, the presence of an R2-phenyl group containing a basic amine (e.g., dimethylamine (**17c**−**f**,**j**−**m**), morpholine (**17h**−**i**,**r**−**u**), or pyrrolidine (**17g**,**n**−**q**)) led to improved cellular activity. Replacing the phenyl group with amides (**22a**−**c**) resulted in potent Aurora B inhibitors but modest cellular potency. Aminomethyl derivatives **28a**−**f** exhibited reduced biochemical and cellular potency. No significant solubility or cell permeability differences were noted that could account for the attenuated activity of **28a**−**f**. On the basis of their improved potency in cells, R2-aryl groups containing a basic amine were selected for further SAR investigations.

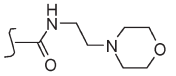
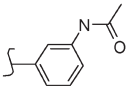
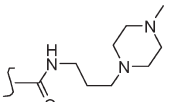
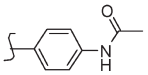
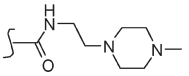
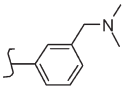
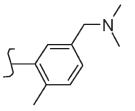
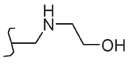
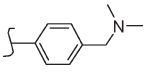
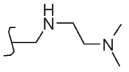
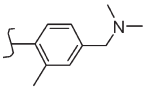
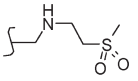
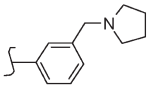
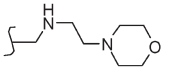
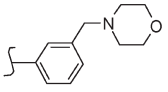
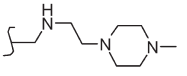
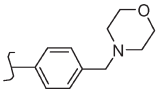
With the addition of aryl amines at the R2-position, we reinvestigated phenyl urea SAR with the intention of identifying groups that led to a reduction in overall molecular weight and lipophilicity of the compounds. Furthermore, taking into account the previously discussed SAR trends, we postulated that various combinations of R2 and R3 groups would affect the Aurora B potency and selectivity over Aurora A. As such, R2 and R3 combination analogues were prepared and evaluated in the biological assays (Table 3). A majority of the hybrid derivatives were highly potent against Aurora B and demonstrated excellent antiproliferative activity against A549 tumor cells. In fact, some compounds from this set have in vitro Aurora B/INCENP IC_{50}s that are similar to their EC_{50}s on cells, for example compound **17c**. Compound **17c** also has a slow Aurora B/INCENP dissociation half-life (520 ± 110 min) and, as discussed above, it is possible that its true potency is underestimated in our in vitro biochemical assay even with a 30 min enzyme−inhibitor preincubation.[34]

Modulation in selectivity over Aurora A depending on the R2/R3 combination was also noted. For example, replacement of the phenylurea of **17c** with an ethylurea (**17j**) resulted in a modest improvement in Aurora B inhibitory activity and an increase in selectivity over Aurora A from 3-fold to 42-fold while maintaining excellent antiproliferative activity. Selectivity was further improved to 252-fold through combination of the R3-dimethylurea group with the R2-*meta*-(dimethylaminomethyl)phenyl, providing **17k**. The observed selectivity may be attributed to the corresponding R2 group's potential role in orienting the urea group in the distinct lipophilic back pockets of Aurora B/INCENP and Aurora A/TPX2.[7] In addition to good selectivity over Aurora A, **17k** demonstrated excellent Aurora B inhibition (IC_{50} = 5 nM) and antiproliferative activity (A549 EC_{50} = 7 nM). Transposition of the dimethylaminomethyl tail moiety to the *para*-position (**17m**) led to retention in biochemical and cellular activity (cf. **17k**) and a slight diminution in Aurora B/A selectivity, from 252- to 156-fold. In general, *meta*-dimethylamino and morpholino tails were slightly favored over their *para* counterparts with respect to Aurora B vs A selectivity, regardless of the R3 group (cf. **17k** vs **17m** and **17s** vs **17u**) for this set of derivatives.

Selectivity over a panel of non-Aurora kinases was assessed for several of the compounds that showed potent in vitro activity and/or selectivity over Aurora A (Figure 3). Compound **12c** demonstrated >70-fold selectivity against this panel of kinases; however, when an aminoaryl group was introduced at the azaindole 2-position (compound **17c**), significant activity against LCK, LYN, MET, and ROCK

Table 2. Biochemical and Cellular Data for R2 Group Derivatives[a]



Cmpd	R2	Aur B IC_{50} (nM)	Aur A IC_{50} (nM)	A549 EC_{50} (nM)	Cmpd	R2	Aur B IC_{50} (nM)	Aur A IC_{50} (nM)	A549 EC_{50} (nM)
12c	H	2	631	79	**22a**		5	197	200
17a		44	126	156	**22b**		8	228	638
17b		44	62	110	**22c**		5	203	417
17c		20	53	14	**28a**		58	1701	4388
17d		60	113	174	**28b**		46	2819	18621
17e		23	45	8	**28c**		276	5477	NT
17f		26	42	16	**28d**		24	579	11539
17g		11	22	12	**28e**		22	2445	2857
17h		57	94	30	**28f**		83	5111	>20000
17i		66	59	17					

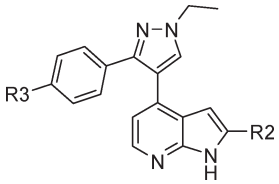
[a] NT = not tested.

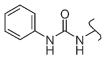
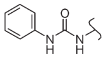
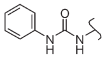
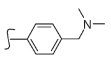
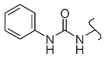
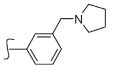
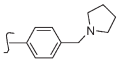
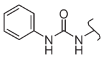
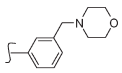
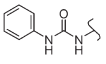
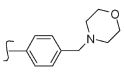
was observed. Truncating the phenylurea moiety of compound **17c** to an ethylurea (compound **17j**) resulted in significant attenuation of these off-target activities, and even further attenuation (>140-fold selectivity) was observed with dimethylurea **17k**. Compound **17k** represented the best combination of biochemical/cellular potency and selectivity within this set of analogues and was thus selected for further study.

Evaluation of 17k. The selectivity of **17k** was further determined by measuring its ability to inhibit 328 unique human protein and lipid kinases using either in vitro activity or binding assays.[39] Furthermore, we generated full dose−response analysis for a subset of 58 kinases to determine their IC_{50} values. In addition to the Aurora kinases, only five kinases were identified with IC_{50} values below 100 nM (Table 4), indicating that compound **17k** is a highly selective inhibitor of Aurora B and C kinase.

We recently reported that compound **17k** is a reversible, ATP-competitive inhibitor of Aurora B/INCENP and Aurora C/INCENP with K_i* values of 0.38 ± 0.29 and 1.5 ± 0.4 nM, respectively, and is >250-fold selective over Aurora A/TPX2, which had a K_i value of 490 ± 60 nM.[34] The K_i* values take into account the slow onset of inhibition and define the true potency of **17k** against the enzyme, as previously described.[34] Remarkably, **17k** exhibited >480 min and 270 ± 28 min dissociation half-lives in Aurora B/INCENP and Aurora C/INCENP, respectively, resulting in prolonged inhibition of kinase activity. The extremely slow off-rate of compound **17k** from Aurora B/INCENP is in contrast to compounds **1** and **2**, which display a dissociation

Table 3. Biochemical and Cellular Data for R2 and R3 Group Combinations



Cmpd	R3	R2	Aur B IC_{50} (nM)[a]	Aur A IC_{50} (nM)[a]	A549 EC_{50} (nM)
12c		H	2	631	79
12p			26	>10000	1530
17c			20	53	14
17j			3	128	12
17k			5	1259	7
17e			23	45	8
17l			1.7	39	6
17m			3.6	514	6
17g			11	22	12
17n			1.4	58	9
17o			2.1	366	7
17p			1.5	42	8
17q			4.5	414	6
17h			57	94	30
17r			5	70	26
17s			4.7	495	18
17i			66	59	17
17t			4.7	23	12
17u			8.1	250	9

[a] NT = not tested.

half-life of <30 min under the same conditions.[34] The potential measurable advantage of **17k**'s long dissociation rate is that it may confer a selective advantage such as less frequent dosing and perhaps greater tolerance over compounds with shorter half-lives. This hypothesis will ultimately be tested in clinical trials.

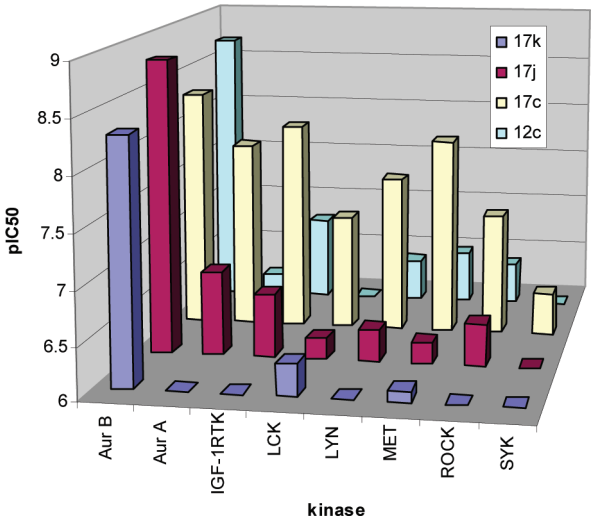


Figure 3. Kinase selectivity comparison for compounds **12c**, **17c**, **17j**, and **17k**.

Table 4. Inhibitory Activity of **17k** against Other Kinases

kinase	IC_{50} (nM)
AurA/TPX2	1259
AurB/INCENP	5
AurC/INCENP	6.5
FLT1	42
FLT4	74
TIE2	59
SIK	70
FGFR1	76

As we reported previously, compound **17k** follows a one-step Aurora B/INCENP binding model with an on rate of $0.022 \pm 0.004\ \mu M^{-1}\ s^{-1}$, and an off rate of $< 0.0014\ min^{-1}$, resulting in a dissociation half-life of >480 min.[34] To identify inhibitor structural features that could potentially contribute to a long residence time, Aurora B/INCENP dissociation rates were determined for a number of azaindole derivatives with varying R2 and R3 groups. Compound **12c**, which lacks substitution of the azaindole 2-position (R2), had a short dissociation rate of <10 min (Table 5). Incorporation of a *meta*-(dimethylaminomethyl)phenyl group onto the azaindole 2-position in combination with a phenyl urea at R3 (**17c**) resulted in a compound with a long dissociation half-life of 520 ± 110 min. Truncating the phenyl urea of **17c** to an ethyl (**17j**) or dimethyl urea (**17k**) also provided compounds with long Aurora B/INCENP dissociation half-lives of 200 and >480 min, respectively. Furthermore, acetamide **17a** had a long dissociation half-life, indicating that a basic amine at R2 is not necessary for the prolonged residence time on Aurora B/INCENP. For this limited set of derivatives, these results suggest that incorporation of a 2-aryl group on the azaindole ring contributes to the long dissociation half-life. Although the absence of a cocrystal structure makes it difficult to rationalize inhibitor−enzyme interactions that could explain the long dissociation half-life of these inhibitors, it is possible that the back pocket may take time to undergo conformational changes until it reaches a conformation accessible to compound

Table 5. Aurora B/INCENP Dissociation Half Life Values for Inhibitors

	12c	17a	17c	17j	17k
Aur B/INCENP $t_{1/2}$ (min)	7.7 ± 0.8	320 ± 120	520 ± 110	200 ± 50	> 480

Table 6. CYP450 IC_{50} Values (μM) for **17k** in Human Liver Microsomes

1A2 phenacetin	2C9 diclofenac	2C19 S-mephenytoin	2D6 bufuralol	3A4 nifedipine	3A4 midazolam
> 33	38	81	12	15	activator

binding. Additional conformational change may then lock the compound in the pocket, hence giving rise to the time dependent inhibition. However, it is apparent that some other undetermined factors also contribute to the time dependence as certain back-pocket binders (e.g., **12c**) do not show significant time dependent inhibition.

To test for the potential of compound **17k** to affect the metabolism and or clearance of other coadministered agents leading to clinical drug−drug interactions, IC_{50}s were generated against six CYP450 isozymes in human liver microsomes (Table 6). Compound **17k** displayed IC_{50} values ≥ 12 μM against the panel of CYP450 isozymes, with the exception of the 3A4 (midazolam) for which it was an activator. Our P450 inhibition assay in human liver microsomes was performed using selective probe substrates, and product formation was monitored by LC/MS/MS. The enzyme activity in the presence of compound **17k** was normalized with the enzyme activity in the absence of compound and expressed as a percentage of control activity. In the study with CYP3A4 and midazolam, increased enzyme activity was observed with increased inhibitor concentration (> 100% of control activity).

Treatment of a panel of human tumor cell lines with compound **17k** results in potent inhibition of histone H3 phosphorylation (pHH3) at serine 10, a substrate and marker of intracellular Aurora B activity.[37,40] In light of its on-target in vitro potency in biochemical and cellular assays and good overall kinase selectivity, **17k** made an excellent candidate for in vivo pharmacodynamic and efficacy evaluation using human tumor xenograft models in rodents. As a prelude to these studies, **17k** was evaluated for its intravenous pharmacokinetic parameters in the conscious mouse (Table 7). Following single dose iv administration at 1 mg kg^{-1}, **17k** showed blood clearance of 49.4 mL min^{-1} kg^{-1} and a dose normalized area under the curve (0 − ∞) of 345 ng·h mL^{-1} mg^{-1} kg^{-1}. The iv PK profiles for **17k** in rat, dog, and monkey have been reported elseware.[41] Compound **17k** also demonstrates > 10 mg/mL solubility in clinically acceptable formulations (pH 4).[41]

In an in vivo pharmacodynamic study, compound **17k** was assessed for its capacity to inhibit the phosphorylation of histone H3 (pHH3) at serine 10 in mice with advanced subcutaneous Colo205 tumors. The study was designed to measure the percent inhibition of pHH3 relative to control at 30 h post dose using a pHH3 ELISA. After intraperitoneal (ip) treatment of the mice with the indicated doses of **17k** at 30 h, a robust dose-dependent pharmacodynamic response, as measured by a decrease in phosphohistone H3 (serine 10), was observed and is consistent with in vivo Aurora B inhibition (Figure 4).

Compound **17k** was also evaluated for in vivo efficacy against human leukemia HL-60 tumors grown as a subcutaneous xenograft in nude mice (Figure 5). Compound **17k** was dosed daily (ip) at 75 or 100 mg kg^{-1} for five days and for two cycles (qdx5 × 2; doses indicated by arrows in Figure 5). In contrast to the untreated control mice, complete regression (CR) of the tumor was observed in all mice that received **17k** at both dose levels. Notably for the 100 mg kg^{-1} dose, no tumor regrowth was observed 51 days post the last dose. Further in vivo characterization of **17k** against solid human tumor xenografts and human leukemia has been reported.[37]

Table 7. Intravenous Pharmacokinetic Profile of **17k** in the Conscious Mouse[a]

dose (mg kg^{-1})	CL_b (mL min^{-1} kg^{-1})	$DNAUC_{(0-\infty)}$ (ng·h mL^{-1} mg^{-1} kg^{-1})	V_{dss} (L kg^{-1})	MRT (h)
2.0	49.4[b]	345	0.8[b]	0.3[b]

[a] n = 3. [b] CL_b was calculated using AUC_{0-t}; V_{dss} and MRT were estimated using AUC_{0-t} and $AUMC_{0-t}$.

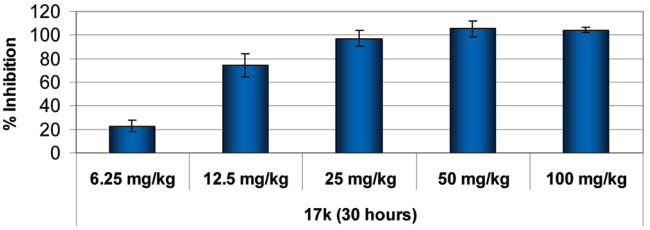


Figure 4. Inhibition of pHH3 after treatment of advanced Colo205 tumors in mice with **17k**.

Conclusion

In summary, lead optimization efforts of a 7-azaindole series of kinase inhibitors led to the discovery of compound **17k**, a potent, selective, long acting inhibitor of Aurora B/C suitable for evaluation in cancer patients. Key to the advancement of the series was the introduction of a 2-aryl group containing a basic amine onto the azaindole, leading to significantly improved cellular activity. The presence of a 2-aryl group also allowed for truncation of the phenylurea R3 group, leading to compounds with dramatically improved kinase selectivity without compromising Aurora B activity or cellular potency. Compound **17k** is a novel, highly potent, and selective Aurora B and C/INCENP inhibitor (K_i* = 0.38 ± 0.29 and 1.5 ± 0.4 nM, respectively)[34] that exhibits potent antiproliferative activity in human tumor cell culture (A459 lung cell EC_{50} = 7 nM).[37,40] This activity was manifested in vivo as measured by a dose dependent inhibition of histone H3 phosphorylation at serine 10, a hallmark of Aurora B inhibition, in human colon cancer tumors (Colo205) and tumor regression in human leukemia (HL-60) mouse xenografts following intraperitoneal administration. Isoform selectivity of compound **17k** may be attributed to the urea group (R3) imparting unfavorable interactions with the smaller, less accessible hydrophobic back pocket of Aurora A/TPX2 relative to that of Aurora B/INCENP.[7] The extremely slow dissociation half-life of compound **17k** from Aurora B/INCENP is a clear distinction from clinical compounds **1** and **2**. A structure based rationale for the time dependent inhibition is difficult in absence of an inhibitor−enzyme cocrystal structure. One possible explanation is that the back pocket may take time to undergo conformational changes until it reaches a conformation accessible to compound binding, and additional conformational change may then lock the compound in the pocket, hence giving rise to the time dependent

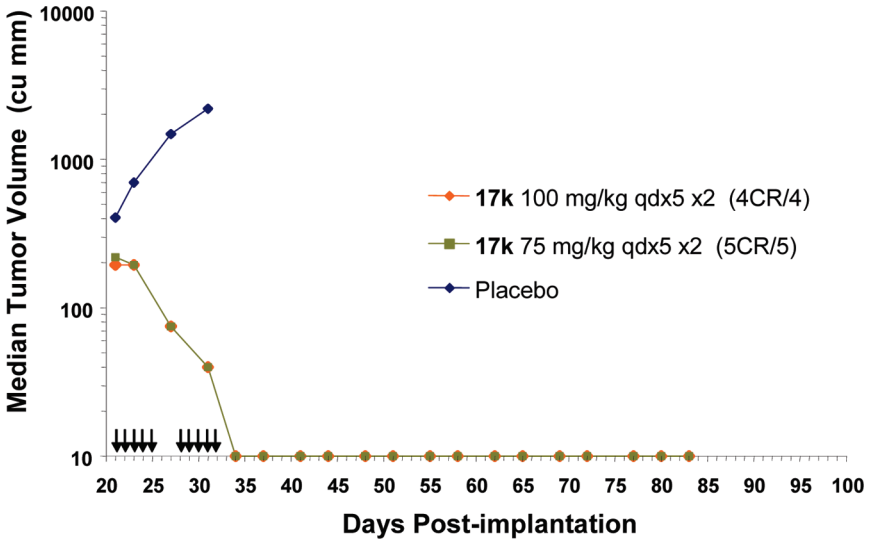


Figure 5. Evaluation of **17k** against advanced HL-60 (acute monocytic human leukemia) tumors in nude mice.

inhibition. Despite Aurora B being relatively short-lived in cells prior to degradation,[42] the >8 h half-life of compound **17k** suggests that it can stay bound until Aurora B is degraded. This is the maximum inhibition one can ever achieve for Aurora B. Furthermore, it is possible that the slow enzyme off-rate of the compound may in fact extend the half-life of the protein, although this has not yet been demonstrated. Although the clinical relevance of a slow dissociation rate of an enzyme−inhibitor complex remains to be seen, the long residence time of **17k** may prove advantageous by prolonged inhibition of Aurora B in vivo, after it has been cleared from systemic circulation.[32,33,34] Evaluation of compound **17k** in human clinical trials is planned.

Experimental Section

Chemistry. General Methods. Unless otherwise noted, starting materials and reagents were purchased from commercial sources and used without further purification. Air- or moisture-sensitive reactions were carried out under a nitrogen atmosphere. Anhydrous solvents were obtained from Sigma-Aldrich. Microwave irradiation was carried out in a Personal Chemistry Emrys Optimizer microwave. Flash chromatography was performed using silica gel (EM Science, 230−400 mesh) under standard techniques or using silica gel cartridges (RediSep normal phase disposable flash columns) on an Isco CombiFlash. Reverse phase HPLC purification was conducted on a Gilson HPLC (monitoring at a wavelength of 214 or 254 nm) with a YMC ODS-A C18 column (5 μm, 75 mm × 30 mm), eluting with 5−90% CH_3CN in H_20 with 0.1% TFA unless otherwise noted. ^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. Chemical shifts (δ) are reported in ppm relative to an internal solvent reference. Apparent peak multiplicities are described as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), or m (multiplet). Coupling constants (J) are reported in hertz (Hz) after the integration. LCMS analysis was conducted on a Shimadzu 10Avp LC/UV and a PE Sciex single quadruple MS using a Thermo Aquasil column (C18, 40 mm × 1 mm, 5 μ particle diameter) and a gradient of 5−100% MeCN (0.018% TFA)/water (0.02% TFA) over 3.2 min. The retention time (R_t) is expressed in minutes at a UV detection of 214 nm. All tested compounds were determined to be ≥95% purity by LCMS unless otherwise noted. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ.

4-Bromo-1-{[4-(methyloxy)phenyl]methyl}-3-(4-nitrophenyl)-1*H*-pyrazole (7e). To a solution of 4-bromo-3-(4-nitrophenyl)-1*H*-pyrazole (1.9 mmol) in *N*,*N*-dimethylformamide (5.0 mL) was added sodium hydride as a 60% dispersion in mineral oil (2.1 mmol). After 40 min, *p*-methoxybenzylchloride (2.2 mmol) was added and the resulting mixture was stirred for 1 h. The reaction mixture was then poured into water (60 mL), and the precipitate was filtered and rinsed with water (2 × 15 mL). The brown solid was dried under vacuum to yield 97% of the title product (**7e**). MS m/z 388.2 $[M + H]^+$. ^{1}H NMR (DMSO-d_6): δ 8.33 (d, 2H, J = 8.8 Hz), 8.27 (s, 1H), 8.11 (d, 2H, J = 8.6 Hz), 7.32 (d, 2H, J = 8.6 Hz), 6.94 (d, 2H, J = 8.6 Hz), 5.33 (s, 2H), 3.74 (s, 3H).

1-{[4-(Methyloxy)phenyl]methyl}-3-(4-nitrophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (8e). A solution of 4-bromo-1-{[4-(methyloxy)phenyl]methyl}-3-(4-nitrophenyl)-1*H*-pyrazole (**7e**, 1.44 mmol), bis(pinacolato)diboron (1.73 mmol), potassium acetate (4.33 mmol), and dichlorobis(triphenylphosphine)palladium(II) (0.072 mmol) in dioxane (7.0 mL) was heated at 100 °C for 4 h. Crushed and activated 3 Å molecular sieves and additional dichlorobis(triphenylphosphine)-palladium(II) (0.036 mmol) were added to the reaction mixture, which was heated at 100 °C for 17 h. The reaction mixture was cooled, filtered through celite, diluted with water (75 mL), and extracted with (3 × 60 mL) ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated in vacuo. Purification of the residue by reverse phase HPLC (50−100% acetonitrile in water) and concentration in vacuo provided the title product (**8e**) as an orange solid (20%). MS m/z 435.4 $[M + H]^+$. ^{1}H NMR ($CDCl_3$): δ 8.26 (d, 2H, J = 8.9 Hz), 8.21 (d, 2H, J = 9.1 Hz), 7.75 (s, 1H), 7.28 (m, 2H), 6.92 (d, 2H, J = 8.6 Hz), 5.31 (s, 2H), 3.83 (s, 3H), 1.33 (s, 12H).

4-[1-{[4-(Methyloxy)phenyl]methyl}-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridine. A solution of 4-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (0.26 mmol), 1-{[4-(methyloxy)phenyl]-methyl}-3-(4-nitrophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (**8e**, 0.28 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.013 mmol) in 2 M aq potassium carbonate (0.75 mL) and dioxane (0.75 mL) was heated at 98 °C for 19 h. The reaction mixture was cooled, diluted with water (5 mL), and extracted with (3 × 5 mL) ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated in vacuo. Purification of the residue by silica gel chromatography (50−70% ethyl acetate/hexanes) and concentration in vacuo provided the title product as a yellow solid containing ~20% triphenylphosphine oxide (85% yield). The intermediate was used directly in the next

step. MS m/z 426.2 $[M + H]^+$. ^{1}H NMR (DMSO-d_6): δ 11.73 (s, 1H), 8.34 (s, 1H), 8.16−8.14 (m, 3H), 7.62 (d, 2H, J = 9.1 Hz), 7.42 (m, 2H), 7.39 (m, 1H), 6.96 (d, 2H, J = 8.8 Hz), 6.86 (d, 1H, J = 5.0 Hz), 6.12 (m, 1H), 5.41 (s, 2H), 3.75 (s, 3H).

4-[3-(4-Nitrophenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridine. A solution of 4-[1-{[4-(methyloxy)phenyl]methyl}-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridine (0.22 mmol) in trifluoroacetic acid (0.75 mL) was heated at 74 °C for 1.5 h. The reaction mixture was diluted with water (4 mL) and extracted with (3 × 5 mL) ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by reverse phase HPLC (5−85% acetonitrile in water with 0.1% TFA), neutralization of the fractions, and extraction into ethyl acetate, drying over sodium sulfate, and concentration in vacuo afforded the title product as a yellow solid (64%). MS m/z 306.4 $[M + H]^+$. ^{1}H NMR (DMSO-d_6): δ 13.62 (s, 1H), 11.70 (s, 1H), 8.22−8.16 (m, 4H), 7.64 (d, 2H, J = 8.6 Hz), 7.39 (m, 1H), 6.88 (d, 1H, J = 4.8 Hz), 6.10 (s, 1H).

4-[4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]aniline. A mixture of 4-[3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo-[2,3-*b*]pyridine (0.13 mmol) and tin metal (0.67 mmol) in 6N aq hydrochloric acid (0.75 mL) and ethanol (0.75 mL) was heated at 70 °C for 1 h. The reaction mixture was cooled and filtered through celite, and the solution was poured into saturated aq sodium bicarbonate (60 mL) and extracted with (3 × 50 mL) ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The title product (yellow solid, quantitative) was used without further purification in the next step. MS m/z 276.2 $[M + H]^+$.

***N*-Phenyl-*N*′-{4-[4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]phenyl}urea (12a).** To a solution of 4-[4-(1*H*-pyrrolo-[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]aniline (0.13 mmol) and triethylamine (0.20 mmol) in tetrahydrofuran (1.5 mL) was added phenyl isocyanate (0.13 mmol). After 14 h, the reaction mixture was concentrated in vacuo, and the residue was purified by reverse phase HPLC (10−90% acetonitrile to water with 0.1% TFA) to provide a mixture of bis- and monourea adducts (∼2:1 ratio).

This mixture was dissolved in methanol (1.0 mL), treated with 6N aq sodium hydroxide (0.01 mL), and heated at 70 °C for 45 min. The resultant precipitate was filtered, rinsed with methanol, and dried in vacuo. Formation of the hydrochloride salt of the title product (**12a**) with 4 M HCl in dioxane gave a yellow powder in 25% yield. MS m/z 395.0 $[M + H]^+$. ^{1}H NMR (DMSO-d_6): δ 12.75 (s, 1H), 9.63 (s, 1H), 9.45 (s, 1H), 8.32 (d, 1H, J = 5.8 Hz), 8.24 (s, 1H), 7.65 (m, 1H), 7.48 (d, 2H, J = 8.5 Hz), 7.46 (d, 2H, J = 7.6 Hz), 7.32 (d, 2H, J = 8.8 Hz), 7.27 (t, 2H, J = 8.0 Hz), 7.16 (d, 1H, J = 6.0 Hz), 6.96 (t, 1H, J = 7.4 Hz), 6.56 (m, 1H).

4-Bromo-1-ethyl-5-(4-nitrophenyl)-1*H*-pyrazole (7a). The crude mixture of 4-bromo-1-ethyl-5-(4-nitrophenyl)-1*H*-pyrazole (minor) and 4-bromo-1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazole (major) (∼15 g) was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to 20% ethyl acetate in hexane. This provided 5.92 g of a 1:1 mixture of 4-bromo-1-ethyl-5-(4-nitrophenyl)-1*H*-pyrazole (minor) and 4-bromo-1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazole (major). This mixture was separated by reverse phase HPLC, eluting with acetonitrile and water (no TFA). The desired fractions were concentrated to furnish the title compound (2.542 g). MS m/z 296.6 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.26 (3 H, t, J = 7.20 Hz) 4.10 (2 H, d, J = 7.33 Hz) 7.73−7.88 (3 H, m) 8.40 (2 H, d, J = 8.84 Hz).

***N*-[4-(4-Bromo-1-ethyl-1*H*-pyrazol-5-yl)phenyl]-*N*′-phenylurea (10b).** A mixture of 4-bromo-1-ethyl-5-(4-nitrophenyl)-1*H*-pyrazole (**7a**, 0.5 g, 1.688 mmol), tin metal (1 g, 8.44 mmol), 6N hydrochloric acid (aq) (9 mL), and ethanol (9 mL) was stirred at 70 °C for 4.75 h. The reaction mixture was filtered, the filtrate concentrated in vacuo, and the residue used directly in the next reaction.

The residue was dissolved in pyridine (16 mL), phenylisocyanate (0.203 mL, 1.857 mmol) was added, and the reaction mixture was stirred at room temperature under an atmosphere of nitrogen for 2 h. The solution was purifed directly on a silica gel column, eluting with 40−80% ethyl acetate in hexanes to provide the title compound (**10b**, 0.37 g, 57%). MS m/z 385.3, 387.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.19−1.31 (3H, m), 4.05 (2H, q, J = 7.33 Hz), 6.99 (1H, t, J = 7.33 Hz), 7.23−7.40 (4H, m), 7.48 (2H, d, J = 7.58 Hz), 7.58−7.69 (3H, m), 8.79 (1H, s), 8.95 (1H, s).

***N*-{4-[1-Ethyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-5-yl]phenyl}-*N*′-phenylurea (12b).** A mixture of *N*-[4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)phenyl]-*N*′-phenylurea (**10b**, 0.135 g, 0.352 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (86 mg, 0.352 mmol), tetrakis-(triphenylphosphine)palladium(0) (20.3 mg, 0.0176 mmol), anhydrous 1,4-dioxane (2 mL), and 2.0 M aq potassium carbonate (2 mL) was stirred at 100 °C in a sealed tube for 18 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and the organic portion separated. The aq portion was extracted with ethyl acetate (3 × 3 mL), and the combined organic layers were dried over magnesium sulfate and concentrated in vacuo. Purification of the residue by reverse phase HPLC provided the title compound (**12b**) as a white solid (73 mg, 49%). MS m/z 423.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (3H, t, J = 7.20 Hz), 4.07 (2H, q, J = 7.16 Hz), 6.38 (1H, dd, J = 3.54, 1.77 Hz), 6.59 (1H, d, J = 5.05 Hz), 6.98 (1H, t, J = 7.33 Hz), 7.22−7.34 (4H, m), 7.37−7.41 (1H, m), 7.46 (2H, d, J = 7.58 Hz), 7.55 (2H, d, J = 8.59 Hz), 7.91−8.05 (2H, m), 8.77 (1H, s), 8.92 (1H, s), 11.60 (1H, br s).

5-(4-Nitrophenyl)-1*H*-pyrazole (5a). A solution of 1-(4-nitrophenyl)ethanone (100 g, 605 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (86.5 g, 726 mmol) in *N*,*N*-dimethylformamide (1000 mL) was stirred for 1 h at 80 °C. The reaction was concentrated, redissolved in ethanol, (1000 mL) and treated with hydrazine monohydrate (100 mL, 1816 mmol). After the reaction was stirred 2 h at 70 °C, it was cooled to room temperature and poured into ice−water (2000 mL). Solid precipitated out of the solution and was filtered, washed with water (4 × 500 mL), and dried to provide the title product (**5a**) as a yellow powder (98%). MS m/z 190.2 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.04−9.29 (m, 1H), 8.34 (d, J = 8.84 Hz, 2H), 8.12 (d, J = 8.84 Hz, 2H), 7.78 (s, 1H).

4-Bromo-3-(4-nitrophenyl)-1*H*-pyrazole (6a). A solution of 5-(4-nitrophenyl)-1*H*-pyrazole (113 g, 595 mmol) in *N*,*N*-dimethylformamide (1000 mL) was treated with *N*-bromosuccinimide (116 g, 654 mmol). The reaction was stirred for 30 min at room temperature and was poured into ice−water (1000 mL). Solid precipitated out of the solution and was filtered, washed with water (4 × 500 mL), and dried to provide the title product (**6a**) as an off-white powder (90%). MS m/z 269.2 $[M + H]^+$. ^{1}HNMR (400 MHz, DMSO-d_6) δ ppm 8.16 (d, J = 8.59 Hz, 2H), 8.20 (s, 1H), 8.34 (d, J = 8.34 Hz, 2H), 13.70 (br s, 1H).

4-Bromo-1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazole (7b). A 0 °C solution of 4-bromo-3-(4-nitrophenyl)-1*H*-pyrazole (130 g, 485 mmol) in *N*,*N*-dimethylformamide (1000 mL) was slowly treated with sodium hydride (19 g, 485 mmol) and then iodoethane (47 mL, 582 mmol). The reaction mixture was stirred for 30 min at room temperature and then poured into ice−water (1000 mL). Solid was precipitated out of the solution and was collected by filtration, washed with water (4 × 500 mL), and dried to provide 4-bromo-1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazole (**7b**) as a light-brown powder (94%). MS m/z 297.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.43 (t, J = 7.33 Hz, 3H), 4.22 (q, J = 7.33 Hz, 2H), 8.13 (d, J = 8.84 Hz, 2H), 8.22 (s, 1H), 8.34 (d, J = 8.84 Hz, 2H).

1-Ethyl-3-(4-nitrophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (8a). A solution of 4-bromo-1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazole (8 g, 27 mmol), 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi-1,3,2-dioxaborolane (7.6 g, 30 mmol), potassium

acetate (8 g, 81 mmol), and bis(triphenylphosphine)palladium(II) dichloride (758 mg, 1.08 mmol) in 1,4-dioxane (30 mL) was stirred for 3 h at 100 °C in a sealed tube. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (200 mL), filtered though a silica-gel plug, and concentrated. Purification of the residue by reverse phase HPLC provided the title product (**8a**) as a yellow powder (28%). MS *m*/*z* 344.2 $[M + H]^+$. ^{1}HNMR (400 MHz, DMSO-d_6) δ ppm 1.29 (s, 12 H), 1.42 (t, $J = 7.20$ Hz, 3 H), 4.23 (q, $J = 7.16$ Hz, 2 H), 8.11 (s, 1 H), 8.15−8.21 (m, 2 H), 8.26 (d, $J = 9.09$ Hz, 2 H).

4-[1-Ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo-[2,3-*b*]pyridine. 4-[1-Ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridine. A solution of 1-ethyl-3-(4-nitrophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (2.6 g, 7.5 mmol), 4-bromo-1*H*-pyrrolo[2,3-*b*]pyridine[43] (1.2 g, 6.3 mmol), and tetrakis(tripheylyphosphine)palladium(0) (291 mg, 0.25 mmol) in 1,4-dioxane (12 mL) and 2 M aq potassium carbonate (12 mL) was stirred for 18 h at 100 °C in a sealed tube. Upon cooling to room temperature, product precipitated out of solution, which was filtered and dried to provide the title product as a light-yellow powder (80%). MS *m*/*z* 334.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 (t, $J = 7.20$ Hz, 3H), 4.31 (q, $J = 7.33$ Hz, 2H), 6.15 (dd, $J = 3.41$, 1.89 Hz, 1H), 6.87 (d, $J = 4.80$ Hz, 1H), 7.35−7.44 (m, 1H), 7.59−7.69 (m, 2H), 8.13−8.19 (m, 2H), 8.25 (s, 1H), 11.72 (br s, 1H).

4-[1-Ethyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]-aniline. A solution of 4-[1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridine (59 mmol) in glacial acetic acid (25 mL) was treated with zinc dust (41 mmol) and stirred for 1 h at room temperature. The reaction was then filtered and concentrated in vacuo. The resultant residue was suspended in a 1:1 mixture of ethyl acetate (10 mL) and saturated aq sodium bicarbonate (10 mL) and stirred 30 min. The organic layer was separated, filtered, washed with brine (1 × 5 mL), dried over sodium sulfate, and concentrated. Purification of the residue by flash chromatography (80−100% ethyl acetate/hexanes) provided the title product as a white powder (85%). MS *m*/*z* 304.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 (t, $J = 7.20$ Hz, 3H), 4.20 (q, $J = 7.33$ Hz, 2H), 5.14 (br s, 2H), 6.28 (br s, 1H), 6.45 (d, $J = 8.59$ Hz, 2H), 6.81 (d, $J = 5.05$ Hz, 1H), 7.03 (d, $J = 8.59$ Hz, 2H), 7.38 (d, $J = 3.28$ Hz, 1H), 8.02−8.12 (m, 2H), 11.67 (br s, 1H).

***N*-{4-[1-Ethyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (12c).** A solution of 4-[1-ethyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]aniline (2.2 mmol) in pyridine (4 mL) was treated with phenyl isocyanate (2.4 mmol) and stirred for 1 h at room temperature. The reaction mixture was concentrated in vacuo, and purification of the residue by flash chromatography (80−100% ethyl acetate/hexanes) provided the title product (**12c**) as a white powder (50%). MS *m*/*z* 424.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (t, 3H), 4.25 (q, $J = 7.24$ Hz, 2H), 6.25 (dd, $J = 3.41$, 1.89 Hz, 1H), 6.82 (d, $J = 5.05$ Hz, 1H), 6.97 (t, $J = 7.33$ Hz, 1H), 7.21−7.33 (m, 4H), 7.34−7.41 (m, 3H), 7.45 (d, $J = 7.58$ Hz, 2H), 8.11 (d, $J = 5.05$ Hz, 1H), 8.15 (s, 1H), 8.70 (d, $J = 11.62$ Hz, 2H), 11.63 (br s, 1H).

1-(1,1-Dimethylethyl)-5-(4-nitrophenyl)-1*H*-pyrazole (5b). To a round bottomed flask equipped with a stir bar was added 4-nitroacetophenone (2.21 g, 13.37 mmol), *N*,*N*-dimethylformamide dimethyl acetal (2.13 mL, 16.04 mmol), and *N*,*N*-dimethylformamide (33.4 mL). The reaction mixture was stirred at 80 °C under a reflux condenser for 1 h 20 min. The solution was concentrated in vacuo, the residue taken up in ethanol, treated with *tert*-butylhydrazine hydrochloride (5 g, 40.125 mmol), and the solution stirred at 70 °C for 2.5 h under an atmosphere of nitrogen. LCMS did not show complete consumption of starting material so the reaction mixture was heated for a further 5 h at 70 °C. The reaction mixture was then cooled to room temperature, poured into water, and the deep-yellow precipitate that formed was collected, washed with water (× 3). This precipitate (2.62 g, 80%) was determined to be the desired isomer (**5b**) following bromination and NOE studies. MS *m*/*z* 190.0 $(M - C(CH_3)_3 + 2H)$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 (9H, s), 6.25 (1H, d, $J = 1.52$ Hz), 7.49 (1H, d, $J = 1.52$ Hz), 7.70 (2H, app d, $J = 8.59$ Hz), 8.28 (2H, app d, $J = 8.59$ Hz).

4-Bromo-1-(1,1-dimethylethyl)-5-(4-nitrophenyl)-1*H*-pyrazole (6b). To a solution of 1-(1,1-dimethylethyl)-5-(4-nitrophenyl)-1*H*-pyrazole (**5b**, 1.77 g, 7.22 mmol) in dry *N*,*N*-dimethylformamide (22 mL) was added *N*-bromosuccinimide (1.413 g, 7.94 mmol). The reaction mixture was stirred at room temperature for 30 min and then poured into water. The white precipitate that formed was collected and washed with water and then hexanes to provide the title compound (**6b**, 2.176 g, 93%). MS *m*/*z* 268.0, 270.0 $[M - C(CH_3)_3 + 2H]$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.38 (9H, s), 7.62−7.79 (3H, m), 8.35 (2H, d, $J = 8.59$ Hz).

1-(1,1-Dimethylethyl)-5-(4-nitrophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (8d). In a sealed tube was combined 4-bromo-1-(1,1-dimethylethyl)-5-(4-nitrophenyl)-1*H*-pyrazole (**6b**, 2.08 g, 6.416 mmol), potassium acetate (1.89 g, 19.248 mmol), bis(pinacolato)diboron (1.792 g, 7.058 mmol), and bis(diphenylphosphino)palladium(II)dichloride (0.18 g, 0.257 mmol) followed by anhydrous 1,4-dioxane (64.16 mL). The reaction mixture was stirred at 100 °C for 16.5 h then cooled to rt. The solution was diluted with EtOAc (5 mL) and washed with water (× 1). The aq solution was extracted with ethyl acetate (× 4) and the combined organic layers dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by reverse phase HPLC to give the title compound (**8d**, 0.273 g, 11%). MS *m*/*z* 315.2 $[M - C(CH_3)_3 + H]$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 (9H, s), 1.30 (12H, s), 7.63−7.67 (3H, m), 8.23−8.27 (2H, m).

***N*-{4-[1-(1,1-Dimethylethyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-5-yl]phenyl}-*N*′-phenylurea (12d).** A mixture of 1-(1,1-dimethylethyl)-5-(4-nitrophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (**8d**, 0.103 g, 0.277 mmol), 4-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (46 mg, 0.0.231 mmol), 1,4-dioxane (2 mL), 2 M aq potassium carbonate (2 mL), and tetrakis(triphenylphosphine)palladium(0) (26.7 mg, 0.028 mmol) in a sealed tube was stirred at 100 °C for 18 h. The solution was cooled to rt, diluted with ethyl acetate, and washed with water (× 1). The organic layer was separated, and the aqueous portion was further extracted with ethyl acetate (× 3). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo. This residue was purified by reverse phase HPLC to give the 0.100 g of 4-[1-(1,1-dimethylethyl)-5-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridine with 91% purity by LCMS (0.091 g, 91%). This 91% pure material was used in the next reaction without further purification. MS *m*/*z* 362.2 $[M + H]^+$. A mixture of 4-[1-(1,1-dimethylethyl)-5-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridine (~0.100 g, 0.276 mmol), glacial acetic acid (15 mL), zinc dust (90.4 mg, 1.38 mmol), and ethanol (1.5 mL) was stirred at room temperature for 1.5 h. The reaction mixture was filtered through a fritted funnel, concentrated in vacuo, and dried in vacuo. The residue was dissolved in pyridine (2.75 mL) and phenylisocyanate (30 μL, 0.276 mmol) added. The reaction mixture was stirred at room temperature overnight. The solution was concentrated in vacuo and the residue purified by reverse phase HPLC to furnish the title compound (**12d**, 72 mg, 58%). MS *m*/*z* 451.2 $[M + H]^+$. LCMS purity 92%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.47 (9H, s), 6.40 (1H, d, $J = 5.05$ Hz), 6.59 (1H, dd, $J = 3.41$, 1.89 Hz), 7.50−7.72 (6H, m), 7.86 (1H, d, $J = 4.80$ Hz), 7.95 (1H, s), 8.68 (4H, s), 8.77 (1H, s), 8.91 (1H, s), 11.60 (1H, br s).

1-(1,1-Dimethylethyl)-3-(4-nitrophenyl)-1*H*-pyrazole (5c). To a round bottomed flask equipped with a stir bar was added 4-nitroacetophenone (2.21 g, 13.37 mmol), *N*,*N*-dimethylformamide dimethyl acetal (2.13 mL, 16.04 mmol), and *N*,*N*-dimethylformamide (33.4 mL). The reaction mixture was stirred at 80 °C under reflux for 1 h 20 min. The solution was concentrated in vacuo, the residue taken up in ethanol, treated with

tert-butylhydrazine hydrochloride (5 g, 40.125 mmol), and the solution stirred at 70 °C for 2.5 h under an atmosphere of nitrogen. LCMS analysis did not show complete consumption of starting material so the reaction mixture was heated for a further 5 h at 70 °C. The reaction mixture was then cooled to room temperature and poured into water, and the deep-yellow precipitate that formed was collected and washed with water (× 3). This precipitate (2.62 g, 79.9%) was determined to be the undesired isomer after bromination and NOE studies. The filtrate was concentrated and a second crop of yellow precipitate formed, containing the desired title compound (**5c**) as the minor isomer (0.539 g, 16%). This material was used in the next step without further purification. MS *m*/*z* 190.0 [(M − $C(CH_3)_3$ + 2H].

4-Bromo-1-(1,1-dimethylethyl)-3-(4-nitrophenyl)-1*H*-pyrazole (6c). To a solution of 1-(1,1-dimethylethyl)-3-(4-nitrophenyl)-1*H*-pyrazole (**5c**, 0.375 g, 1.529 mmol) in anhydrous *N*,*N*-dimethylformamide (5 mL) was added *N*-bromosuccinimide (0.299 g, 1.68 mmol). The reaction mixture was stirred at room temperature for 30 min and then poured into water. The white precipitate that resulted was collected to furnish the title compound (**6c**) as a white solid (0.48 g, 97%). MS *m*/*z* 268.0, 270.0 [M − $C(CH_3)_3$ + 2H].

***N*-{4-[4-Bromo-1-(1,1-dimethylethyl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (10d).** A mixture of 4-bromo-1-(1,1-dimethylethyl)-3-(4-nitrophenyl)-1*H*-pyrazole (**6c**, 48 mg, 0.148 mmol), zinc dust (67.7 mg, 1.036 mmol), acetic acid (1 mL), and ethanol (1 mL) was stirred at room temperature for 5 h. The solution was filtered and the filtrate concentrated in vacuo. This residue was dissolved in anhydrous pyridine (2 mL), and phenylisocyanate (17.8 μL, 0.163 mmol) was added. The reaction mixture was stirred under an atmosphere of nitrogen for 1 h and 45 min. The solution was concentrated in vacuo to a provide a crude sample of the title compound (**10d**, 61 mg, quantitative), which was used in the next reaction without further purification. MS *m*/*z* 415.4 $[M + H]^+$.

***N*-{4-[1-(1,1-Dimethylethyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (12e).** A mixture of *N*-{4-[4-bromo-1-(1,1-dimethylethyl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (**10d**, 61 mg, 0.148 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (36 mg, 0.148 mmol), tetrakis(triphenylphosphine)palladium(0) (17.1 mg, 0.015 mmol), anhydrous *N*,*N*-dimethylformamide (1.5 mL), and satd aq sodium bicarbonate (0.44 mL) was stirred at 100 °C in a sealed tube for 5 h and 15 min. The reaction mixture was cooled to room temperature, filtered, and concentrated in vacuo. The residue was taken in ethyl acetate and purified by silica gel chromatography, eluting with 20−100% ethyl acetate in hexane followed by a second silica gel purification, eluting with 90−100% ethyl acetate. Final purification by reverse phase HPLC provided the title compound (**12e**) as a white solid (4 mg, 6%). MS *m*/*z* 451.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.47 (10H, s), 6.51 (1H, d, *J* = 5.31 Hz), 6.75 (1H, br s), 6.97 (1H, t, *J* = 7.33 Hz), 7.26−7.35 (5H, m), 7.47 (2H, d, *J* = 7.58 Hz), 7.52−7.59 (3H, m), 7.99 (1H, d, *J* = 5.56 Hz), 8.05 (1H, s), 9.25 (1H, s), 9.49 (1H, s), 12.08 (1H, br s).

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo-[2,3-*b*]pyridine (11). In a sealed tube was combined 4-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (92 mg, 0.47 mmol), potassium acetate (0.14 g, 1.40 mmol), bis(pinacolato)diboron (0.24 g, 0.93 mmol), and 1,1′-bis(diphenylphosphino)ferrocenepalladium(II)dichloride dichloromethane complex (15.25 mg, 0.018 mmol) followed by anhydrous 1,4-dioxane (3.11 mL). The reaction mixture was stirred at 90 °C for 18 h and then cooled to room temperature. After dilution with ethyl acetate (5 mL) and filtration through a pad of celite, the filtrate was concentrated in vacuo. The residue was purified by reverse phase HPLC to provide the title product (**11**) as a white solid (48 mg, 64%). MS *m*/*z* 302.2 [M − $(CH_3)_2CC(CH_3)_2$ + 2H]. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (12H, s), 6.66 (1H, dd, *J* = 3.28, 1.77 Hz), 7.29 (1H, d, *J* = 4.55 Hz), 7.48−7.59 (1H, m), 8.22 (1H, d, *J* = 4.55 Hz), 11.65 (1H, br s).

***N*-[4-(4-Bromo-1*H*-pyrazol-3-yl)phenyl]-*N*′-phenylurea (10a).** A heterogeneous mixture of 4-bromo-3-(4-nitrophenyl)-1*H*-pyrazole (2.1 g, 7.83 mmol), elemental tin dust (4.65 g, 39.16 mmol), 6.0N aq HCl (30 mL), and absolute ethanol (30 mL) was stirred at 70 °C for 1 h. The solution was filtered through celite and concentrated in vacuo. The residue was dissolved in anhydrous pyridine (20 mL) and anhydrous CH_2Cl_2 (10 mL). Phenylisocyanate (0.86 mL, 7.83 mmol) was added dropwise and the reaction mixture stirred at room temperature overnight. Concentration in vacuo and purification by reverse phase HPLC afforded the title compound as a white solid (**10a**, 1.6 g, 57%). MS *m*/*z* 357.0 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.91−7.04 (1H, m), 7.21−7.35 (2H, m), 7.40−7.51 (2H, m), 7.57 (2H, m, *J* = 8.59 Hz), 7.71 (2H, m, *J* = 8.59 Hz), 7.86 (1H, br s), 8.80 (1H, s), 8.91, (1H, br s), 13.29 (1H, br s).

***N*-{4-[4-Bromo-1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (10e).** To a solution of *N*-[4-(4-bromo-1*H*-pyrazol-3-yl)phenyl]-*N*′-phenylurea (**10a**, 0.1 g, 0.28 mmol) in *N*,*N*-dimethylformamide (5 mL) cooled to −78 °C was added 1 M potassium *t*-butoxide in THF (0.765 mL, 0.765 mmol) slowly. The reaction mixture was stirred at −78 °C for 10 min, and then trifluoromethanesulfonic acid 2,2,2-trifluoroethylester (60.34 mg, 0.26 mmol) was added. The reaction mixture was stirred for 2 h at −78 °C and then allowed to warm to room temperature and stirred for a further 21 h. The reaction was quenched by addition of saturated ammonium chloride (aq). The solution was filtered and purified directly by reverse phase HPLC to provide the title compound (**10e**) confirmed by NOE studies (43 mg, 38%). MS *m*/*z* 439.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.20 (2H, q, *J* = 9.09 Hz), 6.92−7.03 (1H, m), 7.29 (2H, t, *J* = 7.96 Hz), 7.49 (2H, d, *J* = 7.58 Hz), 7.58 (2H, app d, *J* = 8.59 Hz), 7.73 (2H, app d, *J* = 8.59 Hz), 8.19 (1H, s), 9.05 (1H, s), 9.18 (1H, s).

***N*-Phenyl-*N*′-{4-[4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl]phenyl}urea (12f).** A mixture of *N*-{4-[4-bromo-1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (**10e**, 26 mg, 0.059 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (**11**, 14.5 mg, 0.059 mmol), tetrakis(triphenylphosphine)palladium(0) (3.4 mg, 0.003 mmol), saturated sodium bicarbonate (0.177 mL), and anhydrous DMF (1 mL) was stirred at 100 °C in a sealed tube for 4 h and cooled to rt. Filtration through a pad of celite, concentration in vacuo, and reverse phase HPLC purification furnished the title compound (**12f**) as a white solid (10 mg, 35%). MS *m*/*z* 477.2 $[M + H]^+$. LCMS purity 93%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.15−5.39 (2H, m), 6.14−6.30 (1H, m), 6.84 (1H, d, *J* = 4.80 Hz), 6.91−7.04 (1H, m), 7.17−7.53 (9H, m), 8.14 (1H, d, *J* = 4.80 Hz), 8.28 (1H, s), 8.68−8.79 (2H, m), 11.71 (1H, br s).

***N*-{4-[4-Bromo-1-(2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-ethyl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (10f).** To a solution of *N*-[4-(4-bromo-1*H*-pyrazol-3-yl)phenyl]-*N*′-phenylurea (**10a**, 1 g, 2.8 mmol) in dry DMF cooled to 0 °C was added 1 M potassium *tert*-butoxide in THF (11.2 mL, 11.2 mmol). The reaction mixture was stirred for 15 min and then (2-bromoethoxy)-*tert*-butyldimethylsilane (0.6 mL, 2.8 m,mol) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 2 days. The reaction mixture was quenched with aq ammonium chloride, extracted with ethyl acetate (× 3), and the combined organic layers dried (Na_2SO_4) and concentrated in vacuo. Purification by silica gel chromatography, eluting with 20−50% ethyl acetate in hexanes, afforded the title product (**10f**, 0.806 g, 56%) and 39% recovered starting material. MS *m*/*z* 515.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm −0.08 (6H, s), 0.80 (9H, s), 3.93 (2H, t, *J* = 4.67 Hz), 4.21 (2H, t, *J* = 5.05 Hz), 6.97−7.00 (1H, m), 7.28−7.31 (2H, m), 7.47 (2H, d, *J* = 7.58 Hz), 7.54 (2H, d, *J* = 8.59 Hz), 7.73 (2H, d, *J* = 8.59 Hz), 7.98 (1H, s), 8.72 (1H, s), 8.80 (1H, s).

***N*-{4-[1-(2-Hydroxyethyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (12g).** A mixture of *N*-{4-[4-bromo-1-(2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-ethyl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (**10f**, 0.775 g, 1.503 mmol), 1-(phenylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (**11**, 0.866 g, 2.25 mmol), tetrakis(triphenylphosphine)palladium (0.086 g, 0.0759 mmol), saturated sodium bicarbonate (aq) (4.5 mL), and *N*,*N*′-dimethylformamide (15 mL) was heated at 100 °C in a sealed pressure vessel for 15.5 h. The reaction mixture was cooled to room temperature, filtered through celite, and concentrated in vacuo. To the resulting residue was added 6N aq sodium hydroxide (5 mL) and methanol (10 mL). The solution was stirred at 70 °C under a reflux condenser overnight. The solution was concentrated in vacuo and the residue taken up in ethyl acetate and purified by silica gel chromatography, eluting with 20−50% ethyl acetate in hexane, followed by 1% methanol in ethyl acetate. The product obtained was further purified by reverse phase HPLC to provide the title compound (**12g**, 0.345 g, 52%). MS *m*/*z* 439.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.85 (2H, q, J = 5.56 Hz), 4.26 (2H, t, J = 5.56 Hz), 5.02 (1H, t, J = 5.31 Hz), 6.26 (1H, dd, J = 3.41, 1.89 Hz), 6.82 (1H, d, J = 5.05 Hz), 6.92−7.03 (1H, m), 7.27−7.31 (4H, m), 7.37 (1H, s), 7.38−7.41 (2H, m), 7.44 (2H, d, J = 7.58 Hz), 8.11 (2H, t, J = 2.53 Hz), 8.70 (1H, s), 8.67 (1H, s), 11.64 (1H, br s).

4-Bromo-3-(4-nitrophenyl)-1-(2-propen-1-yl)-1*H*-pyrazole (7c). To a cooled (0 °C) solution of 4-bromo-3-(4-nitrophenyl)-1*H*-pyrazole (10 g, 37.3 mmol) in anhydrous *N*,*N*′-dimethylformamide (74.6 mL) was added sodium hydride, 60% dispersed in mineral oil (1.492 g, 37.3 mmol). This was followed by slow addition of allylbromide (3.87 mL, 44.76 mmol). The reaction mixture was stirred at room temperature for 1 h and then poured into an ice−water mixture (100 mL). The precipitate that formed was collected, washed with water, and air-dried. The precipitate was dissolved in dichloromethane and treated with hexane to crash out the product. This product was collected by suction filtration to provide the title compound (**7c**, 11.3 g, 98%). MS *m*/*z* 308.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.85 (2H, d, J = 5.81 Hz), 5.18−5.34 (2H, m), 6.07 (1H, m), 8.13 (2H, app d, J = 9.09 Hz), 8.19 (1H, s), 8.34 (2H, app d, J = 8.84 Hz).

3-(4-Nitrophenyl)-1-(2-propen-1-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (8b). In a sealed tube was combined 4-bromo-3-(4-nitrophenyl)-1-(2-propen-1-yl)-1*H*-pyrazole (**7c**, 5 g, 16.22 mmol), potassium acetate (4.778 g, 48.69 mmol), bis(pinacolato)diboron (4.532 g, 17.849 mmol), and bis-(diphenylphosphino)palladium(II)dichloride (0.4555 g, 0.649 mmol), followed by anhydrous 1,4-dioxane (160 mL). The reaction mixture was purged with nitrogen and then stirred at 100 °C for 18.75 h. The reaction mixture was filtered through celite, concentrated in vacuo, and the residue purified by reverse phase HPLC to provide the title compound (**8b**, 3.145 g, 55%). MS *m*/*z* 356.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (12H, s), 4.86 (2H, d, J = 5.81 Hz), 5.15−5.31 (2H, m), 6.07 (1H, m), 8.09 (1H, s), 8.14−8.22 (2H, m), 8.23−8.32 (2H, m).

4-[3-(4-Nitrophenyl)-1-(2-propen-1-yl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridine. A mixture of 3-(4-nitrophenyl)-1-(2-propen-1-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (**8b**, 2.05 g, 5.78 mmol), 4-bromo-1*H*-pyrrolo[2,3-*b*]-pyridine (1.14 g, 5.78 mmol), tetrakis(triphenylphosphine)-palladium (0.334 g, 0.289 mmol), 2 M potassium carbonate (aq) (20 mL), and 1,4-dioxane (20 mL) was heated at 100 °C in a sealed pressure vessel overnight. The solution was cooled to room temperature, the organic layer separated, and the aqueous portion extracted with ethyl acetate. The combined organic layers were filtered through a plug of celite and the filtrate concentrated in vacuo. The residue was taken up in ethyl acetate, and the product crashed out of solution. This precipitate was purified by reverse phase HPLC to give the title compound as a bright-yellow solid (0.905 g, 46%). MS *m*/*z* 346.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.94 (2H, d, J = 6.06 Hz), 5.27−5.37 (2H, m), 6.07−6.25 (2H, m), 6.88 (1H, d, J = 5.05 Hz), 7.38−7.46 (1H, m), 7.59−7.67 (2H, m), 8.13−8.20 (4H, m), 8.23 (1H, s), 11.74 (2H, br s).

***N*-Phenyl-*N*′-{4-[1-(2-propen-1-yl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]phenyl}urea (12h).** A mixture of 4-[3-(4-nitrophenyl)-1-(2-propen-1-yl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo-[2,3-*b*]pyridine (0.5 g, 1.448 mmol), tin metal (0.895 g, 7.239 mmol), 6N aq hydrochloric acid (1 mL), and ethanol (5 mL) was stirred at 70 °C for 1 h, concentrated in vacuo, and the residue taken up in ethyl acetate and washed with saturated sodium bicarbonate (aq). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was dissolved in pyridine (5 mL), and phenylisocyanate (0.174 mL, 1.593 mmol) was added. The reaction mixture was stirred for 1 h and then concentrated in vacuo, redissolved in ethyl acetate, filtered, and the filtrate concentrated in vacuo. The residue was purified by reverse phase HPLC to provide the title compound (**12h**, 0.342 g, 54%). MS *m*/*z* 435.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.87 (2H, d, J = 5.81 Hz), 5.25−5.38 (2H, m), 6.08−6.33 (2H, m), 6.83 (1H, d, J = 4.80 Hz), 6.87−7.05 (6H, m), 7.33−7.43 (3H, m), 7.65−7.78 (1H, m), 8.03−8.21 (2H, m), 8.71−8.82 (2H, m), 11.65 (1H, br s).

***N*-{4-[1-(2,3-Dihydroxypropyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (12i).** To a solution of *N*-phenyl-*N*′-{4-[1-(2-propen-1-yl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]phenyl}urea (**12i**, 80 mg, 0.18 mmol) in 5:1 acetone:water (1.2 mL) was added *N*-methylmorpholine *N*-oxide (32.4 mg, 0.276 mmol) followed by a 2.5% solution of osmium tetroxide in *t*-butanol (93.5 mg). The reaction mixture was stirred at room temperature for 18 h. The reaction was quenched with satd aq Na_2SO_3 (1 mL), filtered through a pad of celite (rinsing with ethyl acetate), and concentrated in vacuo. The residue was purified by reverse phase HPLC to afford the title compound as a white solid (**12i**, 12 mg, 14%). MS *m*/*z* 469.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.5 (2H, br s), 3.96 (2H, m), 4.05−4.17 (1H, m), 4.35 (1H, dd, J = 13.77, 3.66 Hz), 6.37 (1H, br s), 6.90 (1H, d, J = 5.31 Hz), 6.97 (1H, t, J = 7.33 Hz), 7.21−7.34 (4H, m), 7.36−7.56 (5H, m), 8.13−8.19 (2H, m), 8.67−8.77 (2H, m).

3-{3-(4-Nitrophenyl)-4-[1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]-pyridin-4-yl]-1*H*-pyrazol-1-yl}-1-propanol. To a solution of 0.5 M 9-borabicyclo[3.3.1]nonane in THF (6.16 mL) cooled to 0 °C was added a solution of 4-[3-(4-nitrophenyl)-1-(2-propen-1-yl)-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1 g, 2.06 mmol) in THF (14 mL). The reaction mixture was stirred at room temperature under an inert atmosphere for 4.5 h and then recooled to 0 °C followed by quenching with water (1.7 mL). After 15 min of stirring at 0 °C, 6N aq NaOH (1.24 mL) was added dropwise, followed by 30% aq H_2O_2 (0.865 mL). The reaction mixture was stirred for 1.5 h at 0 °C, neutralized with 6N aq HCl, and concentrated in vacuo. Water (10 mL) was added to the residue and the solution extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried over magnesium sulfate and concentrated in vacuo to afford the title compound (0.87 g, 84%). This material was used without further purification. MS *m*/*z* 504.2 $[M + H]^+$.

3-[3-(4-Nitrophenyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl]-1-propanol. A solution of 3-{3-(4-nitrophenyl)-4-[1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1*H*-pyrazol-1-yl}-1-propanol (1.04 g, 2.06 mmol), 6N aq NaOH (1.03 mL), and methanol (10 mL) was heated at 70 °C for 18 h. The reaction mixture was concentrated in vacuo and purified by silica gel chromatography (Analogix, 5% methanol/ethyl acetate) to afford the title compound (0.653 g, 87%). MS *m*/*z* 364.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.01−2.12 (2H, m), 3.42−3.52 (2H, m), 4.23 (2H, t, J = 6.95 Hz), 4.66 (1H, t, J = 5.18 Hz), 6.46 (1H, s), 6.70−6.84 (1H, m), 7.04 (1H, d, J = 8.34 Hz), 7.28−7.35 (2H, m), 7.60 (2H, dd, J = 7.45, 1.89 Hz), 8.06 (1H, s), 11.59 (1H, br s).

***N*-{4-[1-(3-Hydroxypropyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (12j).** A mixture of 3-[3-(4-nitrophenyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl]-1-propanol (0.653 g, 1.787 mmol), ethanol (10 mL), 6N aq hydrochloric acid (5 mL), and tin metal (1.06 g, 8.936 mmol) was heated at 70 °C for 1 h. The reaction mixture was cooled, filtered, and neutralized with saturated sodium bicarbonate (aq) and then concentrated in vacuo. The residue was dissolved in pyridine (10 mL), and phenylisocyanate (0.216 mL, 1.977 mmol) added. The reaction mixture was stirred at room temperature for 16 h and then filtered. The filtrate was concentrated in vacuo, and the residue was taken into DMSO and purified by reverse phase HPLC. The desired fractions were concentrated in vacuo to provide the title compound as a white solid (**12j**, 0.140 g, 17%). MS *m*/*z* 453.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.03 (2H, quin, J = 6.63 Hz), 3.49 (2H, q, J = 6.15 Hz), 4.28 (2H, t, J = 7.07 Hz), 4.67 (1H, t, J = 5.05 Hz), 6.25 (1H, dd, J = 3.54, 1.77 Hz), 6.82 (1H, d, J = 5.05 Hz), 6.98 (1H, q, J = 7.58 Hz), 7.25−7.31 (4H, m), 7.35−7.42 (3H, m), 7.44 (2H, d, J = 7.58 Hz), 8.08−8.18 (2H, m), 8.70 (1H, s), 8.67 (1H, s), 11.64 (1H, br s).

1-(Phenylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine. In a sealed tube were combined 4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3.87 g, 11.48 mmol), potassium acetate (3.38 g, 34.43 mmol), bis(pinacolato)diboron (3.50 g, 13.77 mmol), and 1,1′-bis(diphenylphosphino)ferrocenepalladium(II)dichloride dichloromethane complex (0.375 g, 0.46 mmol) followed by anhydrous 1,4-dioxane (115 mL). The reaction mixture was stirred at 100 °C for 45 min and then cooled to room temperature. After dilution with EtOAc (50 mL) and filtration through a pad of celite, the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with 20−50% ethyl acetate/hexanes to provide the title product as a white solid (4.06 g, 92%). MS *m*/*z* 384.0 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (12H, s), 6.97 (1H, d, J = 4.04 Hz), 7.48 (1H, d, J = 4.80 Hz), 7.61 (2H, t, J = 7.71 Hz), 7.71 (1H, t, J = 7.45 Hz), 7.98 (1H, d, J = 4.04 Hz), 8.05−8.15 (2H, m), 8.38 (1H, d, J = 4.55 Hz).

***N*-{4-[4-Bromo-1-(tetrahydro-2-furanylmethyl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (10g).** To a solution of *N*-[4-(4-bromo-1*H*-pyrazol-3-yl)phenyl]-*N*′-phenylurea (**10a**, 0.1 g, 0.28 mmol) in anhydrous DMF (6 mL) cooled to 0 °C was added 1.0 M potassium *tert*-butoxide in THF (1.12 mL, 1.12 mmol) dropwise. The reaction mixture was stirred for a further 15 min before dropwise addition of tetrahydrofuryl bromide (31.82 uL, 0.28 mmol). The reaction mixture was stirred at room temperature overnight, followed by quenching with saturated aq NH_4Cl (1 mL). The reaction mixture was diluted with water (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by reverse phase HPLC to afford the title compound (**10g**, 65 mg, 53%). MS *m*/*z* 441.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.60−1.97 (4H, m), 3.60−3.82 (2H, m), 4.09−4.26 (3H, m), 6.94−7.03 (1H, m), 7.24−7.33 (2H, m), 7.47 (2H, d, J = 7.58 Hz), 7.54 (2H, m, J = 8.59 Hz), 7.73 (2H, m, J = 8.59 Hz), 8.00 (1H, s), 8.82 (1 H, s), 8.93 (1 H, s).

***N*-Phenyl-*N*′-{4-[4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1-(tetrahydro-2-furanylmethyl)-1*H*-pyrazol-3-yl]phenyl}urea (12k).** A mixture of *N*-{4-[4-bromo-1-(tetrahydro-2-furanylmethyl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (65 mg, 0.147 mmol), 1-(phenylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (92.9 mg, 0.162 mmol), DMF (1.5 mL), saturated aq sodium bicarbonate (0.44 mL), and tetrakis-(triphenylphosphine)palladium(0) (8.5 mg, 0.007 mmol) in a sealed tube was stirred at 100 °C for 18 h. The solution was cooled to rt, filtered through celite, and concentrated in vacuo. The residue was dissolved in methanol (5 mL) and 6.0N aq NaOH (1 mL) and stirred at 70 °C for 6 h. The reaction mixture was concentrated in vacuo, dissolved in water (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over magnesium sulfate and concentrated in vacuo. Purification of the residue by reverse phase HPLC afforded the title compound as a white solid (**12k**, 8 mg, 11%). MS *m*/*z* 479.4 $[M + H]^+$. LCMS purity 92%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.64−1.89 (2H, m), 3.76−3.93 (2H, m), 4.14−4.36 (3H, m), 4.80−5.00 (1H, m), 5.22−5.40 (1H, m), 6.22−6.31 (1H, m), 6.58−6.70 (1H, m), 6.80−6.86 (1H, m), 6.91−7.02 (1H, m), 7.21−7.76 (7H, m), 8.02−8.21 (3H, m), 9.01−9.23 (2H, m), 11.74 (1H, br s).

1,1-Dimethylethyl [4-bromo-3-(4-nitrophenyl)-1*H*-pyrazol-1-yl]acetate (7d). To a cooled (0 °C) solution of 4-bromo-3-(4-nitrophenyl)-1*H*-pyrazole (3 g, 11.12 mmol) in anhydrous DMF (25 mL) was added 60% NaH in mineral oil portionwise (0.445 g, 11.12 mmol). This was followed by slow addition of 1,1-dimethylethyl bromoacetate (1.98 mL, 13.43 mmol). The reaction mixture was stirred for 1 h at room temperature and then poured into an ice−water mixture (50 mL). The resulting precipitate was collected by filtration and washed with water (20 mL). The residue was dissolved in methylene chloride and precipitated out with hexanes to furnish the title compound as a white solid (**7d**, 3.5 g, 83%). MS *m*/*z* 382.0 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (9H, s), 5.08 (2H, s), 8.13 (2H, m, J = 8.84 Hz), 8.19 (1H, s), 8.35 (2H, m, J = 8.84 Hz).

1,1-Dimethylethyl [3-(4-nitrophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl]acetate (8c). In a sealed tube were combined 1,1-dimethylethyl [4-bromo-3-(4-nitrophenyl)-1*H*-pyrazol-1-yl]acetate (**7d**, 2.4 g, 6.28 mmol), potassium acetate (1.849 g, 18.84 mmol), bis(pinacolato)diboron (1.754 g, 6.91 mmol), bis(triphenylphosphine)palladium-(II) chloride (0.176 g, 0.25 mmol), and anhydrous dioxane (62.8 mL). The reaction mixture was stirred at 100 °C in a sealed tube for 18 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (40 mL) and washed with water (20 mL). The aqueous solution was then extracted with EtOAc (2 × 10 mL) and the combined organic solutions dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (10−30% ethyl acetate in hexane) to yield the title compound as a white solid (**8c**, 1.2 g, 44%). MS *m*/*z* 430.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (9H, s), 5.06 (2H, s), 8.05−8.10 (2H, m), 8.18 (1H, s), 8.25−8.30 (2H, m).

[3-(4-Nitrophenyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl]acetic acid. In a sealed tube was combined 1,1-dimethylethyl [3-(4-nitrophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl]acetate (0.272 g, 0.633 mmol), 4-bromo-7-azaindole (**9**, 0.104 g, 0.527 mmol), tetrakis-(triphenylphosphine)palladium(0) (60.9 mg, 0.0527 mmol), 2.0 M aq potassium carbonate (3.25 mL), and 1,4-dioxane (3.25 mL). This mixture was stirred at 100 °C for 15 h. The reaction mixture was filtered through a pad of celite and concentrated in vacuo. Purification by reverse phase HPLC afforded the title product as a white solid (0.13 g, 68%). MS *m*/*z* 364.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.51 (2H, s), 6.14 (1H, d, J = 3.28 Hz), 6.86 (1H, d, J = 5.05 Hz), 7.40 (1H, d, J = 3.28 Hz), 7.50−7.73 (2H, m), 8.05 (1H, s), 8.10−8.22 (3H, m), 11.72 (1H, br s).

[3-(4-{[(Phenylamino)carbonyl]amino}phenyl)-4-(1*H*-pyrrolo-[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl]acetic acid (12l). A heterogeneous mixture of [3-(4-nitrophenyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl]acetic acid (0.387 g, 0.31.065 mmol), elemental tin dust (0.632 g, 5.325 mmol), 6.0N aq HCl (5.3 mL), and absolute ethanol (5.3 mL) was stirred at 70 °C for 1 h. The solution was filtered through celite and concentrated in vacuo. The residue was dissolved in anhydrous pyridine (10 mL) and phenylisocyanate (0.128 mL, 11.17 mmol) added dropwise. The reaction mixture was stirred at room temperature for 4 h. After concentration in vacuo, purification by reverse phase HPLC afforded the title compound as a white solid (**12l**, 0.45 g, 93%). MS *m*/*z* 453.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.09 (2H, s), 6.18−6.41 (1H, m), 6.80−7.04

(2H, m), 7.19−7.34 (4H, m), 7.37−7.52 (5H, m), 8.19 (1H, d, J = 5.05 Hz), 8.25 (1H, s), 8.71 (1H, s), 8.77 (1H, s), 11.94 (1H, br s), 13.21 (1H, s).

2-[3-(4-{[(Phenylamino)carbonyl]amino}phenyl)-4-(1*H*-pyrrolo-[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl]acetamide (12m). To a cooled (0 °C) solution of [3-(4-{[(phenylamino)carbonyl]amino}phenyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl]acetic acid (**12l**, 75 mg, 0.166 mmol) in anhydrous THF (3.3 mL) was added triethylamine (34.7 uL, 0.25 mmol) and ethylchloroformate (17.3 uL, 0.18 mmol). After 30 min at 0 °C, ammonium hydroxide (50 μL) was added and the reaction stirred at room temperature for 1 h. Concentration in vacuo followed by reverse phase HPLC furnished the title compound as a white solid (**12m**, 10 mg, 13%). MS m/z 452.4 $[M + H]^+$. LCMS purity 94%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.88 (2H, s), 6.25 (1H, dd, J = 3.41, 1.64 Hz), 6.83 (1H, d, J = 5.05 Hz), 6.93 (1H, t, J = 7.33 Hz), 7.23−7.32 (4H, m), 7.33−7.51 (6H, m), 7.65 (1H, s), 8.03−8.20 (2H, m), 9.65−9.77 (2H, m), 11.65 (1H, br s).

***N*-Ethyl-2-[3-(4-{[(phenylamino)carbonyl]amino}phenyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl]acetamide (12n).** To a solution of [3-(4-{[(phenylamino)carbonyl]amino}phenyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl]acetic acid (**12l**, 75 mg, 0.166 mmol), EDCI (47.7 mg, 0.249 mmol), DMAP (30.4 mg, 0.249 mmol), and DMF (3.2 mL) at room temperature was added a 2 M solution of ethylamine in THF (204 mL, 0.415 mmol). The reaction mixture was stirred for 3 days at room temperature, concentrated in vacuo, taken up in DMSO, filtered, and the filtrate concentrated and purified by reverse phase HPLC to provide the title compound (**12n**, 32 mg, 40%). MS m/z 480.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 (3H, s), 3.16 (2H, s), 4.89 (2H, s), 6.25 (1H, br s), 6.77−7.01 (3H, m), 7.21−7.32 (3H, m), 7.34−7.49 (5H, m), 8.03−8.21 (2H, m), 8.29−8.48 (1H, m), 9.49−9.73 (2H, m), 11.67 (1H, br s).

***N*-{4-[1-[2-(4-Morpholinyl)-2-oxoethyl]-4-(1*H*-pyrrolo[2,3-*b*]-pyridin-4-yl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (12o).** To a solution of [3-(4-{[(phenylamino)carbonyl]amino}phenyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl]acetic acid (**12l**, 75 mg, 0.166 mmol) in anhydrous *N*,*N*-dimethylformamide (4 mL) was added *N*,*N*-carbonyldiimidazole (32.2 mg, 0.20 mmol). The reaction mixture was stirred at room temperature for 30 min, and then morpholine (43 uL, 0.50 mmol) was added. The reaction mixture was stirred for a further 3 h. Concentraton in vacuo and purification by reverse phase HPLC afforded the title compound as a white solid (**12o**, 23 mg, 26%). MS m/z 522.4 $[M + H]^+$. LCMS purity 94%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.47−3.71 (8H, m), 5.18−5.34 (2H, m), 6.23 (1H, dd, J = 3.28, 1.77 Hz), 6.83 (1H, d, J = 4.80 Hz), 6.97 −7.51 (7H, m), 8.05−8.19 (2H, m), 8.68−8.83 (4H, m), 11.66 (1H, br s).

***N*′-{4-[1-Ethyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]phenyl}-*N*,*N*-dimethylurea (12p).** A solution of 4-[1-ethyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]aniline (80 mg, 0.26 mmol) in pyridine (1 mL) was treated with dimethylcarbamoyl chloride (26 μL, 0.29 mmol). The reaction stirred for 18 h at room temperature and concentrated in vacuo. Purification of the residue by reverse phase HPLC provided the title product (**12s**) as a white powder (38%). MS m/z 375.0 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (t, J = 7.33 Hz, 3H), 2.92 (s, 6H), 4.26 (q, J = 7.16 Hz, 2H), 6.40−6.52 (m, 1H), 6.97 (d, J = 5.56 Hz, 1H), 7.25 (d, J = 8.84 Hz, 2H), 7.43 (d, J = 8.59 Hz, 2H), 7.55−7.61 (m, 1H), 8.22 (d, J = 5.56 Hz, 1H), 8.30−8.37 (m, 2H), 12.22 (br s, 1H).

***N*-{3-[4-Bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]phenyl}acetamide (14e).** In a glass pressure tube was added 4-bromo-2-iodo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1.0 g, 2.2 mmol), [3-(acetylamino)phenyl]boronic acid (0.39 g, 2.2 mmol), tetrakis(triphenylphosphine)palladium(0) (125 mg, mmol), aq satd sodium bicarbonate (5 mL), and dimethylformamide (20 mL). The reaction was purged with nitrogen, capped, and stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was evaporated to dryness under vacuum, taken up in ethyl acetate, washed with water, brine, dried (Na_2SO_4), filtered, and concentrated under vacuum. Purification by flash chromatography on silica gel eluting with 80% ethyl acetate in hexanes gave the product (**14e**, 0.67 g, 1.4 mmol, 64% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.28 (d, J = 5.30 Hz, 1H), 7.93 (d, J = 7.33 Hz, 2H), 7.82 (s, 1H), 7.65 (d, J = 5.81 Hz, 2H), 7.54 (t, J = 7.45 Hz, 1H), 7.38−7.46 (m, 4H), 7.28 (d, J = 7.58 Hz, 1H), 6.60 (s, 1H), 2.24 (s, 3H). MS m/z 470.2 $[M + H]^+$.

***N*-{3-[4-[1-Ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]phenyl}acetamide (15e).** In a glass pressure tube was added *N*-{3-[4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]phenyl}acetamide (**14e**, 0.50 g, 1.0 mmol), 1-ethyl-3-(4-nitrophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.40 g, 1.1 mmol), tetrakis(triphenylphosphine)palladium(0) (70 mg, mmol), aq satd sodium bicarbonate (4 mL), and dimethylformamide (16 mL). The reaction was purged with nitrogen and capped and stirred at 100 °C for 6 h. After cooling to room temperature, the reaction was evaporated to dryness under vacuum, taken up in ethyl acetate, filtered to remove insolubles, and concentrated under vacuum. Purification of the residue by flash chromatography on silica gel eluting with ethyl acetate gave the product (**15e**, 0.55 g, 0.91 mmol, 91% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.09 (s, 1H), 8.33 (s, 1H), 8.31 (d, J = 5.05 Hz, 1H), 8.14 (d, J = 8.84 Hz, 2H), 7.90−7.92 (m, 2H), 7.85 (s, 1H), 7.73 (t, J = 7.45 Hz, 1H), 7.53−7.65 (m, 5H), 7.38 (t, J = 7.83 Hz, 1H), 7.13 (d, J = 7.58 Hz, 1H), 7.04 (d, J = 5.05 Hz, 1H), 6.55 (s, 1H), 4.26 (q, J = 7.24 Hz, 2H), 2.09 (s, 3H), 1.47 (t, J = 7.33 Hz, 3H). MS m/z 607.4 $[M + H]^+$.

***N*-(3-{4-[1-Ethyl-3-(4-{[(phenylamino)carbonyl]amino}phenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl}phenyl)acetamide (17a).** To a stirred solution of *N*-{3-[4-[1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]-pyridin-2-yl]phenyl}acetamide (**15e**, 0.50 g, 0.8 mmol) in ethyl acetate (30 mL) was added 20 wt % palladium hydroxide on carbon (0.1 g). A balloon of hydrogen was attached, and the reaction was stirred for 3 days. The reaction was filtered through a pad of celite, rinsed with ethyl acetate, and evaporated to dryness to give the product (0.48 g, 0.8 mmol, 100% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.09 (s, 1H), 8.22 (d, J = 5.05 Hz, 1H), 8.17 (s, 1H), 7.85−7.87 (m, 2H), 7.82 (s, 1H), 7.56−7.72 (m, 5H), 7.39 (t, J = 7.96 Hz, 1H), 7.16 (d, J = 7.83 Hz, 1H), 7.01 (d, J = 5.05 Hz, 1H), 6.90 (d, J = 8.59 Hz, 2H), 6.54 (s, 1H), 6.47 (d, J = 8.59 Hz, 2H), 5.23 (s, 2H), 4.15 (q, J = 7.16 Hz, 2H), 2.10 (s, 3H), 1.42 (t, J = 7.20 Hz, 3H). MS m/z 577.4 $[M + H]^+$.

To a stirred solution of *N*-{3-[4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]phenyl}acetamide (200 mg, 0.35 mmol) in THF (5 mL) was added phenylisocyanate (45 uL, 0.41 mmol) and 1 drop of triethylamine. The reaction was stirred at room temperature for 18 h and evaporated to dryness under vacuum. The residue was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum to give *N*-{3-[4-[1-ethyl-3-(4-{[(phenylamino)carbonyl]amino}phenyl)-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]phenyl}acetamide (0.29 g, 0.42 mmol, 100% yield) as a pale-yellow solid. MS m/z 696.4 $[M + H]^+$.

To a stirred solution of *N*-{3-[4-[1-ethyl-3-(4-{[(phenylamino)-carbonyl]amino}phenyl)-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]phenyl}acetamide (0.25 g, 0.36 mmol) in methanol (5 mL) was added aq 6 N sodium hydroxide (120 μL, 0.72 mmol). The reaction was refluxed for 8 h, cooled to room temperature, and diluted with water (5 mL). The solid which precipitated was filtered off and dried under vacuum. Purification by reverse phase HPLC (10−90% CH_3CN/H_2O) gave the product (**17a**, 120 mg, 0.22 mmol, 60% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.19 (br s, 1H), 10.01 (s, 1H), 8.71 (s, 1H), 8.67 (s, 1H), 8.25 (s, 1H),

8.10 (d, J = 4.80 Hz, 1H), 8.00 (br s, 1H), 7.55 (dd, J = 15.16, 7.83 Hz, 2H), 7.25−7.45 (m, 9H), 6.96 (t, J = 7.07 Hz, 1H), 6.81 (d, J = 4.55 Hz, 1H), 6.67 (br s, 1H), 4.28 (q, J = 6.91 Hz, 2H), 2.07 (s, 3H), 1.52 (t, J = 7.20 Hz, 3H). MS m/z 556.4 $[M + H]^+$. Anal. ($C_{33}H_{29}N_7O \cdot 0.5H_2O$) C, H, N.

***N*-{4-[4-Bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]phenyl}acetamide (14f).** The reaction used to prepare **14e** was repeated with [4-(acetylamino)phenyl]boronic acid to give the product (**14f**, 0.63 g, 1.3 mmol, 61% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.17 (s, 1H), 8.24 (d, J = 5.31 Hz, 1H), 7.79−7.81 (m, 2H), 7.66−7.73 (m, 3H), 7.61 (d, J = 5.31 Hz, 1H), 7.54−7.58 (m, 4H), 6.72 (s, 1H), 2.11 (s, 3H). MS m/z 470.2 $[M + H]^+$.

***N*-{4-[4-[1-Ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]phenyl}acetamide (15f).** The reaction used to prepare **15e** was repeated with *N*-{4-[4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]phenyl}-acetamide to give the product (**15f**, 0.53 g, 0.87 mmol, 87% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.13 (s, 1H), 8.32 (s, 1H), 8.29 (d, J = 5.05 Hz, 1H), 8.13 (d, J = 8.84 Hz, 2H), 7.81−7.83 (m, 2H), 7.70−7.73 (m, 1H), 7.66 (d, J = 8.59 Hz, 2H), 7.57−7.61 (m, 2H), 7.53 (d, J = 8.84 Hz, 2H), 7.38 (d, J = 8.59 Hz, 2H), 7.05 (d, J = 5.05 Hz, 1H), 6.48 (s, 1H), 4.26 (q, J = 7.33 Hz, 2H), 2.09 (s, 3H), 1.47 (t, J = 7.20 Hz, 3H). MS m/z 607.4 $[M + H]^+$.

***N*-(3-{4-[1-Ethyl-3-(4-{[(phenylamino)carbonyl]amino}phenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl}phenyl)acetamide.** The nitro reduction reaction used to prepare **17a** was repeated with *N*-{4-[4-[1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]phenyl}-acetamide to give the product (0.25 g, 0.43 mmol, 52% yield) as an off-white solid. MS m/z 577.4 $[M + H]^+$.

***N*-{4-[4-[1-Ethyl-3-(4-{[(phenylamino)carbonyl]amino}phenyl)-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]phenyl}acetamide.** To a stirred solution of *N*-{4-[4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]phenyl}acetamide (170 mg, 0.30 mmol) in THF (5 mL) was added phenylisocyanate (50 μL, 0.46 mmol) and 1 drop of triethylamine. The reaction was stirred at room temperature for 18 h and evaporated to dryness under vacuum. The residue was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum to give the product (0.21 g, 0.30 mmol, 100% yield) as a pale-yellow solid. MS m/z 696.4 $[M + H]^+$.

***N*-(Phenyl)-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-1*H*-pyrrolo-[2,3-*b*]pyridin-2-yl]phenyl}acetamide (17b).** To a stirred solution of *N*-{4-[4-[1-ethyl-3-(4-{[(phenylamino)carbonyl]amino}phenyl)-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]phenyl}acetamide (0.21 g, 0.30 mmol) in methanol (5 mL) was added aq 6 N sodium hydroxide (110 uL, 0.72 mmol). The reaction was refluxed for 8 h, cooled to room temperature, and diluted with water (5 mL). The solid which precipitated was filtered off and dried under vacuum to give the product (**17b**, 110 mg, 0.20 mmol, 66% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.07 (s, 1H), 10.06 (s, 1H), 8.71 (s, 1H), 8.67 (s, 1H), 8.26 (s, 1H), 8.05 (d, J = 5.05 Hz, 1H), 7.83 (d, J = 8.59 Hz, 2H), 7.65 (d, J = 8.59 Hz, 2H), 7.25−7.45 (m, 8H), 6.96 (t, J = 7.33 Hz, 1H), 6.77 (d, J = 5.05 Hz, 1H), 6.75 (d, J = 1.77 Hz, 1H), 4.27 (q, J = 7.24 Hz, 2H), 2.07 (s, 3H), 1.52 (t, J = 7.20 Hz, 3H). MS m/z 556.4 $[M + H]^+$. Anal. ($C_{33}H_{29}N_7O \cdot 0.5H_2O$) C, H, N.

4-Bromo-2-(3-formylphenyl)-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (14a). To a glass pressure tube were added 4-bromo-2-iodo-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (1 g, 2.1 mmol), 3-formylbenzeneboronic acid (0.32 g, 2.1 mmol), dimethylformamide (15 mL), aq satd sodium bicarbonate (5 mL), and tetrakis(triphenylphosphine)palladium(0) (120 mg, 0.1 mmol). The reaction was purged with nitrogen, capped, and stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was concentrated under vacuum, taken up in ethyl acetate, washed with water, brine, dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (0−4% ethyl acetate in dichloromethane) gave the product (**14a**, 0.72 g, 1.6 mmol, 77% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.13 (s, 1H), 8.32 (d, J = 5.31 Hz, 1H), 8.06 (t, J = 1.52 Hz, 1H), 8.03 (dt, J = 7.58, 1.39 Hz, 1H), 7.91−7.97 (m, 2H), 7.89 (ddd, J = 7.83, 1.52, 1.26 Hz, 1H), 7.69 (t, J = 7.71 Hz, 1H), 7.58 (t, J = 6.82 Hz, 1H), 7.43 (d, J = 5.31 Hz, 1H), 7.46 (t, J = 7.83 Hz, 2H), 6.67 (s, 1H). MS m/z 441.0 $[M + H]^+$.

4-[3-(4-Nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-(3-formylphenyl)-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (15a). To a sealed pressure tube were added 4-bromo-2-(3-formylphenyl)-1-phenylsulfonyl-1*H*-pyrrolo[2,3-b]pyridine (0.7 g, 1.6 mmol), 3-(4-nitrophenyl)-1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.6 g, 1.7 mmol), *N*,*N*-dimethylformamide (15 mL), aq satd sodium bicarbonate (4 mL), and tetrakis(triphenylphosphine)palladium(0) (100 mg, 0.09 mmol). The reaction was purged with nitrogen, capped, and stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was concentrated under vacuum, taken up in ethyl acetate, washed with water, brine, dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (5−10% ethyl acetate in dichloromethane) gave the product (**15a**, 0.75 g, 1.3 mmol, 81% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.09 (s, 1H), 8.35 (s, 1H), 8.34 (d, J = 5.05 Hz, 1H), 8.14 (d, J = 8.84 Hz, 2H), 8.02 (d, J = 7.58 Hz, 1H), 7.96 (s, 1H), 7.88 (s, 1H), 7.86 (d, J = 1.26 Hz, 2H), 7.73 (q, J = 7.49 Hz, 2H), 7.61 (t, J = 7.83 Hz, 2H), 7.54 (d, J = 9.09 Hz, 2H), 7.07 (d, J = 5.05 Hz, 1H), 6.72 (s, 1H), 4.26 (q, J = 7.33 Hz, 2H), 1.47 (t, J = 7.33 Hz, 3H). MS m/z 578.3 $[M + H]^+$.

4-[3-(4-Nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(dimethylaminomethyl)phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (15i). To a stirred solution of 4-[3-(4-nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-(3-formylphenyl)-1-phenylsulfonyl-1*H*-pyrrolo-[2,3-*b*]pyridine (0.75 g, 1.3 mmol) in THF (20 mL) was added a solution of 2 M dimethylamine in THF (1 mL, 2.0 mmol) followed by sodium triacetoxyborohydride (0.4 g, 1.9 mmol). The reaction was stirred at room temperature for 4 h and concentrated to dryness under vacuum. The residue was taken up in ethyl acetate, washed with aq 1N sodium carbonate, brine, dried (Na_2SO_4), filtered, and evaporated under vacuum. Purification of the residue by flash chromatography on silica gel [0−5% (5% ammonium hydroxide in methanol) in dichloromethane] gave the product (**15i**, 0.69 g, 1.1 mmol, 87% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.34 (s, 1H), 8.34 (d, J = 5.05 Hz, 1H), 8.13 (d, J = 8.84 Hz, 2H), 7.86−7.88 (m, 2H), 7.74 (t, J = 7.45 Hz, 1H), 7.61 (t, J = 7.83 Hz, 2H), 7.53 (d, J = 8.84 Hz, 2H), 7.33−7.40 (m, 3H), 7.23 (s, 1H), 7.11 (d, J = 5.05 Hz, 1H), 6.43 (s, 1H), 4.26 (q, J = 7.33 Hz, 2H), 3.42 (s, 2H), 2.18 (s, 6H), 1.47 (t, J = 7.33 Hz, 3H). MS m/z 607.4 $[M + H]^+$.

4-[3-(4-Aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(dimethylaminomethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (16a). To a stirred solution of 4-[3-(4-nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(dimethylaminomethyl)phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-b]pyridine (0.69 g, 1.1 mmol) in acetic acid (20 mL) was added portionwise zinc dust (0.52 g, 8.0 mmol) over 5 min. The reaction was stirred at room temperature for 1 h, filtered through a pad of celite, rinsed with acetic acid, and concentrated to dryness under vacuum. The residue was re-evaporated several times from methanol, followed by toluene to remove the excess acetic acid, taken up in methanol (35 mL) and treated with aq 6N sodium hydroxide (1.5 mL). The reaction was stirred and heated at 70 °C for 8 h. After cooling to room temperature, the reaction was concentrated under vacuum, triturated with cold water, filtered, washed with water, and dried under vacuum to give the crude product (**16a**, 0.49 g, 1.1 mmol, 100% yield) (87% pure by LCMS) as a pale-orange solid, which was in the next step without further purification. MS m/z 437.2 $[M + H]^+$.

4-[3-(4-*N*-Phenylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(dimethylaminomethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (17c). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(dimethylaminomethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (0.15 g, 0.34 mmol) in THF (5 mL) was added phenyl isocyanate (45 μL, 0.41 mmol) and two drops of triethylamine. The reaction was stirred at room temperature for 1 h and concentrated to dryness under vacuum. The remaining solid was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum. Purification of the residue by reverse phase HPLC (10−90% CH_3CN/H_2O with 0.1% TFA) gave the TFA salt which was basified with 1N aq sodium carbonate, extracted with dichloromethane, dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. The residue was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum gave the product (**17c**, 83 mg, 0.15 mmol, 44% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.15 (d, J = 1.77 Hz, 1H), 8.75 (s, 1H), 8.71 (s, 1H), 8.27 (s, 1H), 8.09 (d, J = 5.05 Hz, 1H), 7.76−7.79 (m, 2H), 7.39−7.46 (m, 5H), 7.31−7.36 (m, 2H), 7.25−7.29 (m, 3H), 6.96 (t, J = 7.33 Hz, 1H), 6.82 (d, J = 5.05 Hz, 1H), 6.74 (d, J = 2.02 Hz, 1H), 4.28 (q, J = 7.33 Hz, 2H), 3.45 (s, 2H), 2.18 (s, 6H), 1.52 (t, J = 7.20 Hz, 3H). MS m/z 556.4 $[M + H]^+$. Anal. ($C_{34}H_{33}N_7O \cdot 1.0H_2O$) C, H, N.

3-Bromo-4-methylbenzaldehyde. To a stirred solution of 3-bromo-4-methylbenzyl alcohol (4.43 g, 22 mmol) in chloroform (100 mL) was added manganese dioxide (15 g, 172 mmol). The reaction was stirred and refluxed (70 °C oil bath) for 18 h, cooled to room temperature, filtered through celite, rinsed with chloroform, and concentrated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (10% ethyl acetate in hexanes) gave the product (3.0 g, 15 mmol, 68% yield) as a crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.94 (s, 1H), 8.06 (d, J = 1.52 Hz, 1H), 7.74 (dd, J = 7.83, 1.52 Hz, 1H), 7.42 (d, J = 7.83 Hz, 1H) 2.51 (s, 3H).

3-Formyl-6-methyl-phenylboronate Pinacolato Ester. To a glass pressure bottle were added 3-bromo-4-methylbenzaldehyde (3.0 g, 15 mmol), bis(pinacolato)diboron (4.5 g, 17.7 mmol), potassium acetate (4.5 g, 45.8 mmol), dichlorobis-(triphenylphosphine)palladium(II) (0.5 g, 0.7 mmol), and dioxane (50 mL). The reaction was purged with nitrogen, capped, and stirred at 100 °C for 8 h. The reaction was cooled to room temperature and concentrated to dryness under vacuum. The residue was taken up in ethyl acetate, filtered to remove insolubles, and re-evaporated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (25 to 100% dichloromethane in hexanes) gave the product (2.76 g, 11.2 mmol, 74% yield) as an oil which solidified upon standing in the refrigerator. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.01 (s, 1H), 8.27 (d, J = 2.02 Hz, 1H), 7.86 (dd, J = 7.83, 1.77 Hz, 1H), 7.34 (d, J = 7.83 Hz, 1H), 2.64 (s, 3H), 1.39 (s, 12H). MS m/z 246.4 $[M + H]^+$.

4-Bromo-2-(3-formyl-6-methyl-phenyl)-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (14b). To a glass pressure bottle were added 4-bromo-2-iodo-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]-pyridine (1.18 g, 2.5 mmol), 3-formyl-6-methyl-phenylboronate pinacolato ester (0.71 g, 2.9 mmol), dimethylformamide (15 mL), aq satd sodium bicarbonate (5 mL), and tetrakis-(triphenylphosphine)palladium(0) (120 mg, 0.1 mmol). The reaction was purged with nitrogen, capped, and stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was concentrated under vacuum, taken up in ethyl acetate, washed with water, brine, dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (0−5% ethyl acetate in dichloromethane) gave the product (**14b**, 0.77 g, 1.7 mmol, 67% yield) as a white solid. MS m/z 455.0 $[M + H]^+$.

4-[3-(4-Nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-(3-formyl-6-methyl-phenyl)-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (15b). To a glass pressure bottle were added 4-bromo-2-(3-formyl-6-methyl-phenyl)-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.77 g, 1.7 mmol), 3-(4-nitrophenyl)-1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (**8a**, 0.65 g, 1.9 mmol), dimethylformamide (20 mL), aq satd sodium bicarbonate (5 mL), and tetrakis(triphenylphosphine)palladium(0) (100 mg, 0.09 mmol). The reaction was purged with nitrogen, capped, and stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was concentrated under vacuum, taken up in ethyl acetate, washed with water, brine, dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (4% ethyl acetate in dichloromethane) gave the product (**15b**, 0.80 g, 1.35 mmol, 79% yield) as a yellow solid. MS m/z 592.4 $[M + H]^+$.

4-[3-(4-Nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(dimethylaminomethyl)-6-methyl-phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (15j). To a stirred solution of 4-[3-(4-nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-(3-formyl-6-methyl-phenyl)-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.80 g, 1.4 mmol) in THF (30 mL) was added a solution of 2 M dimethylamine in THF (1.35 mL, 2.7 mmol) followed by sodium triacetoxyborohydride (0.5 g, 2.4 mmol). The reaction was stirred at room temperature for 4 h and concentrated to dryness under vacuum. The residue was taken up in ethyl acetate, washed with aq 1N sodium carbonate, brine, dried (Na_2SO_4), filtered, and evaporated under vacuum. Purification of the residue by flash chromatography on silica gel [3% (5% ammonium hydroxide in methanol) in dichloromethane] gave the product (**15j**, 0.70 g, 1.1 mmol, 83% yield) as a pale-yellow solid. MS m/z 621.6 $[M + H]^+$.

4-[3-(4-Aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(dimethylaminomethyl)-6-methyl-phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (16b). To a stirred solution of 4-[3-(4-nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(dimethylaminomethyl)-6-methyl-phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.70 g, 1.1 mmol) in acetic acid (15 mL) was added portionwise zinc dust (0.32 g, 4.9 mmol) over 5 min. The reaction was stirred at room temperature for 1 h, filtered through a pad of celite, rinsed with acetic acid, and concentrated to dryness under vacuum. The residue was re-evaporated several times from methanol followed by toluene to remove the excess acetic acid, taken up in methanol (25 mL), and treated with 6N aq sodium hydroxide (1.5 mL). The reaction was stirred and heated at 70 °C for 8 h. After cooling to room temperature, the reaction was concentrated under vacuum, triturated with cold water, filtered, washed with water, and dried under vacuum to give the crude product (**16b**, 0.49 g, 1.1 mmol, 100% yield) (74% pure by LCMS) as a pale-orange solid, which was used as is. MS m/z 451.4 $[M + H]^+$.

4-[3-(4-*N*-Phenylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(dimethylaminomethyl)-6-methyl-phenyl]-1*H*-pyrrolo-[2,3-*b*]pyridine (17d). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(dimethylaminomethyl)-6-methyl-phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**16b**, 250 mg, 0.55 mmol) in THF (20 mL) was added phenyl isocyanate (73 uL, 0.67 mmol) and 2 drops of triethylamine. The reaction was stirred at room temperature for 18 h and concentrated to dryness under vacuum. The remaining solid was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum. Purification of the residue by reverse phase HPLC (10−90% CH_3CN/0.1% TFA, H_2O) gave the TFA salt, which was basified with 1N aq sodium carbonate, extracted with (9:1) chloroform/isopropyl alcohol, dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. The residue was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum gave the product (**17d**, 70.6 mg, 0.12 mmol, 22% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.85 (s, 1H), 8.78 (s, 1H), 8.73 (s, 1H), 8.20 (s, 1H), 8.13 (d, J = 5.05 Hz, 1H), 7.45 (d, J = 7.83 Hz, 2H), 7.41 (d, J = 8.59 Hz, 2H), 7.18 − 7.46 (m, 7H), 6.96 (t, J = 7.20 Hz, 1H), 6.89 (d, J = 5.05 Hz, 1H), 6.25 (s, 1H), 4.25 (q, J = 7.07 Hz, 2H), 3.36 (s, 2H), 2.29 (s, 3H), 2.13 (s, 6H), 1.49 (t, J = 7.33 Hz, 3H). MS m/z 570.4 $[M + H]^+$. Anal. ($C_{35}H_{35}N_7O \cdot 1.5H_2O$) C, H, N.

4-Bromo-2-[4-(dimethylaminomethyl)phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (14g). To a glass pressure tube were added 4-bromo-2-iodo-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine

(1.2 g, 2.6 mmol), 4-[(*N*,*N*-dimethylamino)methyl]phenyl boronic acid (0.7 g, 2.17 mmol), dimethylformamide (20 mL), aq satd sodium bicarbonate (8 mL), and tetrakis(triphenylphosphine)palladium(0) (125 mg, 0.11 mmol). The reaction was purged with nitrogen, capped, and stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was concentrated under vacuum, taken up in ethyl acetate, washed with water, brine, dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (0−20% (5% ammonium hydroxide in methanol) in ethyl acetate) gave the product (**14g**, 0.81 g, 1.7 mmol, 66% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.25 (d, J = 5.31 Hz, 1H), 7.81−7.83 (m, 2H), 7.69 (t, J = 6.82 Hz, 1H), 7.62 (d, J = 5.31 Hz, 1H), 7.53−7.60 (m, 4H), 7.42 (d, J = 8.08 Hz, 2H), 6.77 (s, 1H), 3.50 (s, 2H), 2.21 (s, 6H). MS m/z 470.0 $[M + H]^+$.

4-[3-(4-Nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(dimethylaminomethyl)phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (15g). To a glass pressure tube were added 4-bromo-2-[4-(dimethylaminomethyl)phenyl]-1-phenylsulfonyl-1*H*-pyrrolo-[2,3-*b*]pyridine (**14g**, 0.5 g, 1.0 mmol), 3-(4-nitrophenyl)-1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.4 g, 1.1 mmol), dimethylformamide (16 mL), aq satd sodium bicarbonate (4 mL), and tetrakis(triphenylphosphine)palladium(0) (70 mg, 0.06 mmol). The reaction was purged with nitrogen, capped, and stirred at 100 °C for 8 h. After cooling to room temperature, the reaction was concentrated under vacuum, taken up in ethyl acetate, washed with water, brine, dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel [2−6% (5% ammonium hydroxide in methanol) in dichloromethane] gave the product (**15g**, 0.62 g, 1.0 mmol, 100% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.34 (s, 1H), 8.30 (d, J = 5.05 Hz, 1H), 8.14 (d, J = 9.09 Hz, 2H), 7.82−7.84 (m, 2H), 7.72 (t, J = 7.45 Hz, 1H), 7.59 (t, J = 7.83 Hz, 2H), 7.54 (d, J = 8.84 Hz, 2H), 7.41 (d, J = 8.08 Hz, 2H), 7.36 (d, J = 8.08 Hz, 2H), 7.05 (d, J = 5.05 Hz, 1H), 6.54 (s, 1H), 4.26 (q, J = 7.33 Hz, 2 H), 3.47 (s, 2 H), 2.19 (s, 6 H), 1.47 (t, J = 7.20 Hz, 3 H). MS m/z 607.6 $[M + H]^+$.

4-[3-(4-Aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(dimethylaminomethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (16g). To a stirred solution of 4-[3-(4-nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(dimethylaminomethyl)phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (**15g**, 0.60 g, 1.0 mmol) in acetic acid (20 mL) was added portionwise zinc dust (0.46 g, 7.0 mmol) over 5 min. The reaction was stirred at room temperature for 1 h, filtered through a pad of celite, rinsed with acetic acid, and concentrated to dryness under vacuum. The residue was re-evaporated several times from methanol, toluene to remove the excess acetic acid, taken up in methanol (25 mL), and treated with 6N sodium hydroxide (1.5 mL). The reaction was stirred and heated at 70 °C for 8 h. After cooling to room temperature, the reaction was concentrated under vacuum and the residue was triturated with cold water, filtered, washed with water, and dried under vacuum to give the product (**16g**, 0.39 g, 0.90 mmol, 90% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.09 (br s, 1H), 8.20 (s, 1 H), 8.04 (d, J = 5.05 Hz, 1H), 7.85 (d, J = 8.34 Hz, 2H), 7.35 (d, J = 8.08 Hz, 2H), 7.08 (d, J = 8.34 Hz, 2H), 6.81 (s, 1H), 6.79 (d, J = 5.05 Hz, 1H), 6.49 (d, J = 8.59 Hz, 2H), 5.14 (s, 2H), 4.23 (q, J = 7.16 Hz, 2H), 3.41 (s, 2H), 2.16 (s, 6H), 1.49 (t, J = 7.33 Hz, 3H). MS m/z 437.4 $[M + H]^+$.

4-[3-(4-*N*-Phenylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(dimethylaminomethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (17e). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(dimethylaminomethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**16g**, 0.19 g, 0.44 mmol) in THF (10 mL) was added phenyl isocyanate (71 uL, 0.65 mmol) and one drop of triethylamine. The reaction was stirred at room temperature for 1 h and concentrated to dryness under vacuum. The remaining solid was triturated with (1:1) ethyl ether, petroleum ether, filtered, and dried under vacuum. Purification of the residue by reverse phase HPLC (10−90% CH_3CN/0.1% TFA, H_2O) gave the TFA salt which was basified with 1N aq sodium carbonate, extracted with dichloromethane, dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. The residue was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum to give the product (**17e**, 50 mg, 0.09 mmol, 20% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.12 (br s, 1H), 8.71 (s, 1H), 8.67 (s, 1H), 8.27 (s, 1H), 8.08 (d, J = 4.80 Hz, 1H), 7.83 (d, J = 7.83 Hz, 2H), 7.26−7.45 (m, 10H), 6.97 (t, J = 7.33 Hz, 1H), 6.80 (d, J = 5.05 Hz, 1H), 6.75 (s, 1H), 4.27 (q, J = 7.07 Hz, 2H), 3.39 (s, 3H), 2.15 (s, 6H), 1.52 (t, J = 7.20 Hz, 3H). MS m/z 556.4 $[M + H]^+$.

4-Bromo-5-methylbenzylalcohol. To a stirred solution of 4-bromo-5-methylbenzoic acid (5.0 g, 23 mmol) in THF (50 mL) at 0 °C was added dropwise a solution of 1N borane tetrahydrofuran complex in THF (34 mL, 34 mmol). The reaction was allowed to warm to room temperature and stirred for 18 h. The reaction was recooled to 0 °C and slowly quenched with water (10 mL). The reaction was allowed to warm to room temperature and evaporated to dryness under vacuum. The residue was taken up in ethyl acetate, washed with 1N aq sodium carbonate followed by brine, dried ($MgSO_4$), filtered, and evaporated to dryness to give the product (5.37 g, 26 mmol, 100% yield) as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.53 (d, J = 8.08 Hz, 1H), 7.26 (d, J = 1.77 Hz, 1H), 7.07 (dd, J = 8.08, 1.52 Hz, 1H), 4.65 (s, 2H), 2.42 (s, 3H).

4-Bromo-5-methylbenzaldehyde. To a stirred solution of 4-bromo-5-methylbenzyl alcohol (5.3 g, 26 mmol) in chloroform (100 mL) was added manganese dioxide (18 g, 207 mmol). The reaction was stirred and refluxed (70 °C oil bath) for 18 h, cooled to room temperature, filtered through celite, rinsed with chloroform, and concentrated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (10% ethyl acetate in hexanes) gave the product (3.53 g, 17.7 mmol, 68% yield) as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 9.98 (s, 1H), 7.75 (d, J = 1.52 Hz, 1H), 7.73 (d, J = 8.08 Hz, 1H), 7.57 (dd, J = 8.08, 1.52 Hz, 1H), 2.50 (s, 3H).

4-Formyl-6-methyl-phenylboronate Pinacolato Ester. To a glass pressure bottle were added 4-bromo-5-methylbenzaldehyde (3.5 g, 17.5 mmol), bis(pinacolato)diboron (5.0 g, 19.6 mmol), potassium acetate (5.2 g, 53 mmol), dichlorobis-(triphenylphosphine)palladium(II) (0.5 g, 0.7 mmol), and dioxane (50 mL). The reaction was purged with nitrogen, capped, and stirred at 100 °C for 8 h. The reaction was cooled to room temperature and concentrated to dryness under vacuum. The residue was taken up in ethyl acetate, filtered to remove insolubles, and re-evaporated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (25 to 100% dichloromethane in hexanes) gave the product (2.73 g, 11.1 mmol, 63% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.03 (s, 1H), 7.92 (d, J = 7.83 Hz, 1H), 7.65−7.72 (m, 2H), 2.63 (s, 3H), 1.59 (s, 1H), 1.39 (s, 12H). MS m/z 246.4 $[M + H]^+$.

4-Bromo-2-(4-formyl-6-methyl-phenyl)-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (14c). To a glass pressure bottle were added 4-bromo-2-iodo-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.0 g, 2.1 mmol), 4-formyl-6-methyl-phenylboronate pinacolato ester (0.6 g, 2.4 mmol), dimethylformamide (15 mL), aq satd sodium bicarbonate (5 mL), and tetrakis(triphenylphosphine)palladium(0) (120 mg, 0.1 mmol). The reaction was purged with nitrogen, capped, and stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was concentrated under vacuum, taken up in ethyl acetate, and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (0−2% ethyl acetate in dichloromethane) gave the product (**14c**, 0.56 g, 1.2 mmol, 58% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.11 (s, 1H), 8.29 (d, J = 5.30 Hz, 1H), 7.84−7.92 (m, 4H), 7.68−7.73 (m, 2H), 7.66 (d, J = 5.31 Hz, 1H), 7.70

(t, J = 7.58 Hz, 1H), 7.60 (t, J = 7.83 Hz, 2H), 6.81 (s, 1H), 2.35 (s, 3H). MS m/z 455.0 $[M + H]^+$.

4-[3-(4-Nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-(4-formyl-6-methyl-phenyl)-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (15c). To a glass pressure bottle were added 4-bromo-2-(4-formyl-6-methyl-phenyl)-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (**14c**, 0.54 g, 1.1 mmol), 3-(4-nitrophenyl)-1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (**8a**, 0.45 g, 1.3 mmol), dimethylformamide (16 mL), aq satd sodium bicarbonate (4 mL), and tetrakis(triphenylphosphine)palladium(0) (65 mg, 0.056 mmol). The reaction was purged with nitrogen, capped, and stirred at 100 °C for 8 h. After cooling to room temperature, the reaction mixture was concentrated under vacuum, taken up in ethyl acetate, and washed with water followed by brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (5−10% ethyl acetate in dichloromethane) gave the product (**15c**, 0.41 g, 0.69 mmol, 63% yield) as a yellow solid. MS m/z 592.4 $[M + H]^+$.

4-[3-(4-Nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(dimethylaminomethyl)-6-methyl-phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (15k). To a stirred solution of 4-[3-(4-nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-(4-formyl-6-methyl-phenyl)-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (**15c**, 0.41 g, 0.69 mmol) in THF (20 mL) was added a solution of 2 M dimethylamine in THF (0.7 mL, 1.4 mmol) followed by sodium triacetoxyborohydride (0.25 g, 1.1 mmol). The reaction was stirred at room temperature for 18 h and concentrated to dryness under vacuum. The residue was taken up in ethyl acetate and washed with aq 1N sodium carbonate followed by brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated under vacuum. Purification of the residue by flash chromatography on silica gel (97:3 dichloromethane/5% ammonium hydroxide in methanol) gave the product (**15k**, 0.50 g, 0.69 mmol, 100% yield) as a pale-yellow solid. MS m/z 621.6 [M + H].

4-[3-(4-Aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(dimethylaminomethyl)-6-methyl-phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (16c). To a stirred solution of 4-[3-(4-nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(dimethylaminomethyl)-6-methyl-phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (**15k**, 0.50 g, 0.69 mmol) in acetic acid (15 mL) was added portionwise zinc dust (0.32 g, 4.9 mmol) over 5 min. The reaction was stirred at room temperature for 1 h, filtered through a pad of celite, rinsed with acetic acid, and concentrated to dryness under vacuum. The residue was re-evaporated several times from methanol followed by toluene to remove the excess acetic acid, taken up in methanol (25 mL), and treated with 6N aq sodium hydroxide (1.5 mL). The reaction was stirred and heated at 70 °C for 8 h. After cooling to room temperature, the reaction was concentrated under vacuum, triturated with cold water, filtered, washed with water, and dried under vacuum to give the crude product (**16c**, 0.46 g, 1.0 mmol, 100% yield) (74% pure by LCMS) as a brown solid. MS m/z 451.4 $[M + H]^+$.

4-[3-(4-*N*-Phenylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(dimethylaminomethyl)-6-methyl-phenyl]-1*H*-pyrrolo-[2,3-*b*]pyridine (17f). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(dimethylaminomethyl)-6-methyl-phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**16c**, 200 mg, 0.44 mmol) in THF (10 mL) was added phenyl isocyanate (58 uL, 0.53 mmol) and 2 drops of triethylamine. The reaction was stirred at room temperature for 4 h and concentrated to dryness under vacuum. The remaining solid was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum. Purification of the residue by reverse phase HPLC (10−90% CH_3CN/0.1% TFA, H_2O) gave the TFA salt which was basified with 1N aq sodium carbonate and extracted with (9:1) chloroform/isopropyl alcohol. The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. The residue was trituration with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum to give the product (**17f**, 57 mg, 0.10 mmol, 23% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.83 (s, 1H), 8.76 (s, 1H), 8.71 (s, 1H), 8.20 (s, 1H), 8.12 (d, J = 4.80 Hz, 1H), 7.46 (s, 1H), 7.45 (d, J = 8.59 Hz, 2H), 7.40 (d, J = 8.59 Hz, 2H), 7.33 (d, J = 8.59 Hz, 2H), 7.28 (t, J = 7.96 Hz, 2H), 7.21 (s, 1H), 7.18 (d, J = 8.08 Hz, 1H), 6.97 (t, J = 7.33 Hz, 1H), 6.88 (d, J = 5.05 Hz, 1H), 6.28 (d, J = 2.02 Hz, 1H), 4.25 (q, J = 7.24 Hz, 2H), 3.36 (s, 2H), 2.30 (s, 3H), 2.15 (s, 6H), 1.49 (t, J = 7.20 Hz, 3H). MS m/z 570.4 $[M + H]^+$. Anal. ($C_{35}H_{35}N_7O \cdot 0.75H_2O$) C, H, N.

4-[3-(4-Nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-pyrrolidinylmethyl)phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (15l). To a stirred solution of 4-[3-(4-nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-(3-formylphenyl)-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (**15a**, 1.0 g, 1.7 mmol) in THF (25 mL) was added pyrrolidine (0.22 mL, 2.6 mmol) followed by sodium triacetoxyborohydride (0.56 g, 2.6 mmol). The reaction was stirred at room temperature for 4 h and concentrated to dryness under vacuum. The residue was taken up in ethyl acetate and washed with aq 1N sodium carbonate followed by brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated under vacuum to give the product (**15l**, 1.05 g, 1.66 mmol, 97% yield) as a yellow solid. MS m/z 633.6 $[M + H]^+$.

4-[3-(4-Aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-pyrrolidinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (16d). To a stirred solution of 4-[3-(4-nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-pyrrolidinylmethyl)phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (**15l**, 1.05 g, 1.66 mmol) in acetic acid (40 mL) was added portionwise zinc dust (0.76 g, 11.6 mmol) over 5 min. The reaction was stirred at room temperature for 1 h, filtered through a pad of celite, rinsed with acetic acid, and concentrated to dryness under vacuum. The residue was re-evaporated several times from methanol followed by toluene to remove the excess acetic acid. The residue was taken up in methanol (35 mL), treated with 6N aq sodium hydroxide (1.5 mL), and heated at 70 °C for 8 h. After cooling to room temperature, the reaction was concentrated under vacuum and the residue was triturated with cold water, filtered, washed with water, and dried under vacuum. Purification of the residue by flash chromatography on silica gel (10 to 20% methanol containing 0.1% triethylamine in dichloromethane) gave the product (**16d**, 0.48 g, 1.0 mmol, 62% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.13 (s, 1H), 8.20 (s, 1H), 8.06 (d, J = 5.05 Hz, 1H), 7.87 (br s, 1H), 7.81 (d, J = 7.58 Hz, 1H), 7.42 (t, J = 7.58 Hz, 1H), 7.32 (d, J = 7.58 Hz, 2H), 7.08 (d, J = 8.59 Hz, 2H), 6.81 (s, 1H), 6.80 (d, J = 5.05 Hz, 2H), 6.49 (d, J = 8.59 Hz, 2H), 5.14 (br s, 2H), 4.23 (q, J = 7.33 Hz, 2H), 3.74 (br s, 2H), 2.60 (br s, 4H), 1.76 (br s, 4H), 1.49 (t, J = 7.20 Hz, 3H). MS m/z 463.4 $[M + H]^+$.

4-[3-(4-*N*-Phenylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-pyrrolidinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (17g). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(N-pyrrolidinylmethyl)phenyl]-1*H*-pyrrolo[2,3-b]pyridine (**16d**, 200 mg, 0.43 mmol) in THF (10 mL) was added phenyl isocyanate (60 uL, 0.55 mmol). The reaction was stirred at room temperature for 3 h and concentrated to dryness under vacuum. The remaining solid was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum. Purification of the residue by reverse phase HPLC (10−90% CH_3CN/0.1% TFA, H_2O) gave the TFA salt which was basified with 1N aq sodium carbonate, extracted with (9:1) chloroform/isopropyl alcohol, dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. Trituration of the residue with (1:1) ethyl ether/petroleum ether, filtration, and drying under vacuum gave the product (**17g**, 166 mg, 0.28 mmol, 66% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.14 (d, J = 1.52 Hz, 1H), 8.74 (s, 1H), 8.70 (s, 1H), 8.26 (s, 1H), 8.10 (d, J = 4.80 Hz, 1H), 7.73−7.81 (m, 2H), 7.40−7.46 (m, 4H), 7.25−7.46 (m, 10H), 6.96 (t, J = 7.33 Hz, 1H), 6.83 (d, J = 5.05 Hz, 1H), 6.70 (d, J = 2.02 Hz, 1H), 4.28 (q, J = 7.24 Hz, 2H), 3.63 (s, 2H), 2.47 (br s, 4H), 1.69 (br s, 4H), 1.52

(t, $J = 7.33$ Hz, 3H). MS m/z 582.7 $[M + H]^+$. Anal. ($C_{36}H_{35}N_7O \cdot 1.0H_2O$) C, H, N.

4-[3-(4-Nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-morpholinylmethyl)phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (15m). To a stirred solution of 4-[3-(4-nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-(3-formylphenyl)-1-phenylsulfonyl-1*H*-pyrrolo-[2,3-*b*]pyridine (**15a**, 1.0 g, 1.7 mmol) in THF (20 mL) was added morpholine (0.35 mL, 4.0 mmol) followed by sodium triacetoxyborohydride (0.83 g, 3.9 mmol). The reaction was stirred at room temperature for 3 days and concentrated to dryness under vacuum. The residue was taken up in ethyl acetate, washed with water, filtered free of a small amount of insolubles, dried (Na_2SO_4), filtered, and concentrated under vacuum. Purification of the residue by flash chromatography on silica gel (a gradient of 100:0 to 96:4 dichloromethane/5% ammonium hydroxide in methanol) gave the product (**15m**, 0.94 g, 1.4 mmol, 85% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.34 (s, 1H), 8.33 (d, $J = 5.05$ Hz, 1H), 8.13 (d, $J = 8.84$ Hz, 2H), 7.84−7.87 (m, 2H), 7.74 (t, $J = 7.45$ Hz, 1H), 7.61 (t, $J = 7.83$ Hz, 2H), 7.53 (d, $J = 8.84$ Hz, 2H), 7.34−7.41 (m, 3H), 7.27 (s, 1H), 7.10 (d, $J = 5.05$ Hz, 1H), 6.45 (s, 1H), 4.26 (q, $J = 7.33$ Hz, 2H), 3.59 (t, $J = 4.29$ Hz, 4H), 3.50 (s, 2H), 2.38 (br s, 4H), 1.47 (t, $J = 7.33$ Hz, 3H). MS m/z 649.4 $[M + H]^+$.

4-[3-(4-Aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-morpholinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (16e). To a stirred solution of 4-[3-(4-nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-morpholinylmethyl)phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (**15m**, 0.94 g, 1.4 mmol) in acetic acid (30 mL) was added portionwise zinc dust (0.7 g, 10.7 mmol) over 5 min. The reaction was stirred at room temperature for 1 h, filtered through a pad of celite, rinsed with acetic acid, and concentrated to dryness under vacuum. The residue was re-evaporated several times from methanol followed by toluene to remove the excess acetic acid, taken up in methanol (30 mL), and treated with 6N aq sodium hydroxide (2.0 mL). The reaction mixture was stirred and heated at 70 °C for 8 h. After cooling to room temperature, the reaction was concentrated under vacuum, triturated with cold water, filtered, washed with water, and dried under vacuum to give the crude product (**16e**, 0.73 g, 1.5 mmol, 100% yield) as a pale-yellow solid. MS m/z 479.4 $[M + H]^+$.

4-[3-(4-*N*-Phenylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-morpholinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (17h). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-morpholinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**16e**, 150 mg, 0.31 mmol) in THF (5 mL) was added phenyl isocyanate (41 μL, 0.37 mmol) and two drops of triethylamine. The reaction was stirred at room temperature for 1 h and concentrated to dryness under vacuum. The remaining solid was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum. Purification of the residue by reverse phase HPLC (10−90% CH_3CN/H_2O with 0.1% TFA) gave the TFA salt which was basified with 1N aq sodium carbonate, extracted with dichloromethane, dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. The residue was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum to give the product (**17h**, 81 mg, 0.14 mmol, 44% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.16 (d, $J = 1.52$ Hz, 1H), 8.72 (s, 1H), 8.67 (s, 1H), 8.27 (s, 1H), 8.10 (d, $J = 5.05$ Hz, 1H), 7.74−7.82 (m, 2H), 7.39−7.46 (m, 5H), 7.31−7.35 (m, 2H), 7.27 (t, $J = 7.83$ Hz, 3H), 6.96 (t, $J = 7.33$ Hz, 1H), 6.82 (d, $J = 5.05$ Hz, 1H), 6.73 (d, $J = 2.02$ Hz, 1H), 4.28 (q, $J = 7.16$ Hz, 2H), 3.58 (t, $J = 4.42$ Hz, 4H), 3.50 (s, 2H), 2.38 (br s, 4H), 1.52 (t, $J = 7.33$ Hz, 3H). MS m/z 598.6 $[M + H]^+$. Anal. ($C_{36}H_{35}N_7O \cdot 1.75H_2O$) C, H, N.

4-Bromo-2-[4-(*N*-morpholinylmethyl)phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (14h). To a glass pressure tube were added 4-bromo-2-iodo-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (**13**, 1.2 g, 2.6 mmol), 4-(*N*-morpholinylmethyl)benzeneboronic acid (0.8 g, 2.6 mmol), dimethylformamide (20 mL), aq satd sodium bicarbonate (5 mL), and tetrakis(triphenylphosphine)palladium(0) (125 mg, 0.11 mmol). The reaction was purged with nitrogen, capped, and stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was concentrated under vacuum, taken up in ethyl acetate, and washed with water followed by brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (a gradient of 100:0 to 95:5 dichloromethane/5% ammonium hydroxide in methanol) gave the product (**14h**, 1.13 g, 2.2 mmol, 84% yield) as a beige foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.25 (d, $J = 5.31$ Hz, 1H), 7.80−7.83 (m, 2H), 7.68 (t, $J = 7.45$ Hz, 1H), 7.61 (d, $J = 5.31$ Hz, 1H), 7.56−7.63 (m, 4H), 7.44 (d, $J = 8.08$ Hz, 2H), 6.77 (s, 1H), 3.62 (t, $J = 4.42$ Hz, 4H), 3.57 (s, 2H), 2.42 (br s, 4H). MS m/z 512.2 $[M + H]^+$.

4-[3-(4-Nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(*N*-morpholinylmethyl)phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (15h). To a sealed pressure tube were added 4-bromo-2-[4-(*N*-morpholinylmethyl)phenyl]-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]-pyridine (**14h**, 0.5 g, 1.0 mmol), 3-(4-nitrophenyl)-1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.4 g, 1.1 mmol), dimethylformamide (16 mL), aq satd sodium bicarbonate (4 mL), and tetrakis(triphenylphosphine)palladium(0) (70 mg, 0.06 mmol). The reaction was purged with nitrogen, capped, and stirred at 100 °C for 8 h. After cooling to room temperature, the reaction was concentrated under vacuum, taken up in ethyl acetate, and washed with water followed by brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (98:2 dichloromethane/5% ammonium hydroxide in methanol) gave the product (**15h**, 0.64 g, 1.0 mmol, 99% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.33 (s, 1H), 8.30 (d, $J = 5.31$ Hz, 1H), 8.14 (d, $J = 8.84$ Hz, 2H), 7.82−7.84 (m, 2H), 7.72 (t, $J = 7.45$ Hz, 1H), 7.57−7.63 (m, 2H), 7.54 (d, $J = 9.02$ Hz, 2H), 7.43 (d, $J = 8.08$ Hz, 2H), 7.39 (d, $J = 8.34$ Hz, 2H), 7.05 (d, $J = 5.05$ Hz, 1H), 6.54 (s, 1H), 4.26 (q, $J = 4.26$ Hz, 2H), 3.61 (t, $J = 4.55$ Hz, 4H), 3.54 (s, 2H), 2.40 (br s, 4H), 1.47 (t, $J = 7.33$ Hz, 4H). MS m/z 649.2 $[M + H]^+$.

4-[3-(4-Aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(*N*-morpholinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (16h). To a stirred solution of 4-[3-(4-nitrophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(*N*-morpholinylmethyl)]-1-phenylsulfonyl-1*H*-pyrrolo-[2,3-*b*]pyridine (**15h**, 0.64 g, 1.0 mmol) in acetic acid (20 mL) was added portionwise zinc dust (0.4 g, 6.1 mmol) over 5 min. The reaction was stirred at room temperature for 1 h, filtered through a pad of celite, rinsed with acetic acid, and concentrated to dryness under vacuum. The residue was re-evaporated several times from methanol followed by toluene to remove the excess acetic acid. The residue was taken up in methanol (25 mL) and treated with aq 6N sodium hydroxide (1.5 mL). The reaction mixture was stirred and heated at 70 °C for 8 h. After cooling to room temperature, the reaction was concentrated under vacuum, and the residue was triturated with cold water, filtered, washed with water, and dried under vacuum to give the crude product (**16h**, 0.46 g, mmol, 0.96 mmol, 96% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.09 (d, $J = 1.77$ Hz, 1H), 8.20 (s, 1H), 8.05 (d, $J = 5.05$ Hz, 1H), 7.85 (d, $J = 8.34$ Hz, 2H), 7.37 (d, $J = 8.34$ Hz, 2H), 7.08 (d, $J = 8.59$ Hz, 2H), 6.80 (br s, 1H), 6.80 (d, $J = 4.80$ Hz, 1H), 6.49 (d, $J = 8.34$ Hz, 2H), 5.14 (s, 2H), 4.23 (q, $J = 7.24$ Hz, 2H), 3.59 (t, $J = 4.42$ Hz, 4H), 3.49 (s, 2H), 2.37 (br s, 4H), 1.49 (t, $J = 7.33$ Hz, 3H). MS m/z 479.4 $[M + H]^+$.

4-[3-(4-*N*-Phenylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(*N*-morpholinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (17i). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(*N*-morpholinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**16h**, 0.22 g, 0.46 mmol) in THF (15 mL) was added phenyl isocyanate (75 uL, 0.69 mmol) and one drop of triethylamine. The reaction was stirred at room temperature for

1 h and concentrated to dryness under vacuum. Purification of the residue by reverse phase HPLC (10−90% CH_3CN/H_2O) gave the product (**17i**, 30 mg, 0.05 mmol, 11% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.13 (br s, 1H), 8.80 (br s, 1H), 8.75 (br s, 1H), 8.26 (s, 1H), 8.08 (d, J = 5.05 Hz, 1H), 7.83 (d, J = 8.08 Hz, 2H), 7.25−7.46 (m, 10H), 6.93−7.00 (m, 1H), 6.81 (d, J = 5.05 Hz, 1H), 6.74 (s, 1H), 4.27 (q, J = 7.16 Hz, 2H), 3.57 (br s, 4H), 3.47 (s, 2H), 2.35 (br s, 4H), 1.52 (t, J = 7.20 Hz, 3H). MS m/z 598.4 $[M + H]^+$. Anal. ($C_{36}H_{35}N_7O \cdot 1.75H_2O$) C, H, N.

4-[3-(4-*N*-Ethylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(dimethylaminomethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (17j). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(dimethylaminomethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**16a**, 0.15 g, 0.34 mmol) in THF (5 mL) was added ethyl isocyanate (55 uL, 0.70 mmol) and two drops of triethylamine. The reaction was stirred at room temperature for 2 days and concentrated to dryness under vacuum. The remaining solid was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum. Purification of the residue by reverse phase HPLC (10−90% CH_3CN/H_2O with 0.1% TFA) gave the TFA salt which was basified with 1N aq sodium carbonate, extracted with dichloromethane, dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. Trituration of the residue with (1:1) ethyl ether/petroleum ether, filtration, and drying under vacuum gave the product (**17j**, 32 mg, 0.064 mmol, 18% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.17 (br s, 1H), 8.56 (s, 1H), 8.25 (s, 1H), 8.09 (d, J = 4.80 Hz, 1H), 7.81−7.88 (m, 2H), 7.44 (t, J = 7.58 Hz, 1H), 7.30−7.37 (m, 3H), 7.24−7.30 (m, 2H), 6.80 (d, J = 4.80 Hz, 1H), 6.77 (s, 1H), 6.17 (t, J = 5.43 Hz, 1H), 5.76 (s, 1H), 4.26 (q, J = 7.07 Hz, 2H), 3.70 (br s, 2H), 3.05−3.13 (m, 2H), 2.35 (br s, 6H), 1.51 (t, J = 7.20 Hz, 3H), 1.03 (t, J = 7.20 Hz, 3H). MS m/z 508.4 $[M + H]^+$.

4-[3-(4-*N*,*N*-Dimethylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(dimethylaminomethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (17k). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(dimethylaminomethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**16a**, 0.45 g, 1.0 mmol) in tetrahydrofuran (15 mL) was added *p*-nitrophenylchloroformate (0.22 g, 1.1 mmol). After stirring for 1 h at room temperature, a solution of 2.0 M dimethylamine in tetrahydrofuran (7 mL, 14 mmol) was added. The reaction was stirred an additional 1 h at room temperature and then concentrated under vacuum. The residue which remained was triturated with aq sodium hydroxide, filtered, washed with cold water, and dried under vacuum. Purification of the residue by Gilson reverse phase HPLC afforded the title compound (**17k**, 235 mg, 0.46 mmol, 46% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.14 (d, J = 1.8 Hz, 1H), 8.31 (s, 1H), 8.27 (s, 1 H), 8.07 (d, J = 4.8 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.77 (s, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 8.6 Hz, 2H), 7.27 (dd, 1H), 6.79 (d, J = 5.1 Hz, 1H), 6.76 (d, J = 2.0 Hz, 1H), 4.27 (q, J = 7.3 Hz, 2H), 3.43 (s, 2H), 2.91 (s, 6H), 2.18 (s, 6H), 1.51 (t, J = 7.2 Hz, 3H). MS m/z 508.4 $[M + H]^+$. Anal. ($C_{30}H_{33}N_7O \cdot 1.0H_2O$) C, H, N.

4-[3-(4-*N*-Ethylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(dimethylaminomethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (17l). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(dimethylaminomethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**16g**, 0.20 g, 0.46 mmol) in THF (5 mL) was added ethyl isocyanate (75 uL, 0.95 mmol). The reaction was stirred at room temperature for 2 days and concentrated to dryness under vacuum. The remaining solid was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum. Purification of the residue by reverse phase HPLC (10−90% CH_3CN/H_2O with 0.1% TFA) gave the TFA salt which was basified with 1N aq sodium carbonate, extracted with dichloromethane, dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. The residue was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum to give the product (**17l**, 115 mg, 0.23 mmol, 49% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.11 (br s, 1H), 8.53 (s, 1H), 8.25 (s, 1H), 8.06 (d, J = 5.05 Hz, 1H), 7.83 (d, J = 8.08 Hz, 2H), 7.33−7.35 (m, 4H), 7.26 (d, J = 8.59 Hz, 2H), 6.78 (d, J = 5.05 Hz, 1H), 6.76 (s, 1H), 6.18 (t, J = 5.56 Hz, 1H), 4.26 (q, J = 7.24 Hz, 2H), 3.40 (s, 2H), 3.05−3.11 (m, 2H), 2.16 (s, 6H), 1.51 (t, J = 7.33 Hz, 3H), 1.04 (t, J = 7.07 Hz, 3H). MS m/z 508.4 $[M + H]^+$. Anal. ($C_{30}H_{33}N_7O \cdot 1.75H_2O$) C, H, N.

4-[3-(4-*N*,*N*-Dimethylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(dimethylaminomethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (17m). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(dimethylaminomethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**16g**, 0.45 g, 1.0 mmol) in THF (15 mL) was added *p*-nitrophenylchloroformate (0.23 g, 1.1 mmol). After stirring for 1 h at room temperature, a solution of 2.0 M dimethylamine in THF (8 mL, 16 mmol) was added. The reaction was stirred an additional 1 h at room temperature and then concentrated under vacuum. The residue which remained was triturated with 0.5N aq sodium hydroxide, filtered, washed with cold water, and dried under vacuum. Purification of the residue by reverse phase HPLC (10−90% CH_3CN/H_2O with 0.1% TFA) gave the TFA salt which was basified with 1N aq sodium carbonate, extracted with dichloromethane, dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. The residue was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum to give the product (**17m**, 234 mg, 0.46 mmol, 46% yield) as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.12 (d, J = 1.52 Hz, 1H), 8.31 (s, 1H), 8.26 (s, 1H), 8.06 (d, J = 4.80 Hz, 1H), 7.84 (d, J = 8.34 Hz, 2H), 7.42 (d, J = 8.84 Hz, 2H), 7.35 (d, J = 8.34 Hz, 2H), 7.28 (d, J = 8.59 Hz, 2H), 6.78 (d, J = 4.80 Hz, 1H), 6.78 (d, J = 2.27 Hz, 1H), 4.27 (q, J = 7.33 Hz, 2H), 3.41 (s, 2H), 2.91 (s, 6H), 2.16 (s, 6H), 1.51 (t, J = 7.20 Hz, 3H). MS m/z 508.4 $[M + H]^+$.

4-[3-(4-*N*-Ethylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-pyrrolidinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (17n). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-pyrrolidinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**16d**, 240 mg, 0.51 mmol) in THF (15 mL) was added ethyl isocyanate (110 μL, 1.4 mmol). The reaction was stirred at room temperature for 4 days and concentrated to dryness under vacuum. The remaining solid was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum. Purification of the residue by reverse phase HPLC (10−90% CH_3CN/H_2O with 0.1% TFA) gave the TFA salt which was basified with 1N aq sodium carbonate, extracted with (9:1) chloroform/isopropyl alcohol, dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. The residue was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum to give the product (**17n**, 205 mg, 0.38 mmol, 73% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.13 (d, J = 1.52 Hz, 1H), 8.46 (s, 1H), 8.25 (s, 1H), 8.07 (d, J = 5.05 Hz, 1H), 7.73−7.81 (m, 2H), 7.38 (t, J = 7.58 Hz, 1H), 7.34 (d, J = 8.59 Hz, 2H), 7.28 (d, J = 7.07 Hz, 1H), 7.26 (d, J = 8.59 Hz, 2H), 6.79 (d, J = 4.80 Hz, 1H), 6.74 (d, J = 2.02 Hz, 1H), 6.10 (t, J = 5.56 Hz, 1H), 4.26 (q, J = 7.24 Hz, 2H), 3.63 (s, 2H), 3.09 (dd, J = 7.07, 5.81 Hz, 2H), 2.47 (br s, 4H), 1.72 (br s, 4H), 1.51 (t, J = 7.33 Hz, 3H), 1.04 (t, J = 7.07 Hz, 3H). MS m/z 534.5 $[M + H]^+$. Anal. ($C_{32}H_{35}N_7O \cdot 1.5H_2O$) C, H, N.

4-[3-(4-*N*,*N*-Dimethylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-pyrrolidinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (17o). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-pyrrolidinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**16d**, 0.15 g, 0.32 mmol) in THF (10 mL) was added *p*-nitrophenylchloroformate (75 mg, 0.37 mmol). The reaction quickly became a suspension. After stirring for 1 h at room temperature, a solution of 2.0 M dimethylamine in THF (1.5 mL, 3 mmol) was added. The reaction was stirred an additional 1 h at room temperature and then concentrated under vacuum. The residue which remained was triturated with 0.5N aq sodium hydroxide, filtered, washed with cold water, and dried under vacuum. Purification of the residue by reverse phase

HPLC (10−90% CH_3CN/H_2O with 0.1% TFA) gave the TFA salt which was basified with 1N aq sodium carbonate, extracted with dichloromethane, dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. The residue was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum to give the product (**17o**, 69 mg, 0.13 mmol, 40% yield) as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.15 (s, 1H), 8.32 (s, 1H), 8.27 (s, 1H), 8.07 (d, J = 5.05 Hz, 1H), 7.74−7.81 (m, 2H), 7.43 (d, J = 8.59 Hz, 2H), 7.38 (t, J = 7.58 Hz, 1H), 7.27 (d, J = 8.59 Hz, 3H), 6.79 (d, J = 5.05 Hz, 1H), 6.76 (d, J = 1.77 Hz, 1H), 4.27 (q, J = 7.24 Hz, 2H), 3.61 (s, 2H), 2.91 (s, 6H), 2.45 (br s, 4H), 1.71 (br s, 4H), 1.51 (t, J = 7.20 Hz, 3H). MS m/z 534.4 $[M + H]^+$. Anal. ($C_{32}H_{35}N_7O \cdot 1.25H_2O$) C, H, N.

4-[4-Bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-benzaldehyde (14d). To a glass pressure tube were added 4-bromo-2-iodo-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (**13**, 3.67 g, 7.93 mmol), 4-formylbenzeneboronic acid (1.19 g, 7.93 mmol), *N*,*N*-dimethylformamide (60 mL), aq satd sodium bicarbonate (20 mL), and tetrakis(triphenylphosphine)palladium(0) (458 mg, 0.40 mmol). The reaction was purged with nitrogen, sealed, and stirred at 100 °C overnight (20 h). After cooling to room temperature, the reaction was diluted with water, brine, and ethyl acetate. The aqueous layer was extracted with two portions of ethyl acetate and the combined extracts were dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (35% ethyl acetate in hexanes) gave the product (**14d**, 2.64 g, 75% yield) as a yellow solid. MS m/z 441.2 $[M + H]^+$. ^{1}H NMR (DMSO-d_6) δ ppm 10.13 (s, 1H), 8.29 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 8.0 Hz, 1H), 7.72−7.65 (m, 2H), 7.58 (app t, J = 8.0 Hz, 2H), 6.96 (s, 2H).

4-[4-[1-Ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]benzaldehyde (15d). To a sealed pressure tube were added 4-[4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]benzaldehyde (**14d**, 2.64 g, 5.99 mmol), 3-(4-nitrophenyl)-1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (2.05 g, 5.99 mmol), dimethylformamide (45 mL), aq satd sodium bicarbonate (15 mL), and tetrakis(triphenylphosphine)palladium(0) (346 mg, 0.30 mmol). The reaction was purged with nitrogen, capped, and stirred at 100 °C overnight (20 h). After cooling to room temperature, the reaction was concentrated under vacuum, taken up in ethyl acetate, and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum. Purification of the residue by flash chromatography on silica gel (50−55% ethyl acetate in hexanes) gave the product (**15d**, 1.86 g, 1.3 mmol, 54% yield) as a yellow solid. MS m/z 578.4 $[M + H]^+$. ^{1}H NMR (DMSO-d_6) δ ppm 10.10 (s, 1H), 8.35 (s, 1H), 8.33 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.0 Hz, 2H), 7.88 (app d, J = 4.0 Hz, 2H), 7.72−7.75 (m, 3H), 7.61 (app t, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 4.0 Hz, 1H), 6.76 (s, 1H), 4.27 (q, J = 8.0 Hz, 2H), 1.47 (t, J = 8.0 Hz, 3H).

4-[1-Ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-2-[4-(1-pyrrolidinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (15n). To a stirred solution of 4-[4-[1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]benzaldehyde (**15d**, 300 mg, 0.52 mmol) in THF (5 mL) was added pyrrolidine (148 mg, 2.1 mmol) followed by sodium triacetoxyborohydride (441 mg, 2.1 mmol). The reaction was stirred at room temperature for 20 h, quenched with water, and diluted with ethyl acetate. The aqueous layer was extracted with four portions of ethyl acetate and the combined extracts were dried (Na_2SO_4), filtered, and evaporated under vacuum. Purification of the residue by flash chromatography on silica gel (95:5 dichloromethane/5% ammonium hydroxide in methanol) gave the product (**15n**, 308 mg, 93% yield) as a golden fluffy solid. MS m/z 633.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.34 (s, 1 H), 8.30 (d, J = 4.0 Hz, 1H), 8.11−8.17 (m, 2H), 7.81−7.87 (m, 2H), 7.72 (t, J = 8.0 Hz, 1H), 7.60 (t, J = 8.0 Hz, 2H), 7.51−7.56 (m, 2H), 7.34−7.43 (m, 4H), 7.05 (d, J = 4.0 Hz, 1H), 6.54 (s, 1H), 4.26 (q, J = 8.0 Hz, 2H), 3.64 (s, 2H), 2.47 (br s, 4H), 1.69−1.75 (m, 4H), 1.47 (t, J = 8.0 Hz, 3H).

[4-(1-Ethyl-4-{2-[4-(1-pyrrolidinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl}-1*H*-pyrazol-3-yl)phenyl]amine (16f). To a stirred solution of 4-[1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1-(phenylsulfonyl)-2-[4-(1-pyrrolidinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**15n**, 308 mg, 0.49 mmol) in acetic acid (4 mL) was added portionwise zinc dust (223 mg, 3.41 mmol) (exotherm observed). The reaction was stirred at room temperature for 1 h, filtered through a pad of celite, rinsed with acetic acid, and concentrated to dryness under vacuum. The residue was re-evaporated several times from methanol followed by toluene to remove the excess acetic acid. The residue was taken up in methanol (5 mL) and treated with aq 6N sodium hydroxide (0.24 mL, 1.46 mmol). The reaction mixture was stirred and heated at 70 °C for 5 h. After cooling to room temperature, the reaction was concentrated under vacuum, triturated with cold water, filtered, washed with water, and dried under vacuum to give the crude product (**16f**, 229 mg, 100% yield) (92% pure by LCMS) as an orange solid. The material was used as is in the subsequent reaction. MS m/z 463 $[M + H]^+$.

***N*-Ethyl-*N*′-[4-(1-ethyl-4-{2-[4-(1-pyrrolidinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl}-1*H*-pyrazol-3-yl)phenyl]urea (17p).** To a stirred solution of [4-(1-ethyl-4-{2-[4-(1-pyrrolidinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl}-1*H*-pyrazol-3-yl)-phenyl]amine (**16f**, 100 mg, 0.216 mmol) in THF (2 mL) was added one drop of triethylamine followed by ethyl isocyanate (20 μL, 0.259 mmol). The reaction was stirred at room temperature for 22 h and concentrated to dryness under vacuum. The remaining solid taken up in DMSO and purified by reverse phase HPLC (10−90% CH_3CN/H_2O with 0.1% TFA) to give the TFA salt which was basified with satd aq sodium bicarbonate and extracted with three portions of dichloromethane. The combined organics were dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum to give the product (**17p**, 22 mg, 19% yield) as a yellow solid. MS m/z 534.4 $[M + H]^+$. ^{1}H NMR (DMSO-d_6) δ ppm 12.10 (s, 1H), 8.45 (s, 1H), 8.25 (s, 1H), 8.06 (d, J = 4.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.32−7.37 (m, 4H), 7.26 (d, J = 8.0 Hz, 2H), 6.78 (d, J = 4.0 Hz, 1H), 6.74 (s, 1H), 6.09 (bs, 1H), 4.26 (q, J = 8.0 Hz, 2H), 3.59 (bs, 2H), 3.09 (m, 2H), 2.45 (app bs, 4H), 1.71 (app bs, 4H), 1.51 (t, J = 8.0 Hz, 3H), 1.04 (t, J = 8.0 Hz, 3H).

***N*′-[4-(1-Ethyl-4-{2-[4-(1-pyrrolidinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl}-1*H*-pyrazol-3-yl)phenyl]-*N*,*N*-dimethylurea (17q).** To a stirred suspension of [4-(1-ethyl-4-{2-[4-(1-pyrrolidinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl}-1*H*-pyrazol-3-yl)phenyl]amine (**16f**, 130 mg, 0.281 mmol) in THF (3 mL) was added *p*-nitrophenyl chloroformate (62 mg, 0.31 mmol), giving a yellow slurry. After 45 min, dimethylamine (0.56 mL of a 2 M solution in THF, 1.12 mmol) was added. After an additional 45 min, the reaction was diluted with ethyl acetate and washed with three portions of 1N NaOH. The combined aq layers were back-extracted with ethyl acetate, and the combined extracts were dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum. The residue was purified by reverse phase HPLC (10−90% CH_3CN/0.1% TFA in H_2O) to give the TFA salt which was basified with satd aq sodium bicarbonate, extracted with three portions of dichloromethane, dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum to give the product (**17q**, 62 mg, 39% yield) as a light-yellow solid. MS m/z 534.4 $[M + H]^+$. ^{1}H NMR (DMSO-d_6) δ ppm 12.11 (s, 1H), 8.31 (s, 1H), 8.26 (s, 1H), 8.06 (d, J = 4.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.78 (d, J = 8.0 Hz, 1H), 6.76 (s, 1H), 4.27 (q, J = 8.0 Hz, 2H), 3.59 (bs, 2H), 2.91 (s, 6H), 2.44 (app bs, 4H), 1.71 (app bs, 4H), 1.51 (t, J = 8.0 Hz, 3H). Anal. ($C_{32}H_{35}N_7O \cdot 1.0H_2O$) C, H, N.

4-[3-(4-*N*-Ethylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-morpholinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (17r). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-morpholinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**16e**, 0.15 g, 0.31 mmol) in THF (5 mL)

was added ethyl isocyanate (50 uL, 0.63 mmol) and two drops of triethylamine. The reaction was stirred at room temperature for 2 days and concentrated to dryness under vacuum. The remaining solid was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum. Purification of the residue by reverse phase HPLC (10−90% CH_3CN/0.1% TFA in H_2O) gave the TFA salt which was basified with 1N aq sodium carbonate, extracted with dichloromethane, dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. The residue was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum to give the product (**17r**, 71 mg, 0.13 mmol, 42% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.15 (s, 1H), 8.47 (s, 1H), 8.25 (s, 1H), 8.08 (d, J = 5.05 Hz, 1H), 7.74−7.81 (m, 2H), 7.40 (t, J = 7.96 Hz, 1H), 7.31−7.36 (m, 2H), 7.24−7.30 (m, 3H), 6.80 (d, J = 5.05 Hz, 1H), 6.73 (d, J = 2.02 Hz, 1H), 6.11 (t, J = 5.56 Hz, 1H), 4.26 (q, J = 7.16 Hz, 2H), 3.59 (t, J = 4.42 Hz, 4H), 3.51 (s, 2H), 3.09 (dd, J = 7.07, 5.81 Hz, 2H), 2.39 (br s, 4H), 1.51 (t, J = 7.33 Hz, 3H), 1.04 (t, J = 7.07 Hz, 3H). MS m/z 550.6 $[M + H]^+$. Anal. ($C_{32}H_{35}N_7O \cdot 1.0H_2O$) C, H, N.

4-[3-(4-*N*,*N*-Dimethylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-morpholinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]-pyridine (17s). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[3-(*N*-morpholinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (0.41 g, 0.85 mmol) in THF (10 mL) was added *p*-nitrophenylchloroformate (207 mg, 1.0 mmol). The reaction mixture quickly became a suspension. After stirring for 1 h at room temperature, a solution of 2.0 M dimethylamine in THF (6.0 mL, 12 mmol) was added. The reaction was stirred an additional 1 h at room temperature and then concentrated under vacuum. The residue which remained was triturated with 0.5N aq sodium hydroxide, filtered, washed with cold water, and dried under vacuum. Purification of the residue by reverse phase HPLC (10−90% CH_3CN/0.1% TFA in H_2O) gave the TFA salt which was basified with 1N aq sodium carbonate, extracted with dichloromethane, dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. The residue was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum to give the product (**17s**, 204 mg, 0.37 mmol, 43% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.15 (s, 1H), 8.31 (s, 1H), 8.26 (s, 1H), 8.08 (d, J = 5.05 Hz, 1H), 7.74−7.81 (m, 2H), 7.37−7.45 (m, 3H), 7.26−7.29 (m, 3H), 6.80 (d, J = 4.80 Hz, 1H), 6.74 (d, J = 1.77 Hz, 1H), 4.27 (q, J = 7.24 Hz, 2H), 3.59 (t, J = 4.29 Hz, 4H), 3.51 (s, 2H), 2.91 (s, 6H), 2.39 (br s, 4H), 1.51 (t, J = 7.20 Hz, 3H). MS m/z 550.4 $[M + H]^+$. Anal. ($C_{32}H_{35}N_7O \cdot 1.0H_2O$) C, H, N.

(4-[3-(4-*N*-Ethylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(*N*-morpholinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (17t). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(N-morpholinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**16h**, 0.18 g, 0.37 mmol) in THF (10 mL) was added ethyl isocyanate (50 μL, 0.63 mmol) and two drops of triethylamine. The reaction was stirred at room temperature for 24 h and concentrated to dryness under vacuum. The remaining solid was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum. Purification of the residue by reverse phase HPLC (10−90% CH_3CN/0.1% TFA in H_2O) gave the TFA salt which was basified with 1N aq sodium carbonate, extracted with dichloromethane, dried ($MgSO_4$), filtered, and evaporated to dryness under vacuum. The residue was triturated with (1:1) ethyl ether/petroleum ether, filtered, and dried under vacuum to give the product (**17t**, 138 mg, 0.25 mmol, 68% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.12 (d, J = 1.52 Hz, 1H), 8.47 (s, 1H), 8.25 (s, 1H), 8.06 (d, J = 4.80 Hz, 1H), 7.83 (d, J = 8.34 Hz, 2H), 7.31−7.39 (m, 4H), 7.23−7.30 (m, 2H), 6.78 (d, J = 5.05 Hz, 1H), 6.75 (d, J = 2.02 Hz, 1H), 6.11 (t, J = 5.56 Hz, 1H), 4.26 (q, J = 7.33 Hz, 2H), 3.59 (t, J = 4.42 Hz, 4H), 3.48 (s, 2H), 3.09 (dd, J = 7.20, 5.68 Hz, 2H), 2.37 (br s, 4H) 1.51 (t, J = 7.33 Hz, 3H), 1.04 (t, J = 7.07 Hz, 3H). MS m/z 550.4 $[M + H]^+$. Anal. ($C_{32}H_{35}N_7O \cdot 1.5H_2O$) C, H, N.

4-[3-(4-*N*,*N*-Dimethylcarbamylaminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(*N*-morpholinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]-pyridine (17u). To a stirred solution of 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-2-[4-(N-morpholinylmethyl)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (**16h**, 105 mg, 0.22 mmol) in THF (2 mL) was added *p*-nitrophenylchloroformate (50 mg, 0.25 mmol). After stirring for 1 h at room temperature, a solution of 2.0 M dimethylamine in THF (1.5 mL, 3 mmol) was added. The reaction mixture was stirred an additional 1 h at room temperature and then concentrated under vacuum. The residue which remained was triturated with 0.5N aq sodium hydroxide, filtered, washed with cold water, and dried under vacuum. The residue was purified by reverse phase HPLC (10−90% CH_3CN/H_2O). Trituration of the residue with (1:1) ethyl ether/petroleum ether, filtration, and drying under vacuum gave the product (**17u**, 95 mg, 0.17 mmol, 78% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.12 (br s, 1H), 8.32 (s, 1H), 8.25 (s, 1H), 8.06 (d, J = 4.80 Hz, 1H), 7.83 (d, J = 8.08 Hz, 2H), 7.42 (d, J = 8.59 Hz, 2H), 7.37 (d, J = 8.08 Hz, 2H), 7.27 (d, J = 8.59 Hz, 2H), 6.79 (d, J = 5.05 Hz, 1H), 6.76 (s, 1H), 4.26 (q, J = 7.24 Hz, 2H), 3.59 (br s, 4H), 3.48 (s, 2H), 2.91 (s, 6H), 2.37 (br s, 4H), 1.51 (t, J = 7.20 Hz, 3H). MS m/z 550.4 $[M + H]^+$. Anal. ($C_{32}H_{35}N_7O \cdot 0.5H_2O$) C, H, N.

Ethyl 1*H*-Pyrrolo[2,3-*b*]pyridine-2-carboxylate 7-Oxide (18). Compound **18** was prepared as described in WO2000044753.[36] ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 8.40 (d, J = 6.32 Hz, 1H), 7.80 (d, J = 7.33 Hz, 1H), 7.28 (s, 1H), 7.17 (dd, J = 8.08, 6.32 Hz, 1H), 4.45 (q, J = 7.07 Hz, 2H), 1.44 (t, J = 7.07 Hz, 3H). MS m/z 207.0 $[M + H]^+$.

Ethyl 4-Bromo-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (19). To a stirred solution of ethyl 1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate 7-oxide (4.35 g, 21 mmol) and tetrabutylammonium-bromide (4.90 g, 31.8 mmol) in 1,2-dimethoxyethane (50 mL) at 0 °C was added portionwise over 5 min methanesulfonic anhydride (7.4 g, 42.5 mmol). The reaction was allowed to warm to room temperature and stirred for 18 h. The reaction was evaporated to dryness under vacuum, neutralized with cold 0.5N aq sodium bicarbonate in water, filtered, rinsed with cold water, and dried under vacuum to give the product (6.20 g, 100%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.97 (br s, 1H), 8.28 (d, J = 5.05 Hz, 1H), 7.48 (d, J = 5.05 Hz, 1H), 7.05 (d, J = 2.02 Hz, 1H), 4.36 (q, J = 7.07 Hz, 2H), 1.35 (t, J = 7.07 Hz, 3H). MS m/z 269.2 $[M + H]^+$.

4-[1-Ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo[2,3-*b*]-pyridine-2-carboxylic Acid (20). A solution of ethyl 4-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (3.31 mmol), 1-ethyl-3-(4-nitrophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (3.97 mmol), and tetrakis(triphenylphosphine)-palladium(0) (0.17 mmol) in 2 M aq potassium carbonate solution (12 mL) and *N*,*N*-dimethylformamide (12 mL) was stirred at 100 °C for 17 h. The reaction mixture was cooled and saturated aq ammonium chloride solution (20 mL) was added, and the product was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. Precipitation from ethyl acetate afforded the title compound (**20**) as a yellow solid (81%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.68 (s, 1H), 8.29 (s, 1H), 8.17 (dd, J = 6.82, 1.77 Hz, 3H), 7.66 (d, J = 8.59 Hz, 2H), 7.29 (br s, 1H), 6.80 (d, J = 4.80 Hz, 1H), 6.53 (s, 1H), 4.32 (q, J = 7.16 Hz, 2H), 1.51 (t, 3H). MS m/z 378.2 $[M + H]^+$.

4-[1-Ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (21a). A solution of 4-[1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylic acid (**20**, 0.212 mmol) and 1,1′-carbonyldiimidazole (0.25 mmol) in anhydrous *N*,*N*-dimethylformamide (1 mL) under nitrogen at room temperature was stirred for 30 min. 4-(2-Aminoethyl)-morpholine (0.64 mmol)

was added to the mixture, and the reaction was stirred for 16.5 h at room temperature. The reaction mixture was concentrated in vacuo. Purification of the residue by reverse phase HPLC (10−90% MeCN/0.1% NH_4OH in H_2O) afforded the title compound (**21a**) as a white solid (15%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.20 (s, 1H), 8.36 (t, J = 5.81 Hz, 1H), 8.28 (s, 1H), 8.27 (d, J = 5.00 Hz, 1H), 8.16 (d, J = 8.84 Hz, 2H), 7.64 (d, J = 8.84 Hz, 2H), 6.95 (s, 1H), 6.89 (d, J = 4.80 Hz, 1H), 4.33 (q, J = 7.33 Hz, 2H), 3.55 (t, J = 4.55 Hz, 4H), 3.35−3.41 (m, 2H), 2.36−2.47 (m, 6H), 1.53 (t, J = 7.33 Hz, 3H). MS m/z 490.4 $[M + H]^+$.

4-[1-Ethyl-3-(4-{[(phenylamino)carbonyl]amino}phenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (22a). To a mixture of 4-[1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrolo-[2,3-*b*]pyridine-2-carboxamide (**21a**, 0.033 mmol) in 6N hydrochloric acid solution (1 mL) and ethanol (1 mL) under nitrogen at room temperature was added tin powder (0.164 mmol). The reaction was stirred at 70 °C for 1 h and then cooled to room temperature. The mixture was filtered through celite, and the filtrate was concentrated in vacuo to give 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide as the crude HCl salt. LCMS showed m/z 460.4 $[M + H]^+$ and 100% purity (UV214). To a solution of this crude product (0.033 mmol theoretical) in anhydrous pyridine (0.5 mL) under nitrogen at room temperature was added phenyl isocyanate (0.036 mmol). The reaction was stirred at room temperature for 30 min and then concentrated in vacuo. Purification of the residue by reverse phase HPLC ($MeCN/H_2O$ + 0.1% NH_4OH) provided the title compound (**22a**) as a white solid (58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.10 (br s, 1H), 8.71 (s, 1H), 8.69 (s, 1H), 8.37 (t, J = 5.68 Hz, 1H), 8.21 (d, J = 5.05 Hz, 1H), 8.18 (s, 1H), 7.44 (d, J = 7.58 Hz, 2H), 7.38 (d, J = 8.59 Hz, 2H), 7.23−7.32 (m, 4H), 7.04 (s, 1H), 6.96 (t, J = 7.33 Hz, 1H), 6.83 (d, J = 4.80 Hz, 1H), 4.27 (q, J = 7.33 Hz, 2H), 3.56 (t, J = 4.55 Hz, 4H), 3.37−3.43 (m, 2H), 2.36−2.48 (m, 6H), 1.51 (t, J = 7.20 Hz, 3H). MS m/z 579.6 $[M + H]^+$.

4-[1-Ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (21b). A solution of 4-[1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylic acid (**20**, 0.265 mmol), [3-(4-methyl-1-piperazinyl)propyl]amine (0.795 mmol), and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.318 mmol) in anhydrous *N*,*N*-dimethylformamide (1 mL) under nitrogen was stirred at room temperature over the weekend. LCMS showed that 41% of the starting material was still present. The reaction was concentrated in vacuo and the residue was purified by reverse phase HPLC (5−75% MeCN/0.1% NH_4OH in H_2O, 15 min) to afford the title compound (**21b**) as a solid (19%). This compound was used directly in the next reaction without NMR characterization. MS m/z 517.4 $[M + H]^+$.

4-[1-Ethyl-3-(4-{[(phenylamino)carbonyl]amino}phenyl)-1*H*-pyrazol-4-yl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]-1*H*-pyrrolo-[2,3-*b*]pyridine-2-carboxamide (22b). To a mixture of 4-[1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-*N*-[3-(4-methyl-1-piperazinyl)-propyl]-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (**21b**, 0.05 mmol) in 6N hydrochloric acid solution (1 mL) and ethanol (1 mL) under nitrogen at room temperature was added tin powder (0.25 mmol). The reaction was stirred at 70 °C for 1 h and then filtered through celite. The filtrate was concentrated in vacuo to give 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide as the crude HCl salt. LCMS showed m/z 487.4 $[M + H]^+$, and 100% purity (UV214). To a solution of this crude product (0.05 mmol max) in anhydrous pyridine (0.5 mL) under nitrogen at room temperature was added phenyl isocyanate (0.055 mmol). The reaction was stirred at room temperature for 30 min and left to stand overnight. The reaction mixture was concentrated in vacuo. Purification of the residue by reverse phase HPLC ($MeCN/H_2O$ + 0.1% NH_4OH) provided the title compound (**22b**) as a white solid (15%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.09 (br s, 1H), 8.70 (s, 1H), 8.67 (s, 1H), 8.43 (t, J = 5.56 Hz, 1H), 8.20 (d, J = 5.05 Hz, 1H), 8.18 (s, 1H), 7.44 (d, J = 7.83 Hz, 2H), 7.37 (d, J = 8.70 Hz, 2H), 7.24−7.32 (m, 4H), 7.03 (s, 1H), 6.96 (t, J = 7.33 Hz, 1H), 6.83 (d, J = 4.80 Hz, 1H), 4.26 (q, J = 7.24 Hz, 2H), 3.25−3.31 (m, 2H), 2.31 (t, J = 7.26 Hz, 10H), 2.09 (s, 3 H), 1.66 (quin, J = 7.20 Hz, 2H), 1.51 (t, J = 7.20 Hz, 3H). MS m/z 606.6 $[M + H]^+$.

4-[1-Ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-methyl-1-piperazinyl)ethyl]-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (21c). A solution of 4-[1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylic acid (**20**, 0.331 mmol), 2-(4-methyl-piperazin-1-yl)-ethylamine (0.993 mmol), and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.397 mmol) in anhydrous *N*,*N*-dimethylformamide (1 mL) under nitrogen was stirred for 17 h at room temperature. The reaction was concentrated in vacuo, and the residue was purified by reverse phase HPLC ($MeCN/0.1\%$ NH_4OH in H_2O) to afford the title compound (**21c**) as a solid (20%). This compound was used directly in the next reaction without NMR characterization. MS m/z 503.4 $[M + H]^+$.

4-[1-Ethyl-3-(4-{[(phenylamino)carbonyl]amino}phenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-methyl-1-piperazinyl)ethyl]-1*H*-pyrrolo-[2,3-*b*]pyridine-2-carboxamide (22c). To a mixture of 4-[1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-methyl-1-piperazinyl)-ethyl]-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (**21c**, 0.066 mmol) in 6N hydrochloric acid solution (1 mL) and ethanol (1 mL) under nitrogen at room temperature was added tin powder (0.33 mmol). The reaction was stirred at 70 °C for 1 h and then cooled to room temperature. The mixture was filtered through celite, and the filtrate was concentrated in vacuo to give 4-[3-(4-aminophenyl)-1-ethyl-1*H*-pyrazol-4-yl]-*N*-[2-(4-methyl-1-piperazinyl)ethyl]-1*H*-pyrrolo-[2,3-*b*]pyridine-2-carboxamide as the crude HCl salt. LCMS showed m/z 473.4 $[M + H]^+$ and 100% purity (UV214). To a solution of this crude product (0.066 mmol theoretical) in anhydrous pyridine (0.5 mL) under nitrogen at room temperature was added phenyl isocyanate (0.072 mmol). The reaction was stirred at room temperature for 30 min and left to stand overnight. The reaction mixture was concentrated in vacuo. Purification of the residue by reverse phase HPLC ($MeCN/H_2O$ + 0.1% NH_4OH) provided the title compound (**22c**) as a white solid (52%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.11 (br s, 1H), 8.72 (br s, 1H), 8.70 (s, 1H), 8.35 (t, J = 5.56 Hz, 1H), 8.21 (d, J = 4.80 Hz, 1H), 8.17 (s, 1H), 7.44 (d, J = 7.83 Hz, 2H), 7.38 (d, J = 8.59 Hz, 2H), 7.22−7.34 (m, 4H), 7.04 (s, 1H), 6.96 (t, J = 7.60 Hz, 1H), 6.83 (d, J = 4.80 Hz, 1H), 4.27 (q, J = 7.24 Hz, 2H), 3.35−3.44 (m, 4H), 2.22−2.48 (m, 8H), 2.13 (s, 3H), 1.51 (t, J = 7.33 Hz, 3H). MS m/z 592.4 $[M + H]^+$.

[4-(4-Bromo-1-ethyl-1*H*-pyrazol-3-yl)phenyl]amine. In a sealed tube, a mixture of 4-bromo-1-ethyl-3-(4-nitrophenyl)-1*H*-pyrazole (**7b**, 7.63 mmol) and tin powder (38.16 mmol) in 6N HCl (25 mL) and ethanol (25 mL) was stirred at 70 °C for 1 h. The reaction mixture was cooled to room temperature, filtered through celite, and concentrated in vacuo. The residue was treated with ethyl acetate (30 mL) and neutralized using saturated aq sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and concentrated in vacuo to give the title compound as a solid. This crude product was used as is in the next reaction. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.98 (s, 1H), 7.48 (d, J = 8.59 Hz, 2H), 6.60 (d, J = 8.34 Hz, 2H), 5.26 (s, 2H), 4.11 (q, J = 7.33 Hz, 2H), 1.38 (t, J = 7.33 Hz, 3H). MS m/z 266.0 $[M + H]^+$.

***N*-[4-(4-Bromo-1-ethyl-1*H*-pyrazol-3-yl)phenyl]-*N*′-phenylurea (10c).** To a solution of [4-(4-bromo-1-ethyl-1*H*-pyrazol-3-yl)phenyl]amine (7.63 mmol) in anhydrous pyridine (30 mL) under nitrogen was added phenyl isocyanate (8.39 mmol). The reaction was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was triturated with ethyl acetate to give the title compound (**10c**) as an off-white solid (63% over 2 steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.80 (s, 1H), 8.71 (s, 1H), 8.07 (s, 1H), 7.74 (m, J = 8.59 Hz, 2H), 7.53 (m, J = 8.59 Hz, 2H), 7.47 (d, J = 7.58 Hz, 2H), 7.29 (t, J = 7.96

Hz, 2H), 6.98 (t, J = 7.33 Hz, 1H), 4.16 (q, J = 7.33 Hz, 2H), 1.40 (t, J = 7.20 Hz, 3H). MS m/z 385.0 $[M + H]^+$.

4-Bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbaldehyde (24). *n*-Butyllithium (2.5 M in hexanes, 3.56 mmol) was added dropwise to a solution of diisopropylamine (3.56 mmol) in anhydrous THF (5 mL) at −78 °C under nitrogen. The reaction was stirred for 30 min at −78 °C, and then a solution of 4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2.97 mmol) in anhydrous THF (1 mL) was added dropwise by syringe. The resulting reaction was stirred at −78 °C for 2 h and then a solution of *N*,*N*-dimethylformamide (11.88 mmol) in THF (1 mL) was added dropwise by syringe. The reaction was stirred at −78 °C for 2 h and then quenched with saturated aq ammonium chloride solution (10 mL). The mixture was extracted with ethyl acetate (2 × 20 mL), and the combined organic layers were dried over magnesium sulfate and concentrated in vacuo. Purification of the residue by silica gel chromatography (Analogix IF280, 70−100% CH_2Cl_2/hexanes) afforded the title compound (**24**) as a white solid (66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.45 (s, 1H), 8.45 (d, J = 5.30 Hz, 1H), 8.24 (d, J = 8.34 Hz, 2H), 7.72−7.90 (m, 2H), 7.59−7.72 (m, 2H), 7.46 (s, 1H). MS m/z 365.0 $[M + H]^+$.

{[4-Bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-methyl}dimethylamine (25a). A solution of 4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbaldehyde (**24**, 0.55 mmol), dimethylamine (1.1 mmol, 2 M solution in tetrahydrofuran), and sodium triacetoxyborohydride (1.1 mmol) in dichloromethane (4 mL) and acetic acid (1 mL) under nitrogen was stirred at room temperature for 30 min. The reaction was quenched with 1N sodium hydroxide solution (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over magnesium sulfate, and concentrated in vacuo. Purification of the residue by silica gel chromatography (Analogix IF280, 0−10% MeOH/CH_2Cl_2 with 10% NH_4OH) afforded recovered starting material and the title product (**25a**) as a solid (46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.43−7.50 (m, 2H), 7.33−7.40 (m, 1H), 6.84 (t, J = 7.71 Hz, 1H), 6.71−6.77 (m, 2H), 6.66−6.70 (m, 1H), 5.88 (br s, 1H), 3.16 (br s, 2H), 1.52 (s, 6H). MS m/z 394.2 $[M + H]^+$.

***N*-(4-{4-[2-[(Dimethylamino)methyl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1-ethyl-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (27a).** A suspension of {[4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]methyl}dimethylamine (**25a**, 0.25 mmol), bis(pinacolato)diboron (0.30 mmol), potassium acetate (0.76 mmol), and dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (0.01 mmol) in anhydrous 1,4-dioxane (2 mL) was stirred at 90 °C for 16 h. The reaction was cooled to room temperature, filtered through celite, washed with dioxane, and concentrated in vacuo to give the boronic ester. LCMS showed $[M + H]^+ = 359.2$ for the boronic acid because the ester cleaves to the acid due to the presence of TFA in the LCMS solvent mixture. A solution of this crude boronic ester (0.25 mmol), *N*-[4-(4-bromo-1-ethyl-1*H*-pyrazol-3-yl)phenyl]-*N*′-phenylurea (**10c**, 0.21 mmol), and tetrakis-(triphenylphosphine) palladium(0) (0.01 mmol) in saturated aq sodium bicarbonate solution (0.64 mmol, assume 1 M solution) and *N*,*N*-dimethylformamide (2 mL) was stirred at 100 °C for 17 h. The reaction mixture was cooled to room temperature, and water (5 mL) and ethyl acetate (5 mL) were added. The layers were separated and the organic layer was washed with brine (5 mL), dried over magnesium sulfate, and concentrated in vacuo. Purification of the residue by reverse phase HPLC (10−90% MeCN/H_2O + 0.1% NH_4OH) provided the title compound (**27a**, 45%). This product was 100% pure by LCMS and was used without further characterization. MS m/z 620.6 $[M + H]^+$.

***N*-[4-(4-{2-[(Dimethylamino)methyl]-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl}-1-ethyl-1*H*-pyrazol-3-yl)phenyl]-*N*′-phenylurea (28a).** A solution of *N*-(4-{4-[2-[(dimethylamino)methyl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1-ethyl-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (0.1 mmol) and 6N sodium hydroxide solution (0.29 mmol) in methanol (1 mL) was stirred at 70 °C for 1 h. The reaction was cooled to room temperature and concentrated in vacuo. Purification of the residue by reverse phase HPLC (10−90% MeCN/0.1% NH_4OH in H_2O) provided the title compound as a white solid (24%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.54 (s, 1H), 8.77 (br s, 1H), 8.74 (br s, 1H), 8.13 (s, 1H), 8.04 (d, J = 4.80 Hz, 1H), 7.45 (d, J = 8.08 Hz, 2H), 7.37 (d, J = 8.59 Hz, 2H), 7.24−7.31 (m, 4H), 6.96 (t, J = 7.33 Hz, 1H), 6.79 (d, J = 5.05 Hz, 1H), 6.05 (d, J = 1.01 Hz, 1H), 4.25 (q, J = 7.33 Hz, 2H), 3.46 (s, 2H), 2.12 (s, 6H), 1.49 (t, J = 7.20 Hz, 3H). MS m/z 480.4 $[M + H]^+$.

2-({[4-Bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-methyl}amino)ethanol (25b). A solution of 4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbaldehyde (**24**, 0.55 mmol), ethanolamine (1.1 mmol), and sodium triacetoxyborohydride (1.1 mmol) in dichloromethane (4 mL) and acetic acid (1 mL) under nitrogen was stirred at room temperature for 30 min. The reaction was quenched with 1N sodium hydroxide solution (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over magnesium sulfate, and concentrated in vacuo to provide crude product as the title compound (**25b**). This crude product was used as is in the next reaction without further characterization. MS m/z 409.2 $[M + H]^+$.

***N*-(4-{1-Ethyl-4-[2-{[(2-hydroxyethyl)amino]methyl}-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (27b).** A suspension of 2-({[4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]methyl}amino)ethanol (**25b**, 0.55 mmol), bis(pinacolato)diboron (0.66 mmol), potassium acetate (1.64 mmol), and dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (0.02 mmol) in anhydrous 1,4-dioxane (3 mL) was stirred at 90 °C for 16 h. The reaction was cooled to room temperature, filtered through celite, washed with dioxane, and concentrated in vacuo to give the boronic ester. LCMS showed $[M + H]^+ = 375.2$ for the boronic acid because the ester cleaves to the acid due to the presence of TFA in the LCMS mobile phase. A solution of this crude boronic ester (0.55 mmol), *N*-[4-(4-bromo-1-ethyl-1*H*-pyrazol-3-yl)phenyl]-*N*′-phenylurea (**10c**, 0.46 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.02 mmol) in saturated aq sodium bicarbonate solution (1.37 mmol) and *N*,*N*-dimethylformamide (5 mL) was stirred at 100 °C for 5 h. The reaction mixture was cooled to room temperature, and water (10 mL) and ethyl acetate (10 mL) were added. The layers were separated, and the organic layer was washed with brine (10 mL), dried over magnesium sulfate, and concentrated in vacuo. Purification of the residue by reverse phase HPLC (10−90% MeCN/H_2O + 0.1% NH_4OH) provided the title compound (**27b**, 52%). This product was used in the next reaction without further characterization. MS m/z 636.4 $[M + H]^+$.

***N*-{4-[1-Ethyl-4-(2-{[(2-hydroxyethyl)amino]methyl}-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-3-yl]phenyl}-*N*′-phenylurea (28b).** A solution of *N*-(4-{1-ethyl-4-[2-{[(2-hydroxyethyl)amino]-methyl}-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (**27b**, 0.24 mmol) and 6N sodium hydroxide solution (0.71 mmol) in methanol (1 mL) was stirred at 70 °C for 1 h. The reaction was cooled to room temperature and concentrated in vacuo. Purification of the residue by reverse phase HPLC (10−90% MeCN/0.1% NH_4OH in H_2O) provided the title compound (**28b**) as a tan solid (14%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.48 (s, 1H), 8.75 (br s, 1H), 8.73 (br s, 1H), 8.12 (s, 1H), 8.01 (d, J = 4.80 Hz, 1H), 7.45 (d, J = 7.58 Hz, 2H), 7.37 (d, J = 8.84 Hz, 2H), 7.21−7.32 (m, 4H), 6.96 (t, J = 7.07 Hz, 1H), 6.75 (d, J = 5.05 Hz, 1H), 6.16 (s, 1H), 4.45 (t, J = 5.43 Hz, 1H), 4.25 (q, J = 7.49 Hz, 2H), 3.79 (s, 2H), 3.44 (q, J = 5.56 Hz, 3H), 2.08 (br s, 1H), 1.49 (t, J = 7.20 Hz, 3H). MS m/z 496.4 $[M + H]^+$.

***N*-(4-{4-[2-Formyl-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1-ethyl-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (26).** A

suspension of 4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbaldehyde (**24**, 1.31 mmol), bis(pinacolato)diboron (1.57 mmol), potassium acetate (3.92 mmol), and dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (0.05 mmol) in anhydrous 1,4-dioxane (13 mL) was stirred at 90 °C for 18 h. The reaction was cooled to room temperature and quenched with saturated aq ammonium chloride solution (10 mL). The mixture was extracted with ethyl acetate (2 × 20 mL), and the combined organic layers were dried over magnesium sulfate and concentrated in vacuo to give 1-(phenylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]-pyridine-2-carbaldehyde as the crude product. MS *m*/*z* 330.2 $[M + H]^+$ for boronic acid because the ester cleaves to the acid due to the presence of TFA in the LCMS mobile phase. A solution of this crude 1-(phenylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbaldehyde (1.33 mmol), *N*-[4-(4-bromo-1-ethyl-1*H*-pyrazol-3-yl)phenyl]-*N*′-phenylurea (1.21 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.06 mmol) in saturated aq sodium bicarbonate solution (3.63 mmol, assume 1 M solution) and *N*,*N*-dimethylformamide (6 mL) was stirred at 100 °C for 17 h. The reaction mixture was cooled to room temperature, and water (5 mL) and ethyl acetate (10 mL) were added. The layers were separated, and the organic layer was washed with brine (10 mL), dried over magnesium sulfate, and concentrated in vacuo. Purification of the residue by silica gel chromatography (Analogix IF280, 15−100% ethyl acetate/hexanes) afforded the title product (**26**, 21%). MS *m*/*z* 591.4 $[M + H]^+$.

***N*-(4-{4-[2-({[2-(Dimethylamino)ethyl]amino}methyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1-ethyl-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (27c).** A solution of *N*-(4-{4-[2-formyl-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1-ethyl-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (**26**, 0.1 mmol), (2-aminoethyl)-dimethylamine (0.2 mmol), and sodium triacetoxyborohydride (0.2 mmol) in dichloromethane (1 mL) and acetic acid (0.25 mL) under nitrogen was stirred at room temperature for 30 min. The reaction was quenched with 1N sodium hydroxide solution (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over magnesium sulfate, and concentrated in vacuo to give the title compound as the crude product (**27c**). This crude product was used as is without NMR characterization in the next reaction. MS *m*/*z* 663.4 $[M + H]^+$. LCMS purity 93%.

***N*-(4-{4-[2-({[2-(Dimethylamino)ethyl]amino}methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1-ethyl-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (28c).** To a solution of *N*-(4-{4-[2-({[2-(dimethylamino)ethyl]amino}methyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1-ethyl-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (**27c**, 0.1 mmol) and 6N sodium hydroxide solution (0.3 mmol) in methanol (1 mL) was stirred at 70 °C for 1 h. The reaction was cooled to room temperature and concentrated in vacuo. Purification of the residue by reverse phase HPLC (MeCN/0.1% TFA in H_2O) provided the desired product. The product from purification was neutralized using saturated aq sodium bicarbonate solution. The product was extracted with ethyl acetate (2 × 10 mL). The organic layers were combined, dried over magnesium sulfate, and concentrated in vacuo to give the title compound as a white solid (**28c**, 5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.54 (s, 1H), 8.86 (br s, 2H), 8.13 (s, 1H), 8.04 (d, J = 4.80 Hz, 1H), 7.45 (d, J = 8.08 Hz, 2H), 7.37 (d, J = 8.59 Hz, 2H), 7.21−7.34 (m, 4H), 6.92−6.99 (m, 1H), 6.79 (d, J = 4.80 Hz, 1H), 6.06 (s, 1H), 4.25 (q, J = 6.74 Hz, 2H), 3.55 (s, 2H), 2.29−2.43 (m, 5H), 2.24 (s, 3H), 2.09 (s, 3H), 1.49 (t, J = 7.20 Hz, 3H). MS *m*/*z* 523.4 $[M + H]^+$.

***N*-{[4-Bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-methyl}-2-(methylsulfonyl)ethanamine (25c).** A solution of 4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbaldehyde (**24**, 0.685 mmol), 2-aminoethylmethylsulfone hydrochloride (1.37 mmol), and sodium triacetoxyborohydride (1.37 mmol) in dichloromethane (4 mL) and acetic acid (1 mL) under nitrogen was stirred at room temperature for 30 min. The reaction was quenched with 1N sodium hydroxide solution (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over magnesium sulfate, and concentrated in vacuo. Purification of the residue by silica gel chromatography (Analogix IF280, 25−80% ethyl acetate/hexanes) afforded recovered starting material and the title product (**25c**) as a solid (34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.20 (s, 1H), 8.18 (dd, J = 3.28, 1.77 Hz, 2H), 7.73 (t, J = 7.45 Hz, 1H), 7.62 (t, J = 7.83 Hz, 2H), 7.57 (d, J = 5.31 Hz, 1H), 6.77 (s, 1H), 4.25 (d, J = 5.31 Hz, 2H), 3.05 (s, 3H), 3.01−3.08 (m, 2H), 2.62−2.69 (m, 1H). MS *m*/*z* 472.2 $[M + H]^+$.

***N*-(4-{1-Ethyl-4-[2-({[2-(methylsulfonyl)ethyl]amino}methyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (27d).** To a suspension of *N*-{[4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]methyl}-2-(methylsulfonyl)ethanamine (**25c**, 0.23 mmol), bis(pinacolato)diboron (0.28 mmol), potassium acetate (0.69 mmol), and dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (0.01 mmol) in anhydrous 1,4-dioxane (2 mL) was stirred at 90 °C for 16 h. The reaction was cooled to room temperature, filtered through celite, washed with dioxane, and concentrated in vacuo to give the boronic ester. LCMS showed $[M + H]^+$ = 437.4 for the boronic acid because the ester cleaves to the acid due to the presence of TFA in the LCMS mobile pahase. A solution of this crude boronic ester (0.23 mmol), *N*-[4-(4-bromo-1-ethyl-1*H*-pyrazol-3-yl)phenyl]-*N*′-phenylurea (**10c**, 0.19 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.01 mmol) in saturated aq sodium bicarbonate solution (0.58 mmol, assume 1 M solution) and *N*,*N*-dimethylformamide (2 mL) was stirred at 100 °C for 17 h. The reaction mixture was cooled to room temperature, and water (5 mL) and ethyl acetate (10 mL) were added. The layers were separated and the organic layer was washed with brine (10 mL), dried over magnesium sulfate, and concentrated in vacuo. Purification of the residue by reverse phase HPLC (10−90% MeCN/H_2O + 0.1% NH_4OH) provided the title compound (**27d**, 46%), which was used as is without NMR characterization. MS *m*/*z* 698.4 $[M + H]^+$.

***N*-(4-{1-Ethyl-4-[2-({[2-(methylsulfonyl)ethyl]amino}methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (28d).** A solution of *N*-(4-{1-ethyl-4-[2-({[2-(methylsulfonyl)ethyl]amino}methyl)-1-(phenylsulfonyl)-1*H*-pyrrolo-[2,3-*b*]pyridin-4-yl]-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (**27d**, 0.09 mmol) and 6N sodium hydroxide solution (0.27 mmol) in methanol (1 mL) was stirred at 70 °C for 1 h. The reaction was cooled to room temperature and concentrated in vacuo. Purification of the residue by reverse phase HPLC (10−90% MeCN/0.1% NH_4OH in H_2O) provided the title compound (**28d**) as a tan solid (28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.49 (s, 1H), 8.79 (br s, 1H), 8.77 (br s, 1H), 8.12 (s, 1H), 8.02 (d, J = 5.05 Hz, 1H), 7.45 (d, J = 8.08 Hz, 2H), 7.38 (d, J = 8.36 Hz, 2H), 7.24−7.32 (m, 4H), 6.96 (t, J = 7.45 Hz, 1H), 6.76 (d, J = 5.05 Hz, 1H), 6.19 (s, 1H), 4.25 (q, J = 7.33 Hz, 2H), 3.80 (br s, 2H), 3.22 (t, J = 6.44 Hz, 2H), 3.00 (s, 3H), 2.84−2.90 (m, 2H), 2.37 (br s, 1H), 1.49 (t, J = 7.20 Hz, 3H). MS *m*/*z* 558.4 $[M + H]^+$.

***N*-(4-{1-Ethyl-4-[2-({[2-(4-morpholinyl)ethyl]amino}methyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (27e).** A solution of *N*-(4-{4-[2-formyl-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1-ethyl-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (**26**, 0.1 mmol), 4-(2-aminoethyl)-morpholine (0.2 mmol), and sodium triacetoxyborohydride (0.2 mmol) in dichloromethane (1 mL) and acetic acid (0.25 mL) under nitrogen was stirred at room temperature for 30 min. The reaction was quenched with 1N sodium hydroxide solution (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over magnesium sulfate, and concentrated in vacuo to give the title compound (**27e**) as the crude product. MS *m*/*z* 705.6 $[M + H]^+$.

***N*-(4-{1-Ethyl-4-[2-({[2-(4-morpholinyl)ethyl]amino}methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (28e).** A solution of *N*-(4-{1-ethyl-4-[2-({[2-(4-morpholinyl)ethyl]amino}methyl)-1-(phenylsulfonyl)-1*H*-pyrrolo-[2,3-*b*]pyridin-4-yl]-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (**27e**, 0.1 mmol) and 6N sodium hydroxide solution (0.3 mmol) in methanol (1 mL) was stirred at 70 °C for 1 h. The reaction was cooled and concentrated in vacuo. Purification of the residue by reverse phase HPLC (MeCN/0.1% TFA in H_2O) followed by subsequent purification by reverse phase HPLC (MeCN/0.1% NH_4OH in H_2O) provided the title compound (**28e**) as a white solid (10%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.50 (s, 1H), 8.91 (br s, 2H), 8.11 (s, 1H), 8.02 (d, J = 4.80 Hz, 1H), 7.45 (d, J = 7.83 Hz, 2H), 7.37 (d, J = 8.59 Hz, 2H), 7.23−7.30 (m, 4H), 6.95 (t, J = 7.20 Hz, 1H), 6.76 (d, J = 5.05 Hz, 1H), 6.10 (s, 1H), 4.24 (q, J = 7.07 Hz, 2H), 3.77 (br s, 2H), 3.52 (t, J = 4.42 Hz, 4H), 2.68 (dt, J = 3.73, 1.80 Hz, 1H), 2.17−2.40 (m, 8H), 1.49 (t, J = 7.33 Hz, 3H). MS m/z 565.4 $[M + H]^+$.

***N*-{[4-Bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-methyl}-3-(4-methyl-1-piperazinyl)-1-propanamine (25d).** A solution of 4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbaldehyde (**24**, 0.55 mmol), 1-(3-aminopropyl)-4-methylpiperazine (1.1 mmol), and sodium triacetoxyborohydride (1.1 mmol) in dichloromethane (4 mL) and acetic acid (1 mL) under nitrogen was stirred at room temperature for 30 min. The reaction was quenched with 1N sodium hydroxide solution (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over magnesium sulfate, and concentrated in vacuo. Purification of the residue by silica gel chromatography (Analogix IF280, 0−10% MeOH/CH_2Cl_2 with 10% NH_4OH) afforded the title product (**25d**) as a solid (83%). MS m/z 505.4 $[M + H]^+$.

***N*-(4-{1-Ethyl-4-[2-({[3-(4-methyl-1-piperazinyl)propyl]amino}-methyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (27f).** A suspension of *N*-{[4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]methyl}-3-(4-methyl-1-piperazinyl)-1-propanamine (**25d**, 0.45 mmol), bis(pinacolato)diboron (0.54 mmol), potassium acetate (1.36 mmol), and dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (0.02 mmol) in anhydrous 1,4-dioxane (3 mL) was stirred at 90 °C for 16 h. The reaction was cooled to room temperature, filtered through celite, washed with dioxane, and concentrated in vacuo to give the boronic ester. LCMS showed $[M + H]^+$ = 471.6 for the boronic acid because the ester cleaves to the acid due to the presence of TFA in the LCMS mobile phase. A solution of this boronic ester (0.45 mmol), *N*-[4-(4-bromo-1-ethyl-1*H*-pyrazol-3-yl)phenyl]-*N*′-phenylurea (**10c**, 0.38 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.02 mmol) in saturated aq sodium bicarbonate solution (1.13 mmol, assume 1 M solution) and *N*,*N*-dimethylformamide (5 mL) was stirred at 100 °C for 5 h. The reaction mixture was cooled to room temperature, and water (10 mL) and ethyl acetate (15 mL) were added. The layers were separated and the organic layer was washed with brine (15 mL), dried over magnesium sulfate, and concentrated in vacuo. Purification of the residue by reverse phase HPLC (10−90% MeCN/H_2O + 0.1% NH_4OH) provided the title compound (**27f**) as a solid (31%). MS m/z 732.4 $[M + H]^+$.

***N*-(4-{1-Ethyl-4-[2-({[3-(4-methyl-1-piperazinyl)propyl]amino}-methyl)-1*H*-pyrrolo[2,3-b]pyridin-4-yl]-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (28f).** A solution of *N*-(4-{1-ethyl-4-[2-({[3-(4-methyl-1-piperazinyl)propyl]amino}methyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-1*H*-pyrazol-3-yl}phenyl)-*N*′-phenylurea (**27f**, 0.12 mmol) and 6N sodium hydroxide solution (0.35 mmol) in methanol (1 mL) was stirred at 70 °C for 1 h. The reaction was cooled to room temperature and concentrated in vacuo. Purification of the residue by reverse phase HPLC (10−90% MeCN/0.1% NH_4OH in H_2O) provided the title compound (**28f**) as a light-brown solid (42%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.43 (br s, 1H), 8.87 (br s, 2H), 8.10 (s, 1H), 8.01 (d, J = 4.80 Hz, 1H), 7.45 (d, J = 7.58 Hz, 2H), 7.38 (d, J = 8.34 Hz, 2H), 7.23−7.31 (m, 4H), 6.96 (t, J = 7.45 Hz, 1H), 6.76 (d, J = 4.55 Hz, 1H), 6.11 (s, 1H), 4.24 (q, J = 7.16 Hz, 2H), 3.74 (br s, 2H), 2.09−2.47 (m, 13H), 2.08 (s, 3H), 1.51−1.60 (m, 2H), 1.49 (t, J = 7.33 Hz, 3H). MS m/z 592.4 $[M + H]^+$.

Biology. Biochemical Characterization of Aurora Inhibitors. Experimental details describing the (1) in vitro Aurora B/INCENP, Aurora C/INCENP and Aurora A/TPX2 inhibition assays for IC_{50} determination, (2) determination of dissociation rates of **12c**, **17a**, **17c**, **17j**, and **17k** from human Aurora B/INCENP by rapid dilution, and (3) Aurora B/INCENP, Aurora C/INCENP, and Aurora A/TPX2 K_i* determination of **17k** by progress curve analysis are described in separate publications.[30,34]

Tissue Culture and in Vivo Studies. Details of the cellular proliferation (A549 cells) and in vivo pharmacodynamic and efficacy in tumor xenograft studies are described in a separate publication.[37]

Supporting Information Available: Liquid chromatography−mass spectrometry purities and retention times for all tested compounds. Full combustion analysis results for **17a**−**d**, **17f**−**i**, **17k**−**l**, **17n**−**o**, and **17q**−**u**. Statistical limits for biological data in Tables 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

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