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Synthesis and SAR of Novel 4-Morpholinopyrrolopyrimidine Derivatives as Potent Phosphatidylinositol 3-Kinase Inhibitors

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Significant evidence suggests that deregulation of the PI3K/Akt pathway is important in tumor progression. Mechanisms include loss of function of the tumor suppressor PTEN and high frequency of mutation of the PI3K p110α isoform in human malignancies. This connection between PI3K and tumor genesis makes PI3K a promising target for cancer treatment. A series of 4-morpholinopyrrolopyrimidine derivatives were synthesized and evaluated as inhibitors of PI3Kα and mTOR, leading to the discovery of PI3Kα selective inhibitors (e.g., **9**) and dual PI3Kα/mTOR kinase inhibitors (e.g., **46** and **48**). PI3Kα/mTOR dual inhibitors demonstrated inhibition of tumor cell growth in vitro and in vivo and caused suppression of the pathway specific biomarkers [e.g., the phosphorylation of Akt at Thr308 (T308) and Ser473 (S473)] in the human breast cancer cell line MDA361. In addition, compound **46** demonstrated good in vivo efficacy in the MDA361 human breast tumor xenograft model.

Introduction

Phosphatidylinositol-3-kinases (PI3Ks[a]) are lipid kinases that catalyze phosphorylation of the 3-hydroxy position of PIP2 (phosphatidylinositol 4,5-diphosphate) to PIP3 (phosphatidylinositol 3,4,5-triphosphate), an important second messenger modulating activity of the PI3K downstream effectors Akt and mTOR. The consequences of biological activation of Akt include tumor progression, proliferation, survival, growth, invasion, angiogenesis, and metastasis. Significant evidence suggests that the PI3K/Akt pathway is deregulated in many human cancers.[1] PI3Ks are divided into three classes (I, II, and III) based on differences in sequence homology, substrate preference, and function.[2,3] The class I PI3Ks are heterodimers consisting of a catalytic subunit and a regulatory subunit. The catalytic subunits of class I PI3Ks include four isoforms: p110α, p110*β*, p110*δ*, and p110*γ*, encoded by four distinct genes termed *pik3ca*, *pik3cb*, *pik3cd*, and *pik3cg*, respectively. The class I PI3Ks are further divided into class IA and IB subgroups based on different regulatory subunits and activation mechanisms. Class IA includes three isoforms PI3Kα, PI3K*β*, and PI3K*δ* activated by receptor tyrosine kinases (RTKs) and small G-protein-coupled receptors (GPCRs), while class IB has only one isoform, PI3K*γ*, primarily activated by GPCRs. The *pik3ca* gene, which encodes the catalytic subunit of PI3Kα, is mutated and overexpressed in a wide range of human cancers, including breast, ovarian, colorectal, and brain tumors.[4−7] In addition, the activation of the PI3K pathway is negatively regulated by dual phosphatase PTEN, and persistent activation of PI3K and loss of PTEN function often coexist in various cancers. All these factors provide strong evidence for the importance of the PI3K pathway in cancer.[8−11] Therefore, the significant connection between PI3K, in particular PI3Kα, with tumor genesis makes PI3Kα an attractive target for development of anticancer drugs.

To date, several small molecule PI3K inhibitors (Figure 1) have been reported.[12−23] LY294002 (**1a**)[14] and Wortmannin (**1b**)[13] have been extensively studied as PI3K inhibitors; however, their toxicity and poor physicochemical properties limited their potential therapeutic use.

Recently an imidazo[4,5-*c*]quinoline derivative, NVP-BEZ235 (**1c**), was reported by Novartis as a pan-PI3K/mTOR dual inhibitor.[22,23] Compound **1c** was shown to block the activation of the PI3K pathway and potently inhibit cell proliferation, causing G1 phase cell cycle arrest, and is currently in phase I/II clinical trials as an anticancer agent. Compound PI-103 (**1d**), a pyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidine derivative, was equipotent against PI3Kα and PI3K*β* with an IC_{50} of 4 nM and was selective over other tested protein kinases.[18] Genentech recently reported the thieno[3,2-*d*]pyrimidine derivative GDC-0941 (**1e**), a potent and orally bioavailable inhibitor of PI3K, in phase I clinical trials for the treatment of cancer. Notably, compound **1e** was equipotent against wild type PI3Kα and two common PI3Kα mutants (E545K and H1047R) with an IC_{50} of 3 nM.[21] As part of our ongoing research on a variety of fused-pyrimidine scaffolds,[24−27] we now report the synthesis and biological evaluation of novel

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[a] Abbreviations: PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin; Akt, protein kinase B; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; PTEN, phosphatase and tensin homologue; RTK, receptor tyrosine kinase; GPCRs, G-protein-coupled receptors; PDK1, 3-phosphoinositide-dependent kinase 1; S, serine; T, threonine; ATP, adenosine 5′-triphosphate; Her2+, human epidermal growth factor receptor 2+; ELISA, enzyme-linked immunosorbent assay; DELFIA, dissociation-enhanced lanthanide fluorescent immunoassay.

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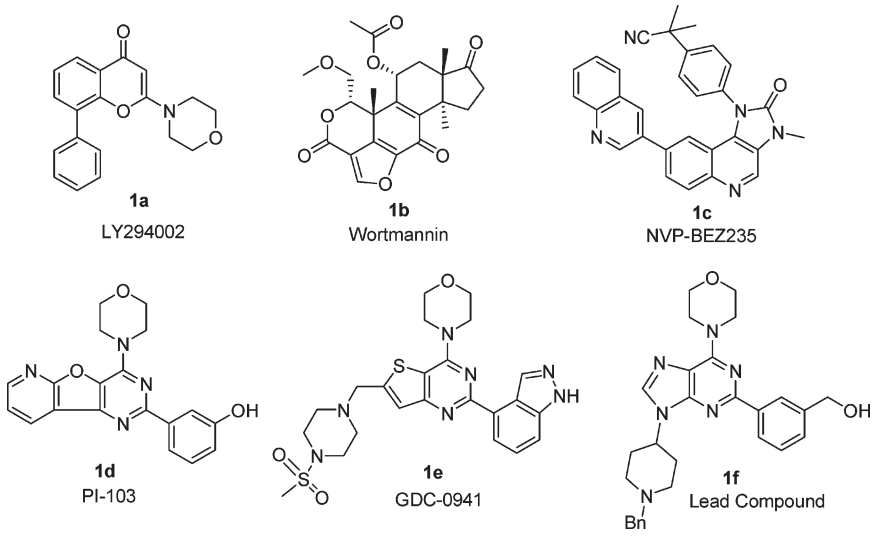
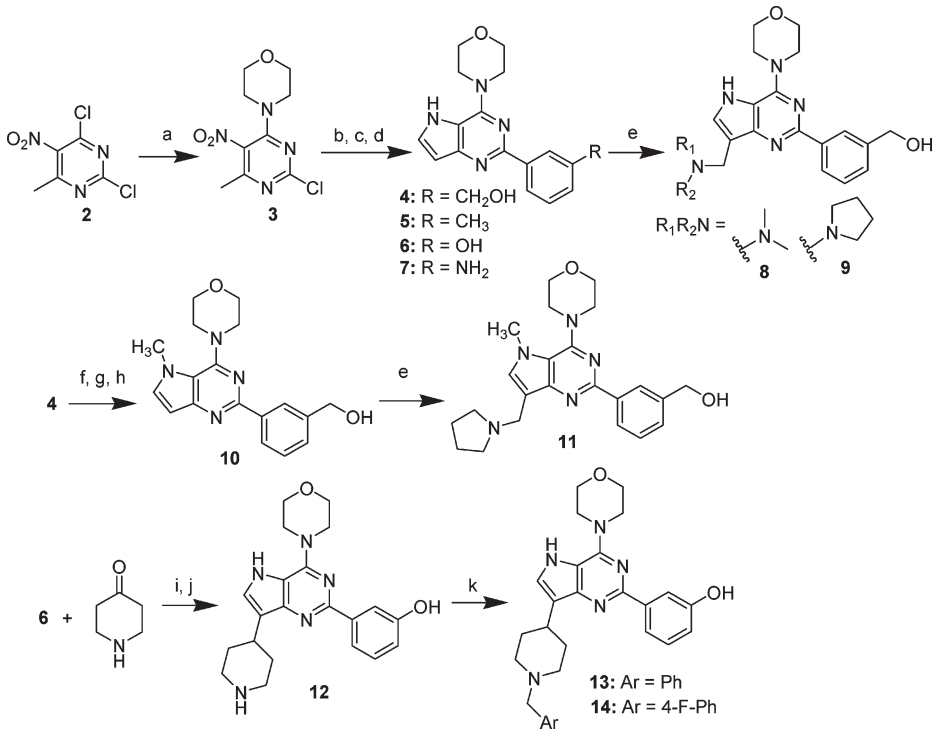


Figure 1. Structures of PI3K inhibitors.

Scheme 1[a]



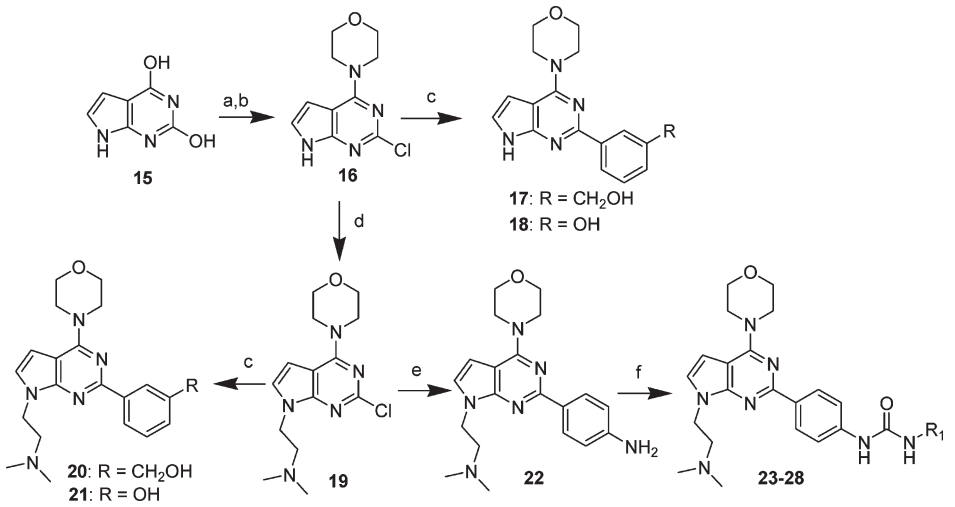
[a] Reagents and conditions: (a) morpholine (1.5 equiv), Et_3N (3 equiv), CH_2Cl_2, room temp, 6 h; (b) $ArB(OH)_2$ (1.5 equiv), $Pd(Ph_3P)_4$ (5 mol %), DME, 2 N Na_2CO_3, 110 °C/30 min, microwave; (c) DMF·DMA (excess), DMF, 110 °C/12−18 h; (d) 10% Pd/C, MeOH, room temp, 2−6 h; (e) formaldehyde (2 equiv), amines (3 equiv), HOAc, 60 °C/6 h; (f) TBSCl (1.2 equiv), imidazole (1.5 equiv), DMF, 80 °C/15 min, microwave; (g) CH_3I (1.2 equiv), NaH (2 equiv), THF, room temp, 2 h; (h) TFA, CH_2Cl_2, room temp, 6 h; (i) 4-piperidone (2.5 equiv), KOH (5 equiv), MeOH, 66 °C/15 h; (j) 10% Pd/C, HCl, MeOH, 50 psi, room temp, 16 h; (k) ArCHO (1.5 equiv), $ZnCl_2$ (1.5 equiv), $NaBH_3CN$ (1.5 equiv), MeOH, room temp, 5 h.

4-morpholinopyrrolopyrimidine derivatives as potent PI3Kα inhibitors.

Chemistry

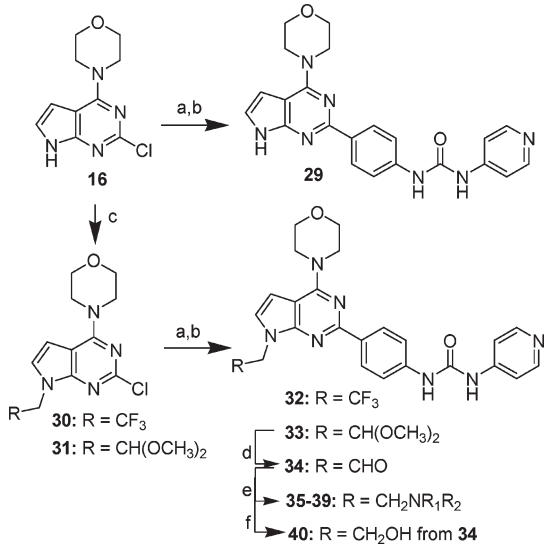
The general synthetic route for the preparation of 4-morpholinopyrrolo[3,2-*d*]pyrimidine derivatives is shown in Scheme 1. The starting material 2,4-dichloro-6-methyl-5-nitropyrimidine (**2**) was treated with morpholine to give the corresponding 4-morpholino substituted intermediate **3**, which was reacted with different boronic acids or esters under Suzuki conditions to provide the corresponding 2-aryl substituted products. Reaction with 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (DMF·DMA) to form the corresponding enamine intermediate followed by the reductive cyclization under catalytic hydrogenation conditions gave the desired 5*H*-pyrrolo[3,2-*d*]pyrimidines **4**−**7**. Mannich-type reaction of **4**, by heating with formaldehyde and different amines in acetic acid solution, proceeded smoothly to yield compounds **8** and **9** with water-solubilizing groups introduced at the C7 position. Protection of the hydroxyl group with TBS in **4** followed by alkylation at the

Scheme 2[a]



[a] Reagents and conditions: (a) $POCl_3$, 120 °C/30 min, microwave; (b) morpholine (1.5 equiv), Et_3N (3 equiv), EtOH, room temp; (c) $ArB(OH)_2$ (1.5 equiv), $Pd(Ph_3P)_4$ (5 mol %), DME, 2 N Na_2CO_3, 150 °C/40 min, microwave; (d) 2-(dimethylamino)ethyl chloride (1.5 equiv), Cs_2CO_3 (3 equiv), DMF, 80 °C/12 h; (e) 4-aminophenylboronic acid, pinacol ester (1.3 equiv), $Pd(Ph_3P)_4$ (5 mol %), DME, 2 M Na_2CO_3, 130 °C/30 min, microwave; (f) triphosgene (0.6 equiv), Et_3N (3 equiv), amines (3−5 equiv), CH_2Cl_2, room temp, 2−6 h.

Scheme 3[a]



[a] Reagents and conditions: (a) 4-aminophenylboronic acid, pinacol ester (1.3 equiv), $Pd(Ph_3P)_4$ (5 mol %), DME, 2 N Na_2CO_3, 130 °C/30 min, microwave; (b) triphosgene (0.6 equiv), Et_3N (3 equiv), 4-aminopyridine (5 equiv), CH_2Cl_2, room temp, 12 h; (c) CF_3CH_2I (2 equiv for **30**) or $(CH_3O)_2CHBr$ (2 equiv for **31**), Cs_2CO_3 (1.2 equiv), DMF, 80 °C/12 h; (d) HCl, dioxane/H_2O, 70 °C/12 h (e) amines (6 equiv), $ZnCl_2$ (2 equiv), $NaBH_3CN$ (2 equiv), MeOH, room temp, 12 h; (f) $NaBH_4$ (1.5 equiv), MeOH/THF, room temp, 2 h.

N5 position and removal of the TBS group afforded **10**, which underwent the Mannich-type reaction to give **11**. Aldol-type reaction of **6** with piperidin-4-one followed by catalytic hydrogenation of the resulting double bond provided derivative **12**. Reductive amination of **12**, using appropriate aldehydes and $NaCNBH_3$, gave compounds **13** and **14**.

The general synthetic routes used for the preparation of 4-morpholinopyrrolo[2,3-*d*]pyrimidine derivatives are outlined in Schemes 2−4. 7*H*-Pyrrolo[2,3-*d*]pyrimidine-2,4-diol (**15**) was prepared, following a known procedure,[28,29] by condensing 6-aminouracil with chloroacetaldehyde. Chlorination of **15** by heating with $POCl_3$ followed by selective substitution with the morpholino group at the C4 position provided intermediate **16**. Suzuki coupling of **16** with different boronic acids gave compounds **17** and **18**. Alternatively, alkylation of **16** with 2-(dimethylamino)ethyl chloride, using Cs_2CO_3 as base, gave intermediate **19**. Reaction of **19** with different boronic acids provided **20** and **21**. Suzuki reaction of **19** with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-aniline provided **22**, which was converted to urea derivatives **23**−**28** by reaction with triphosgene followed by appropriate amines.

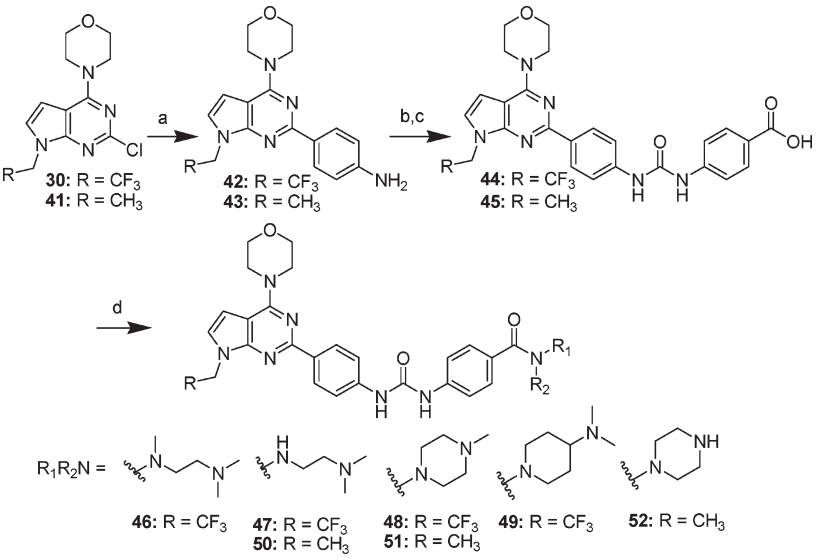
Conversion of intermediate **16** to the 4-pyridylurea analogue **29** was achieved by a two-step sequence, described above for the conversion of **19** to **23**−**28**. Alkylation of **16** provided analogues **30** and **31**, which were converted to the corresponding 4-pyridylurea derivatives **32** and **33**. Hydrolysis of the acetal group in **33**, under acidic conditions, gave the aldehyde **34**. Reductive amination of **34**, using different amines, provided compounds **35**−**39**. Alternatively, reduction of the aldehyde group in **34**, using $NaBH_4$, gave the corresponding alcohol analogue **40** (Scheme 3).

Suzuki reaction of the N7 substituted pyrrolo[2,3-*d*]-pyrimidine intermediates **30** and **41** gave the corresponding anilines **42** and **43**. Treatment of **42** and **43** with methyl 4-isocyanatobenzoate, followed by hydrolysis of the resulting esters under basic conditions, gave the corresponding 4-ureidobenzoic acids **44** and **45**. Finally, coupling of the acids **44** and **45** with different amines afforded the desired 4-ureidobenzamide derivatives **46**−**52** (Scheme 4).

Results and Discussion

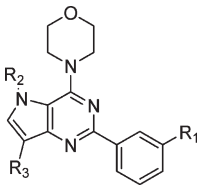
All final compounds **4**−**14**, **16**−**20**, **23**−**29**, **32**−**40**, and **46**−**52** were tested for in vitro potency in a PI3Kα fluorescence polarization format assay[25] and mTOR in a dissociation-enhanced lanthanide fluorescent immunoassay (DELFIA) platform enzyme-linked immunosorbent assay (ELISA).[26] Compounds that showed reasonable PI3Kα potency were selected for further evaluation in the cell growth inhibition assays against PC3 (prostate, PTEN mutant) and MDA-361 (breast, Her2+/PI3KCA [E545K] mutant) human tumor cell lines.[25]

Scheme 4[a]



[a] Reagents and conditions: (a) 4-aminophenylboronic acid, pinacol ester (1.3 equiv), $Pd(Ph_3P)_4$ (5 mol %), DME, 2 N Na_2CO_3, 130 °C/30 min, microwave; (b) methyl 4-isocyanatobenzoate (1.2 equiv), CH_2Cl_2, room temp, 12 h; (c) 1 N NaOH (3 equiv), MeOH/THF, 70 °C/12 h; (d) amines (2 equiv), HOBt (1.5 equiv), EDCI (1.5 equiv), Et_3N (2 equiv), THF, room temp, 12 h.

Table 1[a]



compd	R_1	R_2	R_3	IC_{50} (nM) PI3Kα	mTOR	PC3
1f				63	634	1234
4	$-CH_2OH$	H	H	65	1625	2075
5	$-CH_3$	H	H	1506	5000	ND
6	-OH	H	H	70	355	1551
7	$-NH_2$	H	H	7500	430	ND
8	$-CH_2OH$	H	$-CH_2N(CH_3)_2$	20	108	>3160
9	$-CH_2OH$	H	$-CH_2$-pyrrolinyl	21	3600	>3160
10	$-CH_2OH$	Me	H	1996	>4000	ND
11	$-CH_2OH$	Me	$-CH_2$-pyrrolinyl	4207	>4000	ND
12	-OH	H	4-piperidinyl	354	5900	ND
13	-OH	H	1-benzyl-4-piperidinyl	340	2000	ND
14	-OH	H	1-(4-F-benzyl)-4-piperidinyl	178	3650	1652

[a] The values are averages of at least two separate determinations with a typical variation of less than ±30%. ND: not determined.

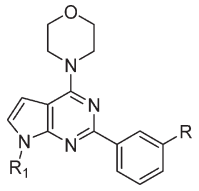
The lead compound **1f**, an imidazolopyrimidine derivative, was previously prepared as a potent PI3K inhibitor.[24] It exhibited good PI3Kα activity (IC_{50} = 63 nM) and moderate cell potency against PC3 (IC_{50} = 1.2 μM), but this compound had low solubility, poor metabolic stability, and poor exposure. Replacement of the imidazole ring in **1f** with a pyrrole ring led to a series of 4-morpholinopyrrolo[3,2-*d*]pyrimidines (Scheme 1). The effects on PI3Kα inhibitory activity of different substituents on the phenyl ring at C3 of the pyrrolo-[3,2-*d*]pyrimidine core are shown in Table 1. The 3-hydroxymethyl and 3-hydroxy analogues, **4** and **6**, showed equal potency against PI3Kα, comparable to that of **1f**. Removal of the hydroxyl group in **4** led to a significant decrease in potency for **5**. Replacement of the 3-OH group in **6** with a 3-NH_2 group resulted in about 100-fold loss in potency for **7**. The hydroxyl group in both **4** and **6** was found to be essential for PI3Kα activity, indicating that it should be involved in protein binding as demonstrated in other fused pyrimidine series.[21,24,25] Introduction of water solubilizing groups ($-CH_2NR_1R_2$) at the C7 position of **4** resulted in about a 3-fold increase in PI3Kα potency for **8** and **9**. Compound **9** showed very good selectivity (171-fold) for PI3Kα over mTOR. However, incorporating a piperidine ring at the C7 position of **6** led to a 5-fold decrease in PI3Kα potency for **12**. Methyl substitution at the N5 position of the pyrrolo[3,2-*d*]pyrimidine core was not tolerated and resulted in a significant loss in activity. The *N*-methyl substituted analogue **10** was about 30-fold less potent than the corresponding NH analogue **4**, while **11** was 200-fold less potent than the corresponding compound **9**.

In the meantime, a series of 4-morpholinopyrrolo[2,3-*d*]-pyrimidines were prepared by replacing the N5 of the imidazole ring in **1f** with "CH". The effects of different substituents on the phenyl ring and the N7 position on enzyme and cell potency are shown in Table 2.

As seen in Table 2, the 3-hydroxymethyl analogue **17** and the 3-hydroxyl analogue **18** maintained PI3Kα inhibitory activity comparable to that of **1f**. Introducing an amino side chain at N7 of **17** led to about a 2-fold increase in PI3Kα potency for **20**, while appending the same group on **18** led to a slight decrease in PI3Kα potency for **21**. Both analogues **20** and **21** exhibited much weaker potency against mTOR. In comparison with **1f**, all four analogues in this series showed comparable or improved cell potency against PC3. It was found that this series of analogues showed good permeability, as well as good solubility except for **18**.

Recent studies showed that the phenolic group was found to be a metabolic liability due to glucuronidation.[21,26] Isosteres for the phenolic group were explored to achieve a metabolically stable clinical candidate.[21] In addition, our own research teams have shown that incorporation of a urea appendage instead of the phenolic group in the fused pyrimidine core not only improved metabolic stability but also increased PI3Kα potency and cell potency.[24,25] Therefore, a series of 4-ureido

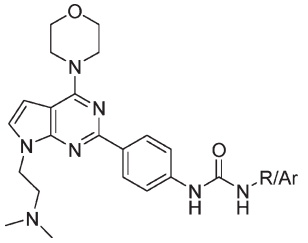
Table 2[a]



compd	R	R_1	IC_{50} (nM) PI3Kα	mTOR	PC3	solubility (μg/mL), pH 7.4	permeability (10^{-6} cm/s)
1f			63	634	1234	1	1.4
17	-CH_2OH	H	80	205	1211	38	2.3
18	-OH	H	43	64	580	2	0.9
20	-CH_2OH	-$(CH_2)_2N(CH_3)_2$	42	> 800	691	> 100	1.9
21	-OH	-$(CH_2)_2N(CH_3)_2$	76	> 800	1181	> 100	2.0

[a] The values are averages of at least two separate determinations with a typical variation of less than ±30%.

Table 3[a]



compd	R/Ar	IC_{50} (nM) PI3Kα	mTOR	PC3	solubility (μg/mL), pH 7.4	stability $T_{1/2}$ (min),[b] rat
1f		63	634	1234	1	2
23	2-pyridyl	142	7	882	21	5
24	3-pyridyl	16	3	137	52	9
25	4-pyridyl	8	2	100	52	2
26	4-F-phenyl	24	8	189	ND	ND
27	Et	226	30	ND	> 100	8
28	Me	54	33	437	> 100	9

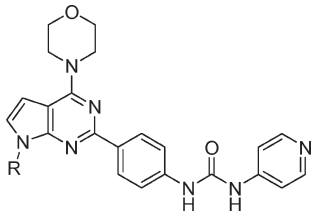
[a] The values are averages of at least two separate determinations with a typical variation of less than ±30%. ND: not determined. [b] Half-life of drug when incubating with rat liver microsomes.

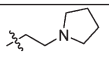
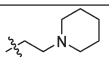
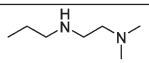
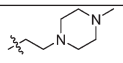
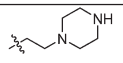
analogues were prepared by replacing the 3-hydroxyl group on the phenyl ring, and their biological data are shown in Table 3.

Among the various pyridyl substituted ureas, the 4-pyridylurea analogue **25** showed the best PI3Kα potency with an IC_{50} of 8 nM, which is 8-fold more potent than the lead compound **1f**. In the meantime, mTOR potency was also dramatically increased (IC_{50} = 2 nM for **25** versus 634 nM for **1f**). More importantly, this compound exhibited a significant improvement in cellular potency against PC3, which is 12-fold more potent than **1f** in the cell assay. For PI3Kα enzyme potency, the 3-pyridylurea analogue **24** was 2-fold less potent than the 4-pyridylurea analogue **25**, while the 2-pyridylurea analogue **23** was 18-fold less potent than **25**. The same trend was observed in their PC3 cell potency, with the order 4-pyridyl > 3-pyridyl > 2-pyridyl. The F-substitued phenylurea analogue **26** was 3-fold more potent against PI3Kα than **1f**; however, it was 3-fold less potent than the 4-pyridylurea analogue **25**. In comparison with the arylurea analogues, the alkylurea analogues **27** and **28** were much less potent against PI3Kα. As for their properties, these urea analogues showed better water solubility, yet no improvements were observed in microsome stability in rat when compared to **1f**.

Since the 4-pyridylurea analogue **25** showed the best in vitro profile in the series, we explored the effects of different substitutions at the N7 position for further optimization. The effects of the substitutions at N7 on PI3Kα activity and cellular activity are shown in Table 4. Compound **29**, with no substitution at N7, was less potent against PI3Kα than **25** (bearing a dimethylaminoethyl group). Introducing cyclic amino substituted ethyl goups at N7 resulted in a decrease in PI3Kα potency (**35**, **36**, and **38**), as well as cellular potency when compared to **25**. The same result was observed for analogue **37**, bearing an ethylenediaminoethyl group at the N7 position. Compound **39**, bearing a 2-piperazinylethyl group at N7, exhibited PI3Kα potency comparable to that of **25** but showed 23-fold less in cell potency against PC3. Replacement of the dimethylamino group in **25** with a hydroxy retained PI3Kα potency as well as PC3 cell potency for **40**. The acetal analogue **33** was slightly less potent in PI3Kα but more potent in cell for PC3 compared to **25**. In contrast to **33**, the aldehyde analogue **34** was more potent in enzyme for PI3Kα; however, it was 6-fold less potent in cell for PC3 compared to **25**. Compound **32**, with a triflouroethyl group at N7, showed a comparable potency against PI3Kα and a better PC3 potency relative to **25**. In terms of pharmaceutical

Table 4[a]



Compound	R =	IC$_{50}$ (nM)			Solubility (μg/mL)	Stability T$_{1/2}$ (min)[b]
		PI3Kα	mTOR	PC3	pH: 7.4	Rat
25		8	2	100	52	2
29	H	28	1	187	ND	ND
32	-CH$_2$CF$_3$	10	1	82	1	>30
33	-CH$_2$CH(OCH$_3$)$_2$	17	1	72	2	4
34	-CH$_2$CHO	2	3	639	2	ND
35		30	7	555	28	4
36		53	52	634	47	4
37		36	11	1147	58	8
38		42	24	964	>100	4
39		7	14	2333	>100	4
40	-(CH$_2$)$_2$OH	5	2	91	1	22

[a] The values are averages of at least two separate determinations with a typical variation of less than ±30%. ND: not determined. [b] Half-life of drug when incubating with rat liver microsomes.

properties, analogues **32** and **40** demonstrated improved microsomal stability; however, both compounds showed poor solubility at pH 7.4. Molecular modeling of analogue **40**, as shown in Figure 2, displays the crucial hydrogen bonding interactions, including the morpholino oxygen binding to the hinge region Val851 and the urea moiety binding to Asp810 and Lys802. It is observed that the pyridyl nitrogen is pointing away from the binding pocket toward the solvent front. Hence, a series of 4-ureidobenzamide derivatives with extended basic amino groups were prepared for further optimization.

The assay results of 4-ureidobenzamide derivatives are shown in Table 5. In general, the 4-ureidobenzamide analogues possessed excellent enzyme potency against PI3Kα and mTOR, as well as high cell potency against PC3 and MDA361. Compound **46** was 11-fold more potent against PI3Kα and 9-fold more potent in cell against PC3 compared to **32**. Analogues **47**−**49** bearing different amide groups also showed excellent PI3Kα potency with IC$_{50}$ values ranging from 0.9 to 6 nM, as well as good cell potency against PC3 with IC$_{50}$ values ranging from 17 to 45 nM. Replacement of 2,2,2-trifluoroethyl group with ethyl at N7, resulted in compounds **50**−**52**, which also showed excellent PI3Kα potency and good cell potency against PC3 and MDA361. Most

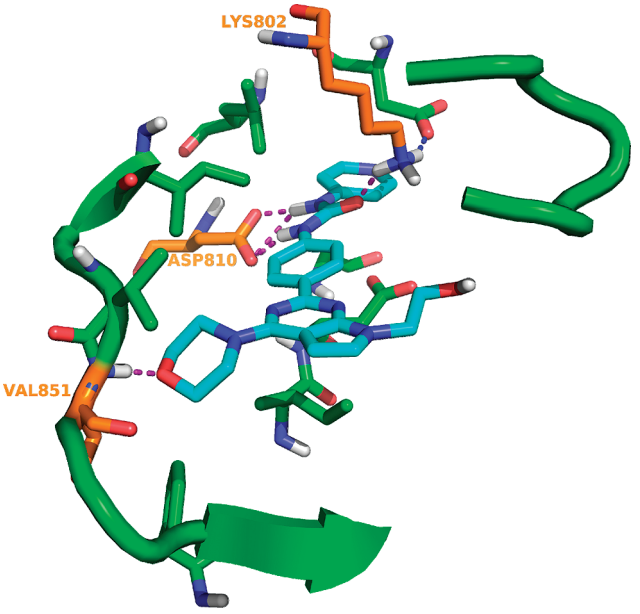


Figure 2. Modeling study of **40** (shown in turquoise for its skeleton) docked in PI3Kα homology model based on PI3Kγ crystal structures.[30]

analogues in this series showed improved stability in rat and human liver microsomes, and compounds **46** and **48** showed good stability in nude mouse liver microsomes with $T_{1/2} > 30$ min. The solubility of these compounds were poor at physiological pH; however, it can be improved at pH 3.0 because of the presence of the basic amino groups in their molecules, as seen in examples for compounds **46**−**48**.

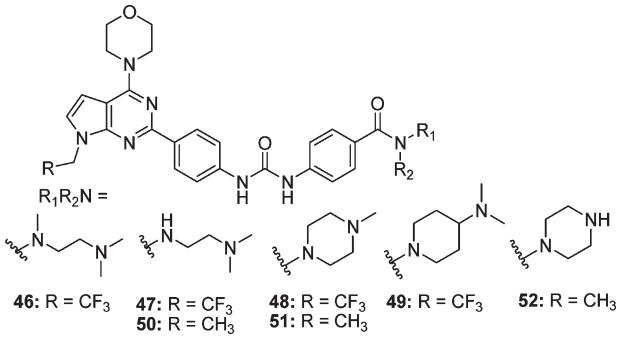
Analogues **46** and **48** were then assayed in vivo for their ability to suppress appropriate biomarkers. Inhibition of PI3Kα should result in suppression of the phosphorylation of Akt, particularly at T308. As can be seen in Figure 3, analogues **46** and **48** suppressed phosphorylation of Akt T308 in MDA361 breast tumor cells for up to 8 h when administered 25 mpk, iv, in nude mouse. The actin (control protein) signal was unaffected by **46** and **48**. Both compounds also inhibited phosphorylation of Akt S473 and S6K, substrates of mTOR, indicating that they are PI3K/mTOR dual inhibitors. Pharmacokinetic analysis showed that the blood concentrations of compounds **46** and **48** at 8 h after a single 25 mpk iv dose (vehicle: 5% dextrose/lactic acid, pH 3.5) were 1731 and 1683 ng/mL, respectively.

In vivo efficacy study of compound **46** was conducted in nude mice bearing MDA361 human breast tumors (Figure 4). Compound **46** was dosed at 50, 25, and 10 mg/kg, iv, once daily for 5 days weekly (two rounds). Significant tumor regression was observed in higher dose of **46** for 50 mpk and no tumor regrowth until day 32. Tumor growth inhibition was also seen in the lower doses at 25 and 10 mpk.

Conclusion

A series of 4-morpholinopyrrolopyrimidine derivatives have been designed, synthesized, and evaluated as PI3K inhibitors. Compound **9** was found to be a selective and potent PI3Kα inhibitor with an IC$_{50}$ of 21 nM and selectivity over mTOR. Replacement of the 3-hydroxymethyl group with a 4-arylurea not only improved enzyme potency against PI3Kα and mTOR but also significantly increased cell potency against PC3 (prostate) and MDA361 (breast) cancer

Table 5[a]



compd	IC$_{50}$ (nM) PI3Kα	mTOR	MDA361	PC3	$T_{1/2}$[b] (Rat)	$T_{1/2}$[b] (Human)	sol.,[c] pH 7.4	sol.,[c] pH 3.0
32	10	1	53	82	> 30	ND	1	ND
46	0.9	0.6	< 3.0	13.0	29	> 30	0	> 100
47	1.4	0.4	10.3	23.0	> 30	> 30	0	68
48	2.4	1.7	6.7	17.0	27	> 30	0	> 100
49	6.0	1.7	11	45	> 30	ND	1	ND
50	1.8	0.5	5.5	26.5	> 30	> 30	1	ND
51	2.7	1.4	4.5	17.0	15	> 30	0	ND
52	0.8	0.9	4.5	27.0	> 30	> 30	1	ND

[a] The values are averages of at least two separate determinations with a typical variation of less than ±30%. ND: not determined. [b] Half-life of drug when incubating with liver microsomes of the species shown. [c] Solubility in μg/mL.

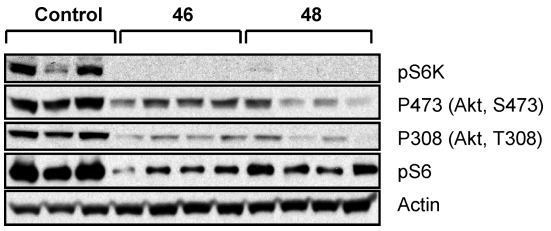


Figure 3. In vivo biomarker studies 8 h after compounds were administered at 25 mpk (iv) to MDA361 tumor bearing nude mice.

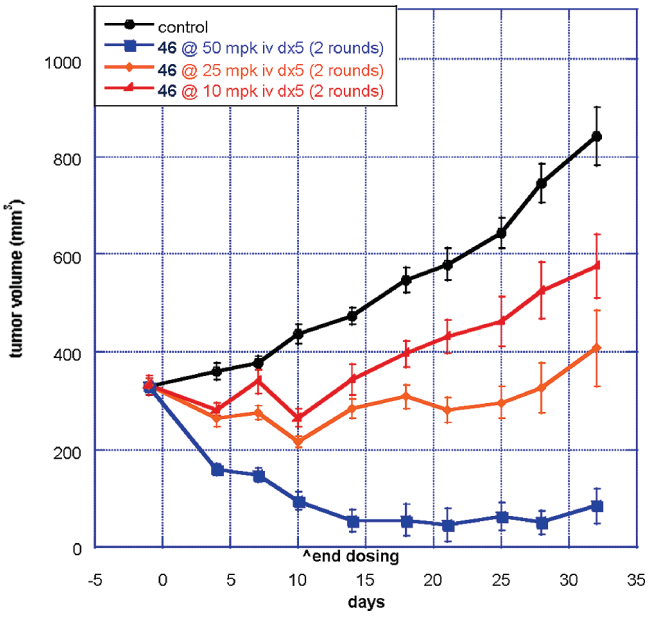


Figure 4. Antitumor efficacy of **46** in the MDA361 xenograft model.

cell lines. By use of molecular modeling, 4-ureidobenzamide derivatives were designed and introduced, most of which exhibited excellent cell potency with single digit nanomolar IC$_{50}$ value in the tumor cell (MDA361) growth inhibition assays. Among them, compounds **46** and **48** were found to have good blood levels at 8 h after iv administration. In vivo biomarker studies showed that both compounds **46** and **48** suppressed the formation of pAkt (T308), pAkt (S473), and pS6K up to 8 h when administered at 25 mpk, iv, in the MDA361 xenograft model. On the basis of the above results, compound **46** was selected for in vivo efficacy studies in which it demonstrated in vivo antitumor efficacy in the MDA361 xenograft model. Evaluating the antitumor efficacy of **46** in other tumor models is in progress.

Experimental Section

General. All solvents and reagents were used as received. ^{1}H NMR spectra were recorded with a Bruker DRX400 spectrometer; Chemical shifts are reported in parts per million (δ) using tetramethylsilane as the internal standard with coupling constants (J) reported in hertz (Hz). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured with an Agilent TOF 2 spectrometer. The purity of final compounds was determined by analytical HPLC using a Prodigy ODS3 column (150 mm × 4.6 mm). Conditions were as follows: ACN/H_2O eluent at 1 mL/min flow (containing 0.05% TFA) at 40 °C, 20 min, gradient 5% ACN to 95% ACN, monitored by UV absorption at 215 nm. All final compounds were found to have ≥95% purity unless otherwise specified. Reversed-phase HPLC (preparative HPLC) purifications were performed on a Gilson preparative HPLC system controlled by Unipoint software using a Phenomenex Gemini column (100 mm × 30 mm). Thin-layer chromatography (TLC) was performed on TLC silica gel 60F$_{254}$ aluminum sheets. The terms "concentrated" and "evaporated" refer to removal of solvents using a rotary evaporator at water aspirator pressure with a bath temperature equal to or less than 40 °C.

4-(2-Chloro-6-methyl-5-nitropyrimidin-4-yl)morpholine (3). To a stirred solution of 2,4-dichloro-6-methyl-5-nitropyrimidine (5.0 g, 24.15 mmol) in CH_2Cl_2 (50 mL) was added a solution

of morpholine (2.1 mL, 24.15 mmol) in CH_2Cl_2 (20 mL), followed by the addition of triethylamine (6.7 mL, 48.3 mmol) at 0 °C. The resulting mixture was stirred at room temperature overnight and diluted with CH_2Cl_2. The organic solution was washed with water and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by flash chromatography to give the title compound as a yellow solid (6.17 g, 99% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46 (s, 3H), 3.57 (t, 4H, J = 4.58 Hz), 3.76 (t, 4H, J = 4.8 Hz). MS (ESI): m/z 259 [M + H].

3-(4-Morpholin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl)phenol (6). Step 1. To a stirred solution of 4-(2-chloro-6-methyl-5-nitropyrimidin-4-yl)morpholine (**3**) (400 mg, 1.55 mmol) in 8 mL of 1,2-dimethoxymethane (DME) were added 3-benzyloxyphenylboronic acid (533 mg, 2.34 mmol), $Pd(Ph_3)_4$ (90 mg, 5 mol %), and 2 N Na_2CO_3 aqueous solution (6 mL). The resulting mixture was heated at 110 °C for 30 min in a microwave oven. The reaction mixture was cooled to room temperature, and the resultant solid was filtered off and washed with THF. The resulting filtrate was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by flash chromatography to give 4-{2-[3-(benzyloxy)phenyl]-6-methyl-5-nitropyrimidin-4-yl}morpholine as a yellow solid (600 mg, 95% yield). MS (ESI): m/z 407 [M + H].

Step 2. A mixture of 4-{2-[3-(benzyloxy)phenyl]-6-methyl-5-nitropyrimidin-4-yl}morpholine (600 mg, 1.48 mmol) and 20 mL of *N*,*N*-dimethylformamide dimethyl acetal (DMF−DMA) was heated at 110 °C overnight. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was diluted with EtOAc and filtered through a short silica gel column. The filtrate was concentrated, and the residue was triturated with diethyl ether. The resulting red solid was collected by filtration to give (*E*)-2-{2-[3-(benzyloxy)phenyl]-6-morpholin-4-yl-5-nitropyrimidin-4-yl}-*N*,*N*-dimethylethenamine (641 mg, 94% yield). MS (ESI): m/z 462 [M + H].

Step 3. To a solution of (*E*)-2-{2-[3-(benzyloxy)phenyl]-6-morpholin-4-yl-5-nitropyrimidin-4-yl}-*N*,*N*-dimethylethenamine (350 mg, 0.76 mmol) in 50 mL of methanol was added 40 mg of 10% Pd/C as catalyst. The resulting mixture was shaken under hydrogen (H_2, 50 psi) at room temperature for 2 h. The reaction mixture was filtered through a pad of Celite. The filtration was concentrated in vacuo, and the residue was purified by flash chromatography (EtOAc/hexanes = 80:20) to give 2-[3-(benzyloxy)phenyl]-4-morpholin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidine as an off-white solid (249 mg, 85% yield). MS (ESI): m/z 387.2 [M + H].

Step 4. To a solution of 2-[3-(benzyloxy)phenyl]-4-morpholin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidine (249 mg, 0.64 mmol) in 20 mL of methanol were added 10% Pd/C (40 mg) and acetic acid (1 mL). The resulting mixture was shaken under hydrogen (H_2, 50 psi) at room temperature overnight. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by flash column chromatography (EtOAc/hexanes = 80:20) to give **6** as an off-white solid (180 mg, 95% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.82−3.77 (m, 8H), 6.52 (d, 1H, J = 3.0 Hz), 6.77 (dd, 1H, J = 8.1, 2.8 Hz), 7.21 (t, 1H, J = 7.8 Hz), 7.58 (t, 1H, J = 3.3 Hz), 7.84−7.80 (m, 2H), 9.36 (s, 1H), 11.44 (s, 1H). MS (ESI): m/z 297 [M + H]. HRMS calcd for $C_{16}H_{16}N_4O_2$ [M + H] 297.1346, obsd 297.1348. HPLC purity 98.9%.

[3-(4-Morpholin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl)phenyl]-methanol (4). Compound **4** was prepared from **3** to give an off-white solid (41% yield), according to the procedure described for **6** (steps 1−3), using 3-(hydroxymethyl)phenylboronic acid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.80 (s, 8H), 4.57 (d, 2H, J = 5.5 Hz), 5.23 (d, 1H, J = 5.8 Hz), 6.54 (dd, 1H, J = 3.3, 1.5 Hz), 7.33 (d, 1H, J = 7.6 Hz), 7.38 (t, 1H, J = 7.6 Hz), 7.59 (t, 1H, J = 3.3 Hz), 8.25 (d, 1H, J = 7.6 Hz), 8.36 (s, 1H), 11.45 (s, 1H). MS (ESI): m/z 311 [M + H]. HRMS calcd for $C_{17}H_{18}N_4O_2$ [M + H] 311.1502, obsd 311.1499. HPLC purity 97.6%.

2-(3-Methylphenyl)-4-morpholin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidine (5). Compound **5** was isolated as an off-white solid (1.4% yield), as a byproduct in the preparation of **4**. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.39 (s, 3H), 3.80 (s, 8H), 6.53 (dd, 1H, J = 3.3, 1.8 Hz), 7.20 (d, 1H, J = 7.8 Hz), 7.32 (t, 1H, J = 7.8 Hz), 7.59 (t, 1H, J = 2.8 Hz), 8.17 (d, 1H, J = 7.8 Hz), 8.20 (s, 1H), 11.46 (s, 1H). MS (ESI): m/z 295 [M + H]. HRMS calcd for $C_{17}H_{18}N_4O$ [M + H] 295.1553, obsd 295.1552. HPLC purity 95%.

3-(4-Morpholin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl)aniline (7). Compound **7** was prepared from **3** to give a yellow solid (53% yield), according to the procedure described for **6** using 3-nitrophenylboronic acid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.85 (t, 4H, J = 4.8 Hz), 4.12 (t, 4H, J = 4.8 Hz), 6.63 (d, 1H, J = 2.5 Hz), 6.91 (d, 1H, J = 7.8 Hz), 7.31 (t, 1H, J = 7.8 Hz), 7.42 (d, 1H, J = 7.8 Hz), 7.49 (s, 1H), 7.89 (t, 1H, J = 2.5 Hz), 12.50 (s, 1H). MS (ESI): m/z 296 [M + H]. HRMS calcd for $C_{16}H_{17}N_5O$ [M + H] 296.1506, obsd 296.1506. HPLC purity 95%.

{3-[4-Morpholin-4-yl-7-(pyrrolidin-1-ylmethyl)-5*H*-pyrrolo-[3,2-*d*]pyrimidin-2-yl]phenyl}methanol (9). To a stirred solution of [3-(4-morpholin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl)phenyl]methanol (**4**) (19 mg, 0.06 mmol) in acetic acid (80% in water, 1 mL) was added formaldehyde (37% in water, 19 mg, 0.24 mmol), followed by addition of pyrrolidine (13 mg, 0.18 mmol). The resulting mixture was heated at 60 °C for 6 h and cooled to room temperature. The reaction mixture was concentrated, and the residue was subjected to HPLC separation to give the title compound **9** as an off-white solid (12 mg, 52% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.67 (m, 4H), 2.54 (m, 4H), 3.80 (m, 8H), 3.82 (s, 2H), 4.58 (br, 2H), 5.23 (br, 1H), 7.33 (d, 1H, J = 7.6 Hz), 7.39 (t, 1H, J = 7.6 Hz), 7.47 (s, 1H), 8.28 (d, 1H, J = 7.6 Hz), 8.36 (s, 1H), 11.33 (s, 1H). MS (ESI): m/z 394 [M + H]. HRMS calcd for $C_{22}H_{27}N_5O_2$ [M + H] 394.2238, obsd 394.2237. HPLC purity 95%.

3-{7-[(Dimethylamino)methyl]-4-morpholin-4-yl-5*H*-pyrrolo-[3,2-*d*]pyrimidin-2-yl}phenyl)methanol (8). Compound **8** was prepared from **4** to give an off-white solid (64% yield), according to the procedure described for **9**, using dimethylamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.19 (s, 6H), 3.66 (s, 2H), 3.81 (m, 8H), 4.58 (br, 2H), 5.23 (br, 1H), 7.33 (d, 1H, J = 7.6 Hz), 7.39 (t, 1H, J = 7.6 Hz), 7.47 (s, 1H), 8.29 (d, 1H, J = 7.6 Hz), 8.37 (s, 1H), 11.37 (s, 1H). MS (ESI): m/z 368 [M + H]. HRMS calcd for $C_{20}H_{25}N_5O_2$ [M + H] 368.2081, obsd 368.2078. HPLC purity 95%.

[3-(5-Methyl-4-morpholin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl)phenyl]methanol (10). Step 1. To a solution of [3-(4-morpholin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl)phenyl]methanol (**4**) (1.469 g, 4.74 mmol) in DMF (5 mL) were added imidazole (0.483 g, 7.10 mmol) and *tert*-butyldimethylsilyl chloride (0.857 g, 5.69 mmol). The resulting mixture was heated at 80 °C for 15 min in microwave oven and cooled to room temperature. The mixture was poured onto 20 mL of water and extracted with EtOAc. The combined organic phases were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by flash chromatography (EtOAc/hexanes = 1:1) to give 2-[3-({[*tert*-butyl-(dimethyl)silyl]oxy}methyl)phenyl]-4-morpholin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidine as a white solid (1.949 g, 97% yield). MS (ESI): m/z 425 [M + H].

Step 2. To a solution of 2-[3-({[*tert*-butyl(dimethyl)silyl]-oxy}methyl)phenyl]-4-morpholin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidine (424 mg, 1.0 mmol) in THF (5 mL) was added NaH (60% in mineral oil, 80 mg, 2.0 mmol) at room temperature. After the mixture was stirred for 10 min, iodomethane (170 mg, 1.2 mmol) was added to the reaction mixture, and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of 2 mL of saturated aqueous ammonium chloride solution, followed by addition of 10 mL of water. The mixture was extracted with EtOAc, and combined organic phases were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was dissolved in 10 mL of

CH_2Cl_2. To this solution was added dropwise trifluoroacetic acid (TFA, 2 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h and concentrated. The residue was treated with 1 N NaOH aqueous solution (10 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by flash chromatography to give **10** as an off-white solid (252 mg, 78% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.40 (t, 4H, J = 4.8 Hz), 3.85 (t, 4H, J = 4.8 Hz), 3.99 (s, 3H), 4.58 (d, 2H, J = 5.8 Hz), 5.26 (t, 1H, J = 5.5 Hz), 6.60 (d, 1H, J = 2.8 Hz), 7.35 (d, 1H, J = 7.6 Hz), 7.41 (t, 1H, J = 7.8 Hz), 7.67 (d, 1H, J = 3.0 Hz), 8.27 (d, 1H, J = 7.8 Hz), 8.38 (s, 1H). MS (ESI): m/z 325 [M + H]. HRMS calcd for $C_{18}H_{20}N_4O_2$ [M + H] 325.1659, obsd 325.1663. HPLC purity 98.4%.

{3-[5-Methyl-4-morpholin-4-yl-7-(pyrrolidin-1-ylmethyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl]phenyl}methanol (11). Compound **11** was prepared from **10** to give an off-white solid (26% yield), according to the procedure described for **9**, using pyrrolidine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.68 (m, 4H), 2.54 (m, 4H), 3.40 (t, 4H, J = 4.5 Hz), 3.80 (s, 2H), 3.85 (t, 4H, J = 4.5 Hz), 3.92 (s, 3H), 4.59 (d, 2H, J = 5.3 Hz), 5.23 (t, 1H, J = 5.3 Hz), 7.35 (d, 1H, J = 7.6 Hz), 7.4 (t, 1H, J = 7.6 Hz), 7.55 (s, 1H), 8.3 (d, 1H, J = 7.6 Hz), 8.4 (s, 1H). MS (ESI): m/z 408 [M + H]. HRMS calcd for $C_{23}H_{29}N_5O_2$ [M + H] 408.2394, obsd 408.2390. HPLC purity 97.0%.

3-(4-Morpholin-4-yl-7-piperidin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl)phenol (12). Step 1. To a solution of 2-[3-(benzyloxy)phenyl]-4-morpholin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidine (see preparation of **6**) (500 mg, 1.29 mmol) in methanol (5 mL) was added KOH (362 mg, 6.45 mmol, 5 equiv) and 4-piperidine monohydrate hydrochloride (495 mg, 3.23 mmol, 2.5 equiv). The resulting solution was heated at 66 °C overnight. The mixture was cooled to room temperature and concentrated. The residue was subjected to HPLC separation to give 2-[3-(benzyloxy)-phenyl]-4-morpholin-4-yl-7-(1,2,3,6-tetrahydropyridin-4-yl)-5*H*-pyrrolo[3,2-*d*]pyrimidine as a yellow solid (300 mg, 50% yield). MS (ESI): m/z 468 [M + H].

Step 2. To a solution of 2-[3-(benzyloxy)phenyl]-4-morpholin-4-yl-7-(1,2,3,6-tetrahydropyridin-4-yl)-5*H*-pyrrolo[3,2-*d*]-pyrimidine (250 mg, 0.53 mmol) in methanol (20 mL) was added 10% Pd/C (50 mg) and concentrated HCl (30%, 0.2 mL). The resulting mixture was shaken under hydrogen (H_2, 50 psi) at room temperature overnight. The reaction mixture was filtered through a pad of Celite. The filtration was concentrated, and the residue was purified by HPLC to give **12** as an off-white solid (200 mg, 99% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.79 (qd, 2H, J = 13.6, 3.5 Hz), 2.14 (d, 2H, J = 13.3 Hz), 3.01 (q, 2H, J = 12.1 Hz), 3.33 (t, 1H, J = 11.8 Hz), 3.45 (d, 2H, J = 12.1 Hz), 3.84 (t, 4H, J = 4.8 Hz), 4.13 (t, 4H, J = 4.8 Hz), 7.11 (dd, 1H, J = 8.1, 2.0 Hz), 7.45 (t, 1H, J = 7.8 Hz), 7.51 (t, 1H, J = 2.0 Hz), 7.54 (d, 1H, J = 7.8 Hz), 7.78 (d, 1H, J = 3.0 Hz), 8.48 (d, 1H, J = 10.3 Hz), 8.64 (d, 1H, J = 10.6 Hz), 12.46 (d, 1H, J = 3.0 Hz). MS (ESI): m/z 380 [M + H]. HRMS calcd for $C_{21}H_{25}N_5O_2$ [M + H] 380.2081, obsd 380.2088. HPLC purity 95%.

3-{7-[1-(4-Fluorobenzyl)piperidin-4-yl]-4-morpholin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl}phenol (14). To a solution of 3-(4-morpholin-4-yl-7-piperidin-4-yl-5*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl)phenol (**12**) (22 mg, 0.058 mmol) in methanol (1 mL) was added 4-fluorobenzaldehyde (22 mg, 0.177 mmol), followed by addition of $ZnCl_2$ (24 mg, 0.174 mmol) and $NaCNBH_3$ (11 mg, 0.174 mmol). The resulting mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was subjected to HPLC separation to give **14** as an off-white solid (TFA salt, 17.2 mg, 49% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.93 (q, 2H, J = 12.6 Hz), 2.27 (d, 2H, J = 12.6 Hz), 3.07 (br, 2H), 3.22 (t, 1H, J = 11.6 Hz), 3.52 (d, 2H, J = 11.6 Hz), 3.81 (t, 4H, J = 4.5 Hz), 3.95 (br, 4H), 4.40 (s, 2H), 6.95 (s, 1H), 7.31 (t, 1H, J = 7.4 Hz), 7.35 (t, 2H, J = 8.6 Hz), 7.54 (br, 1H), 7.63 (dd, 2H, J = 8.6, 5.4 Hz), 7.68 (br, 2H), 9.98 (br, 1H). MS (ESI): m/z 488 [M + H]. HRMS calcd for $C_{28}H_{30}FN_5O_2$ [M + H] 488.2456, obsd 488.2455. HPLC purity 96.1%.

3-[7-(1-benzylpiperidin-4-yl)-4-morpholin-4-yl-5*H*-pyrrolo[3,2-d]-pyrimidin-2-yl]phenol (13). Compound **13** was prepared from **12** to give an off-white solid (TFA salt, 57% yield), according to the procedure described for **14**, using benzaldehyde. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.93 (q, 2H, J = 12.5 Hz), 2.27 (d, 2H, J = 12.5 Hz), 3.09 (br, 2H), 3.12 (t, 1H, J = 11.7 Hz), 3.52 (d, 2H, J = 11.7 Hz), 3.81 (t, 4H, J = 4.5 Hz), 3.95 (br, 4H), 4.40 (s, 2H), 6.95 (br, 1H), 7.33 (t, 1H, J = 7.4 Hz), 7.60−7.47 (m, 6H), 7.65 (br, 2H), 9.97 (br, 1H). MS (ESI): m/z 470 [M + H]. HRMS calcd for $C_{28}H_{31}N_5O_2$ [M + H] 470.2551, obsd 470.2548. HPLC purity 97.7%.

[3-(4-Morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)phenyl]-methanol (17). Step 1. 7*H*-Pyrrolo[2,3-*d*]pyrimidine-2,4-diol (15). To a suspended solution of 6-aminouracil (12.7 g, 100 mmol) and sodium acetate (8.2 g, 100 mmol) in H_2O (100 mL) at a temperature of 70−75 °C was added a solution of chloroacetaldehyde (50% in water, 23.6 g, 150 mmol). The resulting reaction mixture was stirred at 80 °C for 20 min and then cooled to room temperature. The resulting solid was collected by filtration, washed with water and acetone, and dried in vacuo to give **15** as brown solid (14.74 g, 98% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.22 (s, 1H), 6.56 (s, 1H), 10.46 (s, 1H), 11.08 (br, 1H), 11.43 (br, 1H). MS (ESI, negative): m/z 150 [M − H].

Step 2. 2,4-Dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (15a). To a 20 mL vial were added 7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-diol (**15**) (2.5 g, 16.6 mmol), $POCl_3$ (10 mL, 107 mmol), and *N*,*N*-dimethylaniline (1 mL, 7.9 mmol). The resulting mixture was heated at 120 °C for 30 min in a microwave oven. The reaction mixture was cooled to room temperature and poured onto ice (about 200 g). The resulting solid was filtered and washed with water to give dichloro **15a** as a brown solid (1.323 g, 43% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.67 (m, 1H), 7.74 (m, 1H), 12.78 (br, 1H). MS (ESI): m/z 188 [M + H].

Step 3. 2-Chloro-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidine (16). To a solution of 2,4-dichloro-7*H*-pyrrolo[2,3-*d*]-pyrimidine (1.38 g, 7.4 mmol) in CH_2Cl_2 (30 mL) were added morpholine (0.96 mL, 11 mmol) and Et_3N (2.1 mL, 15 mmol). The mixture was stirred at room temperature overnight. The resulting solid was filtered and washed with EtOH and water to give **16** as a yellow solid (1.19 g, 68%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.72 (t, 4H, J = 5.0 Hz), 3.84 (t, 4H, J = 5.0 Hz), 6.67 (dd, 1H, J = 3.3, 1.3 Hz), 7.21(dd, 1H, J = 3.8, 2.3 Hz), 11.91 (br, 1H). MS (ESI): m/z 239 [M + H].

Step 4. [3-(4-Morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)phenyl]methanol (17). To a 10 mL vial were added 2-chloro-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**16**) (150 mg, 0.63 mmol), 3-hydroxymethylphenylboronic acid (144 mg, 0.94 mmol), $Pd(PPh_3)_4$ (36 mg, 5 mol %), 1,2-dimethoxyethane (DME, 2.5 mL), and 2 M Na_2CO_3 aqueous solution (1.5 mL). The resulting mixture was heated at 120 °C for 1 h in a microwave oven. The reaction mixture was cooled to room temperature and diluted with EtOAc. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was subjected to HPLC separation to give **17** as an off-white solid (98 mg, 50% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.78 (t, 4H, J = 4.8 Hz), 3.95 (t, 4H, J = 4.8 Hz), 4.58 (d, 2H, J = 5.8 Hz), 5.24 (t, 1H, J = 5.8 Hz), 6.66 (d, 1H, J = 3.5 Hz), 7.24 (dd, 1H, J = 3.5, 2.8 Hz), 7.35 (d, 1H, J = 7.3 Hz), 7.40 (t, 1H, J = 7.8 Hz), 8.24 (d, 1H, J = 7.8 Hz), 8.35 (s, 1H), 11.80 (s, 1H). MS (ESI): m/z 311 [M + H]. HRMS calcd for $C_{17}H_{18}N_4O_2$ [M + H] 311.1502, obsd 311.1501. HPLC purity 95%.

3-(4-Morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)phenol (18). Following the same procedure as for the preparation of **17**, Suzuki coupling of 2-chloro-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**16**) (150 mg, 0.63 mmol) with 3-hydroxyphenylboronic acid (130 mg, 0.94 mmol) gave **18** as a yellow solid

(130 mg, 70% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.78 (t, 4H, J = 5.0 Hz), 3.93 (t, 4H, J = 5.0 Hz), 6.65 (d, 1H, J = 3.3 Hz), 6.80 (dd, 1H, J = 8.3, 2.5 Hz), 7.23 (dd, 2H, J = 7.8, 4.5 Hz), 7.80 (m, 2H), 9.40 (s, 1H), 11.77 (s, 1H). MS (ESI): m/z 297 [M + H]. HRMS calcd for $C_{16}H_{16}N_4O_2$ [M + H] 297.1346, obsd 297.1347. HPLC purity 95.3%.

2-Chloro-4-morpholin-4-yl-7-[2-(dimethylamino)ethyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (19). To a solution of 2-chloro-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**16**) (154 mg, 0.65 mmol) in DMF (5 mL) were added 2-(dimethylamino)ethyl chloride hydrochloride (140 mg, 0.97 mmol) and Cs_2CO_3 (635 mg, 1.95 mmol). The resulting mixture was heated at 80 °C under nitrogen overnight and cooled to room temperature. Water was added, and the mixture was extracted with EtOAc. The combined extracts were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated to give **19** as a yellow syrup (169 mg, 84% yield), which was used in next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.27 (s, 6H), 2.68 (t, 2H, J = 6.4 Hz), 3.82 (t, 4H, J = 4.9 Hz), 3.94 (t, 4H, J = 5.3 Hz), 4.25 (t, 2H, J = 6.4 Hz), 6.43 (d, 1H, J = 3.8 Hz), 7.03 (d, 1H, J = 3.8 Hz). MS (ESI): m/z 310 [M + H].

(3-{7-[2-(Dimethylamino)ethyl]-4-morpholin-4-yl-7*H*-pyrrolo-[2,3-*d*]pyrimidin-2-yl}phenyl)methanol (20). Following the same procedure as for the preparation of **17**, Suzuki coupling of 2-chloro-4-morpholin-4-yl-7-[2-(dimethylamino)ethyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (**19**) (80 mg, 0.26 mmol) and 3-hydroxymethylphenylboronic acid (58 mg, 0.38 mmol) gave **20** as an off-white solid (96 mg, 88% yield). ^{1}H NMR (CD_3OD, 300 MHz) δ 3.01 (s, 6H), 3.79−3.71 (m, 2H), 3.94 (t, 4H, J = 4.9 Hz), 4.11 (t, 4H, J = 5.3 Hz), 4.76 (s, 2H), 4.87 (m, 2H), 7.09 (d, 1H, J = 3.8 Hz), 7.66−7.56 (m, 3H), 8.07 (d, 1H, J = 7.5 Hz), 8.17 (s, 1H). MS (ESI): m/z 382 [M + H]. HRMS calcd for $C_{21}H_{27}N_5O_2$ [M + H] 382.22386, obsd 382.2235. HPLC purity 97.5%.

3-{7-[2-(Dimethylamino)ethyl]-4-morpholin-4-yl-7*H*-pyrrolo-[2,3-*d*]pyrimidin-2-yl}phenol (21). Following the same procedure as for the preparation of **17**, Suzuki coupling of 2-chloro-4-morpholin-4-yl-7-[2-(dimethylamino)ethyl]-7*H*-pyrrolo[2,3-*d*]-pyrimidine (**19**) (80 mg, 0.26 mmol) and 3-hydroxyphenylboronic acid (54 mg, 0.38 mmol) gave **21** as an off-white solid (81.9 mg, 78% yield). ^{1}H NMR (CD_3OD, 300 MHz) δ 3.01 (s, 6H), 3.74 (t, 2H, J = 6.0 Hz), 3.90 (t, 4H, J = 5.3 Hz), 4.06 (t, 4H, J = 5.3 Hz), 4.79 (t, 2H, J = 6.0 Hz), 6.96 (d, 1H, J = 3.8 Hz), 7.0 (dd, 1H, J = 7.9, 2.3 Hz), 7.37 (t, 1H, J = 7.9 Hz), 7.50 (d, 1H, J = 3.8 Hz), 7.68−7.62 (m, 2H). MS (ESI): m/z 368 [M + H]. HRMS calcd for $C_{20}H_{25}N_5O_2$ [M + H] 368.2081, obsd 368.2082. HPLC purity 98.8%.

4-{7-[2-(Dimethylamino)ethyl]-4-morpholin-4-yl-7*H*-pyrrolo-[2,3-*d*]pyrimidin-2-yl}aniline (22). Following the same procedure as for the preparation of **17**, Suzuki coupling of 2-chloro-4-morpholin-4-yl-7-[2-(dimethylamino)ethyl]-7*H*-pyrrolo[2,3-*d*]-pyrimidine (**19**) (261 mg, 0.84 mmol) and 4-aminophenylboronic acid pinacol ester (277 mg, 1.27 mmol) gave **22** as a yellow oil (278 mg, 90% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 6H), 2.76 (t, 2H, J = 6.4 Hz), 3.86 (t, 4H, J = 5.3 Hz), 4.0 (t, 4H, J = 5.3 Hz), 4.37 (t, 2H, J = 6.4 Hz), 6.42 (d, 1H, J = 3.8 Hz), 6.72 (d, 2H, J = 8.7 Hz), 6.98 (d, 1H, J = 3.8 Hz), 8.30 (d, 2H, J = 8.7 Hz). MS (ESI): m/z 367 [M + H].

1-(4-{7-[2-(Dimethylamino)ethyl]-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}phenyl)-3-pyridin-2-ylurea (23). To a solution of 4-{7-[2-(dimethylamino)ethyl]-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}aniline (**22**) (22 mg, 0.06 mmol) in $CHCl_3$ (1 mL) were added Et_3N (25 μL, 0.18 mmol) and triphosgene (18 mg, 0.06 mmol). The mixture was stirred at room temperature for 15 min, and 2-aminopyridine (17 mg, 0.18 mmol) was added. The mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was subjected to HPLC separation to give **23** as an off-white solid (15 mg, 51% yield). MS (ESI): m/z 487 [M + H]. HRMS calcd for $C_{26}H_{30}N_8O_2$ [M + H] 487.2564, obsd 487.2561. HPLC purity 99.0%.

1-(4-{7-[2-(Dimethylamino)ethyl]-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}phenyl)-3-pyridin-3-ylurea (24). Compound **24** was prepared from **22** to give an off-white solid (45% yield), according to the procedure described for **23**, using 3-aminopyridine. MS (ESI): m/z 487 [M + H]. HRMS calcd for $C_{26}H_{30}N_8O_2$ [M + H] 487.2564, obsd 487.2564. HPLC purity 96.0%.

1-(4-{7-[2-(Dimethylamino)ethyl]-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}phenyl)-3-pyridin-4-ylurea (25). Compound **25** was prepared from **22** to give an off-white solid (62% yield), according to the procedure described for **23**, using 4-aminopyridine. ^{1}H NMR (CD_3OD, 400 MHz) δ 2.34 (s, 6H), 2.83 (t, 2H, J = 6.8 Hz), 3.85 (t, 4H, J = 5.0 Hz), 4.00 (t, 4H, J = 5.3 Hz), 4.42 (t, 2H, J = 7.1 Hz), 6.60 (d, 1H, J = 3.5 Hz), 7.16 (d, 1H, J = 3.5 Hz), 7.52 (t, 2H, J = 1.8 Hz), 7.54 (d, 2H, J = 1.8 Hz), 8.32 (dd, 2H, J = 4.8, 1.5 Hz), 8.39 (d, 2H, J = 8.3 Hz). MS (ESI): m/z 487 [M + H]. HRMS calcd for $C_{26}H_30N_8O_2$ [M + H] 487.2564, obsd 487.2564. HPLC purity 95%.

1-(4-{7-[2-(Dimethylamino)ethyl]-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}phenyl)-3-(4-fluorophenyl)urea (26). Compound **26** was prepared from **22** to give an off-white solid (33% yield), according to the procedure described for **23**, using 4-fluoroaniline. MS (ESI): m/z 504 [M + H]. HRMS calcd for $C_{27}H_{30}FN_7O_2$ [M + H] 504.2518, obsd 504.2515. HPLC purity 95%.

1-(4-{7-[2-(Dimethylamino)ethyl]-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}phenyl)-3-ethylurea (27). Compound **27** was prepared from **22** to give a yellow solid (41% yield), according to the procedure described for **23**, using ethylamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.06 (t, 3H, J = 7.1 Hz), 2.88 (s, 6H), 3.12 (q, 2H, J = 7.1 Hz), 3.61 (br, 2H), 3.77 (t, 4H, J = 4.5 Hz), 3.94 (t, 4H, J = 4.5 Hz), 4.62 (t, 2H, J = 6.1 Hz), 6.27 (br, 1H), 6.75 (d, 1H, J = 3.6 Hz), 7.33 (d, 1H, J = 3.6 Hz), 7.49 (d, 2H, J = 8.7 Hz), 8.28 (d, 2H, J = 8.7 Hz), 8.71 (s, 1H), 9.65 (br, 1H). MS (ESI): m/z 438 [M + H]. HRMS calcd for $C_{23}H_{31}N_7O_2$ [M + H] 438.2612, obsd 438.2609. HPLC purity 97.2%.

1-(4-{7-[2-(Dimethylamino)ethyl]-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}phenyl)-3-methylurea (28). Compound **28** was prepared from **22** to give a yellow solid (34% yield), according to the procedure described for **23**, using methylamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.66 (s, 3H), 2.88 (s, 6H), 3.61 (br, 2H), 3.77 (t, 4H, J = 4.5 Hz), 3.94 (t, 4H, J = 4.5 Hz), 4.61 (t, 2H, J = 6.1 Hz), 6.12 (br, 1H), 6.75 (d, 1H, J = 3.6 Hz), 7.33 (d, 1H, J = 3.6 Hz), 7.50 (d, 2H, J = 8.7 Hz), 8.28 (d, 2H, J = 8.7 Hz), 8.78 (s, 1H), 9.60 (br, 1H). MS (ESI): m/z 424 [M + H]. HRMS calcd for $C_{22}H_{29}N_7O_2$ [M + H] 424.2456, obsd 424.2453. HPLC purity 98.2%.

1-[4-(4-Morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)phenyl]-3-pyridin-4-ylurea (29). To a 10 mL vial were charged 4-isocyantophenylboronic acid, pinacol ester (368 mg, 1.5 mmol), 4-aminopyridine (188 mg, 2.0 mmol), Et_3N (0.28 mL, 2.0 mmol), and DME (3 mL). The mixture was stirred at room temperature for 5 h, and to the mixture were then added 2-chloro-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**16**) (238 mg, 1.0 mmol), Na_2CO_3 aqueous solution (2 M, 2 mL), and $Pd(PPh_3)_4$ (58 mg, 5 mol %). The resulting mixture was heated at 120 °C for 30 min in microwave oven. The reaction mixture was cooled to room temperature and diluted with EtOAc. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was subjected to HPLC separation to give **29** as a yellow solid (66 mg, 16% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.78 (t, 4H, J = 4.5 Hz), 3.95 (t, 4H, J = 5.0 Hz), 6.66 (m, 1H), 7.23 (m, 1H), 7.63 (d, 2H, J = 8.6 Hz), 7.96 (d, 2H, J = 7.3 Hz), 8.34 (d, 2H, J = 8.6 Hz), 8.62 (d, 2H, J = 7.6 Hz), 9.96 (s, 1H), 10.84 (s, 1H), 11.79 (s, 1H). MS(ESI): m/z 416 [M + H]. HRMS calcd for $C_{22}H_{21}N_7O_2$ [M + H] 416.1829, obsd 416.1830. HPLC purity 95%.

2-Chloro-4-morpholin-4-yl-7-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (30). To a solution of 2-chloro-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**16**) (340 mg, 1.4 mmol) in DMF (5 mL) were added 1,1,1-trifluoro-2-iodoethane (0.28 mL, 2.8 mmol) and Cs_2CO_3 (559 mg, 1.7 mmol). The resulting mixture was heated at 80 °C under nitrogen overnight and cooled to room temperature. The reaction mixture was quenched with water and extracted with EtOAc. The combined extracts were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated to give **30** as a light-yellow solid (199 mg, 43% yield), which was used in the next step without further purification. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.72 (t, 4H, J = 5.0 Hz), 3.86 (t, 4H, J = 5.0 Hz), 5.05 (q, 2H, J = 9.3 Hz), 6.84 (d, 1H, J = 3.5 Hz), 7.34 (d, 1H, J = 3.8 Hz). MS (ESI): m/z 321 [M + H].

4-[7-(2,2,2-Trifluoroethyl)-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]-pyrimidin-2-yl]aniline (42). To a 10 mL vial were added 2-chloro-4-morpholin-4-yl-7-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**30**) (294 mg, 0.9 mmol), 4-aminophenylboronic acid pinacol ester (302 mg, 1.4 mmol), $Pd(PPh_3)_4$ (53 mg, 5 mol %), 1,2-dimethoxyethane (DME, 3 mL), and Na_2CO_3 aqueous solution (2 M, 2 mL). The resulting mixture was heated at 130 °C for 30 min in a microwave oven. The reaction mixture was cooled to room temperature and diluted with EtOAc. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by flash chromatography to give **42** as a brown oil (286 mg, 83% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.77 (t, 4H, J = 5.0 Hz), 3.91 (t, 4H, J = 4.8 Hz), 5.12 (q, 2H, J = 9.3 Hz), 5.44 (s, 2H), 6.61 (d, 2H, J = 9.3 Hz), 6.74 (d, 1H, J = 4.0 Hz), 7.25 (d, 1H, J = 4.0 Hz), 8.12 (d, 2H, J = 9.1 Hz). MS (ESI): m/z 378 [M + H].

1-{4-[4-Morpholin-4-yl-7-(2,2,2-trifluoroethyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidin-2-yl]phenyl}-3-pyridin-4-ylurea (32). To a solution of 4-[7-(2,2,2-trifluoroethyl)-4-morpholin-4-yl-7*H*-pyrrolo-[2,3-*d*]pyrimidin-2-yl]aniline (**42**) (25 mg, 0.066 mmol) in $CHCl_3$ (1 mL) were added Et_3N (28 μL, 0.2 mmol) and triphosgene (20 mg, 0.066 mmol). The mixture was stirred at room temperature for 15 min before a solution of 4-aminopyridine (19 mg, 0.2 mmol) in THF (1 mL) was added. The mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was subjected to HPLC separation to give **32** as an off-white solid (24.5 mg, 61% yield). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.78 (t, 4H, J = 5.3 Hz), 3.97 (t, 4H, J = 5.3 Hz), 5.18 (q, 2H, J = 9.8 Hz), 6.82 (d, 1H, J = 3.8 Hz), 7.35 (d, 1H, J = 3.8 Hz), 7.63 (d, 2H, J = 8.7 Hz), 7.94 (d, 2H, J = 7.2 Hz), 8.41 (d, 2H, J = 8.7 Hz), 8.61 (d, 2H, J = 7.2 Hz), 9.85 (s, 1H), 10.64 (s, 1H). MS (ESI): m/z 498 [M + H]. HRMS calcd for $C_{24}H_{22}F_3N_7O_2$ [M + H] 498.1860, obsd 498.1860. HPLC purity 97.6%.

2-Chloro-7-(2,2-dimethoxyethyl)-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidine (31). To a solution of 2-chloro-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**16**) (650 mg, 2.7 mmol) in DMF (10 mL) were added 2-bromo-1,1-dimethoxyethane (0.65 mL, 5.4 mmol) and Cs_2CO_3 (1.067 g, 3.3 mmol). The resulting mixture was heated at 80 °C under nitrogen overnight and cooled to room temperature. Water was added, and the mixture was extracted with EtOAc. The combined extracts were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated to give **31** as a light-yellow solid (665 mg, 75% yield), which was used in the next step without further purification. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.27 (s, 6H), 3.72 (t, 4H, J = 5.0 Hz), 3.84 (t, 4H, J = 5.3 Hz), 4.20 (d, 2H, J = 5.5 Hz), 4.67 (t, 1H, J = 5.3 Hz), 6.7 (d, 1H, J = 4.0 Hz), 7.26 (d, 1H, J = 3.8 Hz). MS (ESI): m/z 327 [M + H].

1-{4-[7-(2,2-Dimethoxyethyl)-4-morpholin-4-yl-7*H*-pyrrolo-[2,3-*d*]pyrimidin-2-yl]phenyl}-3-pyridin-4-ylurea (33). Step 1. To a 20 mL vial were added 2-chloro-7-(2,2-dimethoxyethyl)-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**31**) (665 mg, 2 mmol), 4-aminophenylboronic acid pinacol ester (670 mg, 3 mmol), Pd-$(PPh_3)_4$ (118 mg, 5 mol %), 1,2-dimethoxyethane (DME, 6 mL), and sodium carbonate aqueous solution (2M, 4 mL). The resulting mixture was heated at 130 °C for 30 min in a microwave oven. The reaction mixture was cooled to room temperature and diluted with EtOAc. The aqueous phase was extracted with EtOAc, and the combined organic solution was concentrated. The residue was purified by flash chromatography to give 4-[7-(2,2-dimethoxyethyl)-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]aniline as a brown oil (760 mg, 97% yield). MS (ESI): m/z 384 [M + H].

Step 2. To a solution of 4-[7-(2,2-dimethoxyethyl)-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]aniline (766 mg, 2 mmol) in $CHCl_3$ (10 mL) were added Et_3N (0.55 mL, 3.9 mmol) and triphosgene (594 mg, 2 mmol). The mixture was stirred at room temperature for 15 min before a solution of 4-aminopyridine (564 mg, 6 mmol) in THF (10 mL) was added. The mixture was heated at 50 °C overnight. The solvent was evaporated, and the residue was subjected to HPLC separation to give **33** as a yellow solid (350 mg, 35% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.31 (s, 6H), 3.78 (t, 4H, J = 4.8 Hz), 3.95 (t, 4H, J = 4.8 Hz), 4.35 (d, 2H, J = 5.3 Hz), 4.78 (t, 1H, J = 5.3 Hz), 6.67 (d, 1H, J = 3.5 Hz), 7.27 (d, 1H, J = 3.5 Hz), 7.52 (d, 2H, J = 6.5 Hz), 7.57 (d, 2H, J = 8.8 Hz), 8.35 (d, 2H, J = 8.8 Hz), 8.40 (d, 2H, J = 6.5 Hz), 9.15 (s, 1H), 9.32 (s, 1H). MS (ESI): m/z 504 [M + H]. HRMS calcd for $C_{26}H_{29}N_7O_4$ [M + H] 504.2354, obsd 504.2358. HPLC purity 95%.

1-{4-[4-Morpholin-4-yl-7-(2-oxoethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]phenyl}-3-pyridin-4-ylurea (34). A mixture of 1-{4-[7-(2,2-dimethoxyethyl)-4-morpholin-4-yl-7*H*-pyrrolo-[2,3-*d*]pyrimidin-2-yl]phenyl}-3-pyridin-4-ylurea (**33**) (300 mg, 0.6 mmol), dioxane (3 mL), and 6 M HCl (3 mL) was heated at 70 °C for 3 h and cooled to room temperature. The mixture was concentrated in vacuo, and the residue was triturated with EtOAc. The resulting solid was collected by filtration and washed with EtOAc to give **34** as an off-white solid (479 mg, 85% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.79 (t, 4H, J = 4.5 Hz), 3.96 (t, 4H, J = 4.5 Hz), 5.21(s, 2H), 6.74 (d, 1H, J = 3.6 Hz), 7.25 (d, 1H, J = 3.6 Hz), 7.60 (d, 2H, J = 8.6 Hz), 7.94 (d, 2H, J = 6.7 Hz), 8.35 (d, 2H, J = 8.6 Hz), 8.61 (d, 2H, J = 6.7 Hz), 9.72 (s, 1H), 9.81 (s, 1H), 10.62 (s, 1H). MS (ESI): m/z 458 [M + H]. HPLC purity 95%.

1-{4-[4-Morpholin-4-yl-7-(2-pyrrolidin-1-ylethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]phenyl}-3-pyridin-4-ylurea (35). To a solution of 1-{4-[4-morpholin-4-yl-7-(2-oxoethyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidin-2-yl]phenyl}-3-pyridin-4-ylurea (**34**) (24 mg, 0.05 mmol) in MeOH (2 mL) were added pyrrolidine (22 mg, 0.3 mmol), $ZnCl_2$ (14 mg, 0.1 mmol), and $NaBH_3CN$ (6 mg, 0.1 mmol). The resulting mixture was stirred at room temperature for 2 h, and 0.5 mL of NaOH (1 M in water) was added. The solvent was evaporated, and the residue was subjected to HPLC separation to give **35** as an off-white solid (9.2 mg, 25% yield). MS (ESI): m/z 513 [M + H]. HRMS calcd for $C_{28}H_{32}N_8O_2$ [M + H] 513.2721, obsd 513.2718. HPLC purity 95%.

1-{4-[4-Morpholin-4-yl-7-(2-piperidin-1-ylethyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidin-2-yl]phenyl}-3-pyridin-4-ylurea (36). Compound **36** was prepared from **34** to give an off-white solid (27% yield), according to the procedure described for **35**, using piperidine. MS (ESI): m/z 527 [M + H]. HRMS calcd for $C_{29}H_{34}N_8O_2$ [M + H] 527.2880, obsd 527.2877. HPLC purity 95.7%.

1-{4-[7-(2-{[2-(Dimethylamino)ethyl]amino}ethyl)-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]phenyl}-3-pyridin-4-ylurea (37). Compound **37** was prepared from **34** to give an off-white solid (37% yield), according to the procedure described for **35**, using *N*,*N*-dimethylethylenediamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.81 (s, 6H), 3.33 (m, 2H), 3.42 (m, 2H), 3.54 (t, 2H, J = 6.1 Hz), 3.78 (t, 4H, J = 4.5 Hz), 3.96 (m, 4H), 4.58 (d, 2H, J = 6.3 Hz), 6.77 (d, 1H, J = 3.6 Hz), 7.32 (d, 1H, J = 3.6 Hz), 7.66 (d, 2H, J = 8.7 Hz), 7.98 (d, 2H, J = 6.8 Hz), 8.42 (d, 2H, J = 8.7 Hz), 8.63 (d, 2H, J = 6.8 Hz), 10.46 (s, 1H), 11.38 (s, 1H). MS (ESI): m/z 530 [M + H]. HRMS calcd for $C_{28}H_{35}N_9O_2$ [M + H] 530.2986, obsd 530.2976. HPLC purity 95%.

1-(4-{7-[2-(4-Methylpiperazin-1-yl)ethyl]-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl}phenyl)-3-pyridin-4-ylurea (38). Compound **38** was prepared from **34** to give an off-white solid (42% yield), according to the procedure described for **35**, using 1-methylpiperazine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.74 (s, 3H), 2.95 (t, 2H, J = 6.0 Hz), 3.30 (br, 8H), 3.78 (t, 4H, J = 4.5 Hz), 3.95 (t, 4H, J = 4.5 Hz), 4.42 (t, 2H, J = 6.0 Hz), 6.68 (d, 1H, J = 3.6 Hz), 7.35 (d, 1H, J = 3.6 Hz), 7.66 (d, 2H, J = 8.7 Hz), 7.98 (d, 2H, J = 7.0 Hz), 8.38 (d, 2H, J = 8.7 Hz), 8.63 (d, 2H, J = 7.0 Hz), 10.46 (s, 1H), 11.41 (s, 1H). MS (ESI): m/z 542 [M + H]. HRMS calcd for $C_{29}H_{35}N_9O_2$ [M + H] 542.2986, obsd 542.2981. HPLC purity 96.5%.

1-{4-[4-Morpholin-4-yl-7-(2-piperazin-1-ylethyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidin-2-yl]phenyl}-3-pyridin-4-ylurea (39). Compound **39** was prepared from **34** to give an off-white solid (39% yield), according to the procedure described for **35**, using piperazine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.90 (br, 4H), 2.99 (br, 2H), 3.07 (br, 4H), 3.78 (t, 4H, J = 4.5 Hz), 3.95 (t, 4H, J = 4.5 Hz), 4.43 (t, 2H, J = 6.0 Hz), 6.69 (d, 1H, J = 3.6 Hz), 7.35 (d, 1H, J = 3.6 Hz), 7.66 (d, 2H, J = 8.8 Hz), 7.98 (d, 2H, J = 7.0 Hz), 8.38 (d, 2H, J = 8.8 Hz), 8.62 (d, 2H, J = 7.0 Hz), 10.40 (s, 1H), 11.40 (s, 1H). MS (ESI): m/z 528 [M + H]. HRMS calcd for $C_{28}H_{33}N_9O_2$ [M + H] 528.2830, obsd 528.2828. HPLC purity 95.5%.

1-{4-[7-(2-Hydroxyethyl)-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]-pyrimidin-2-yl]phenyl}-3-pyridin-4-ylurea (40). To a stirred mixture of 1-{4-[4-morpholin-4-yl-7-(2-oxoethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]phenyl}-3-pyridin-4-ylurea (**34**) (215 mg, 0.47 mmol), MeOH (4 mL), and THF (4 mL) was added $NaBH_4$ (27 mg, 0.7 mmol). The resulting mixture was stirred at room temperature for 30 min, and 2 mL of NaOH (1 M in water) was added. The mixture was concentrated, and the residue was subjected to HPLC separation to give **40** as an off-white solid (165 mg, 76% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.78 (t, 6H, J = 5.0 Hz), 3.94 (t, 4H, J = 5.0 Hz), 4.29 (t, 2H, J = 5.5 Hz), 4.96 (t, 1H, J = 5.5 Hz), 6.65 (d, 1H, J = 3.8 Hz), 7.29 (d, 1H, J = 3.8 Hz), 7.45 (d, 2H, J = 6.3 Hz), 7.56 (d, 2H, J = 8.6 Hz), 8.34 (d, 2H, J = 8.6 Hz), 8.37 (d, 2H, J = 6.3 Hz), 9.06 (s, 1H), 9.13 (s, 1H). MS (ESI): m/z 460 [M + H]. HRMS calcd for $C_{24}H_{25}N_7O_3$ [M + H] 460.2092, obsd 460.2092. HPLC purity 98.1%.

4-({[4-(7-(2,2,2-Trifluoroethyl)-4-morpholin-4-yl-7*H*-pyrrolo-[2,3-*d*]pyrimidin-2-yl)phenyl]carbamoyl}amino)benzoic Acid (44). Step 1. To a solution of 4-[7-(2,2,2-trifluoroethyl)-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]aniline (**42**) (479 mg, 1.3 mmol) in CH_2Cl_2 (10 mL) was added methyl 4-isocyanatobenzoate (269 mg, 1.5 mmol), and the resulting mixture was stirred at room temperature overnight. The resulting solid was collected by filtration and washed with CH_2Cl_2 to give methyl 4-[({4-[4-morpholin-4-yl-7-(2,2,2-trifluoroethyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidin-2-yl]phenyl}carbamoyl)amino]benzoate as an off-white solid (539 mg, 77% yield). MS (ESI): m/z 555 [M + H].

Step 2. To a solution of methyl 4-[({4-[4-morpholin-4-yl-7-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]phenyl}-carbamoyl)amino]benzoate (500 mg, 0.9 mmol) in MeOH (30 mL) and THF (10 mL) was added 1 N NaOH aqueous solution (2.7 mL), and the mixture was heated at 70 °C overnight. The mixture was cooled to room temperature and concentrated. The residue was treated water and acidified to pH 4−5 by addition of 1 N HCl, and the resulting solid was collected by filtration, washed with water, and dried in air to give **44** as an off-white solid (486 mg, 100% yield). MS (ESI): m/z 541 [M + H].

***N*-[2-(Dimethylamino)ethyl]-*N*-methyl-4-[({4-[4-morpholin-4-yl-7-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]phenyl}carbamoyl)amino]benzamide (46).** To a solution of 4-({[4-(7-(2,2,2-trifluoroethyl)-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)phenyl]carbamoyl}amino)benzoic acid (**44**) (32 mg, 0.06 mmol) in THF (2 mL) were added *N*,*N*,*N*′-trimethylethylenediamine (12 mg, 0.12 mmol), Et_3N (12 mg, 0.12 mmol), HOBt (16 mg, 0.12 mmol), and EDCI (23 mg, 0.12 mmol). The resulting mixture was stirred at room temperature overnight and concentrated. The residue was subjected to HPLC separation to give **46** as an off-white solid (TFA salt, 38.6 mg, 87% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.83 (br, 6H), 3.02 (s, 3H), 3.35 (q, 2H, J = 5.8 Hz), 3.79 (br, 6H), 3.97 (br, 4H), 5.19 (q, 2H, J = 8.6 Hz), 6.82 (d, 1H, J = 3.8 Hz), 7.35 (d, 1H, J = 3.8 Hz), 7.47 (d, 2H, J = 8.3 Hz), 7.57 (t, 4H, J = 8.3 Hz), 8.36 (d, 2H, J = 8.8 Hz), 9.48 (s, 1H), 9.54 (s, 1H), 10.03 (br, 1H). MS (ESI): m/z 625 [M + H]. HRMS calcd for $C_{31}H_{35}F_3N_8O_3$ [M + H] 625.2857, obsd 625.2857. HPLC purity 96.7%.

***N*-[2-(Dimethylamino)ethyl]-4-[({4-[4-morpholin-4-yl-7-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]phenyl}carbamoyl)amino]benzamide (47).** Compound **47** was prepared from **44** to give an off-white solid (TFA salt, 99% yield), according to the procedure described for **46**, using *N*,*N*-dimethylethylenediamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.83 (s, 3H), 2.84 (s, 3H), 3.26 (q, 2H, J = 5.8 Hz), 3.62 (q, 2H, J = 5.8 Hz), 3.78 (t, 4H, J = 4.8 Hz), 3.96 (t, 4H, J = 4.8 Hz), 5.18 (q, 2H, J = 8.6 Hz), 6.81 (d, 1H, J = 3.8 Hz), 7.34 (d, 1H, J = 3.8 Hz), 7.57 (dd, 4H, J = 8.6, 1.8 Hz), 7.87 (d, 2H, J = 8.6 Hz), 8.35 (d, 2H, J = 8.6 Hz), 8.67 (t, 1H, J = 5.8 Hz), 9.51 (s, 1H), 9.59 (s, 1H), 9.94 (br, 1H). MS (ESI): m/z 611 [M + H]. HRMS calcd for $C_{30}H_{33}F_3N_8O_3$ [M + H] 611.2700, obsd 611.2700. HPLC purity 96.8%.

1-{4-[(4-Methylpiperazin-1-yl)carbonyl]phenyl}-3-{4-[4-morpholin-4-yl-7-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl]phenyl}urea (48). Compound **48** was prepared from **44** to give an off-white solid (TFA salt, 97% yield), according to the procedure described for **46**, using 1-methylpiperazine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.78 (s, 3/2 H), 2.79 (s, 3/2H), 3.07 (m, 2H), 3.40 (m, 4H), 3.78 (t, 4H, J = 4.8 Hz), 3.96 (t, 4H, J = 4.8 Hz), 5.18 (q, 2H, J = 8.6 Hz), 6.81 (d, 1H, J = 3.5 Hz), 7.34 (d, 1H, J = 3.5 Hz), 7.34 (d, 1H, J = 3.5 Hz), 7.42 (d, 2H, J = 8.6 Hz), 7.57 (d, 4H, J = 8.6 Hz), 8.35 (d, 2H, J = 8.6 Hz), 9.42 (s, 1H), 9.50 (s, 1H), 10.94 (s, 1H). MS (ESI): m/z 623 [M + H]. HRMS calcd for $C_{31}H_{33}F_3N_8O_3$ [M + H] 623.2700, obsd 623.2700. HPLC purity 95%.

1-(4-{[4-(Dimethylamino)piperidin-1-yl]carbonyl}phenyl)-3-{4-[4-morpholin-4-yl-7-(2,2,2-trifluoroethyl)-7*H*-pyrrolo[2,3-*d*]-pyrimidin-2-yl]phenyl}urea (49). Compound **49** was prepared from **44** to give an off-white solid (HCl salt, 68% yield), according to the procedure described for 46, using 4-dimethylaminopiperidine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.61 (m, 2H), 2.04 (br, 2H), 2.72 (s, 3H), 2.74 (s, 3H), 3.43 (m, 1H), 3.78 (t, 4H, J = 4.5 Hz), 3.96 (t, 4H, J = 4.5 Hz), 5.18 (q, 2H, J = 8.8 Hz), 6.81 (d, 1H, J = 3.8 Hz), 7.33 (d, 1H, J = 3.8 Hz), 7.38 (d, 2H, J = 8.8 Hz), 7.55 (d, 2H, J = 8.8 Hz), 7.57 (d, 2H, J = 8.8 Hz), 8.35 (d, 2H, J = 8.8 Hz), 9.31 (s, 1H), 9.35 (s, 1H), 10.33 (s, 1H). MS (ESI): m/z 651 [M + H]. HRMS calcd for $C_{33}H_{37}F_3N_8O_3$ [M + H] 651.3013, obsd 651.3013. HPLC purity 95%.

4-(2-Chloro-7-ethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)morpholine (41). Compound **41** was prepared from **16** to give an off-white solid, according to the procedure described for **30**, using iodoethane. MS (ESI): m/z 267 [M + H].

4-(7-Ethyl-4-morpholino-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)-aniline (43). Compound **43** was prepared from **41** to give an off-white solid, according to the procedure described for **42**, using 4-aminophenylboronic acid pinacol ester. MS (ESI): m/z 324 [M + H].

4-({[4-(7-Ethyl-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)phenyl]carbamoyl}amino)benzoic Acid (45). Step 1. To a solution of 4-(7-ethyl-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)aniline (**43**) (1.72 g, 5.3 mmol) in CH_2Cl_2 (50 mL) was added methyl 4-isocyanatobenzoate (1.13 g, 6.4 mmol), and the resulting mixture was stirred at room temperature overnight. The resulting solid was collected by filtration and washed with CH_2Cl_2 to give methyl 4-({[4-(7-ethyl-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)phenyl]carbamoyl}amino)benzoate as an off-white solid (1.81 g, 68% yield). MS (ESI): m/z 501 [M + H].

Step 2. To a solution of methyl 4-({[4-(7-ethyl-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)phenyl]carbamoyl}amino)-benzoate (1.81 g, 3.6 mmol) in MeOH (50 mL) and THF (20 mL)

was added 1 N NaOH aqueous solution (18 mL), and the mixture was heated at 70 °C for 3 h. The mixture was cooled to room temperature and concentrated. The residue was treated with water and acidified to pH 3−4 by addition of 1 N HCl. The resulting solid was collected by filtration, washed with water, and dried in air to give **45** as an off-white solid (1.65 g, 94% yield). MS (ESI): m/z 487 [M + H].

***N*-[2-(Dimethylamino)ethyl]-4-({[4-(7-ethyl-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)phenyl]carbamoyl}amino)benzamide (50).** Compound **50** was prepared from **45** to give an off-white solid (54% yield), according to the procedure described for **46**, using *N*,*N*-dimethylethylenediamine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.40 (t, 3H, J = 7.3 Hz), 2.17 (s, 6H), 2.39 (t, 2H, J = 6.8 Hz), 3.33 (m, 2H), 3.77 (t, 4H, J = 4.8 Hz), 3.94 (t, 4H, J = 4.8 Hz), 4.27 (q, 2H, J = 7.3 Hz), 6.66 (d, 1H, J = 3.8 Hz), 7.33 (d, 1H, J = 3.8 Hz), 7.53 (d, 2H, J = 8.6 Hz), 7.56 (d, 2H, J = 8.6 Hz), 7.79 (d, 2H, J = 8.6 Hz), 8.23 (t, 1H, J = 5.5 Hz), 8.34 (d, 2H, J = 8.6 Hz), 8.98 (br, 2H). MS (ESI): m/z 557 [M + H]. HRMS calcd for $C_{30}H_{36}N_8O_3$ [M + H] 557.2983, obsd 557.2983. HPLC purity 98.6%.

1-[4-(7-Ethyl-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)phenyl]-3-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}urea (51). Compound **51** was prepared from **45** to give an off-white solid (35% yield), according to the procedure described for **46**, using 1-methylpiperazine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.40 (t, 3H, J = 7.1 Hz), 2.20 (s, 3H), 2.31 (br, 4H), 3.49 (br, 4H), 3.77 (t, 4H, J = 5.0 Hz), 3.94 (t, 4H, J = 5.0 Hz), 4.27 (q, 2H, J = 7.1 Hz), 6.66 (d, 1H, J = 3.8 Hz), 7.32 (d, 1H, J = 3.8 Hz), 7.34 (d, 2H, J = 8.8 Hz), 7.53 (d, 2H, J = 8.8 Hz), 7.56 (d, 2H, J = 8.8 Hz), 8.34 (d, 2H, J = 8.8 Hz), 8.93 (s, 1H), 8.94 (s, 1H). MS (ESI): m/z 569 [M + H]. HRMS calcd for $C_{31}H_{36}N_8O_3$ [M + H] 569.2983, obsd 569.2983. HPLC purity 99.6%.

1-[4-(7-Ethyl-4-morpholin-4-yl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-yl)phenyl]-3-[4-(piperazin-1-ylcarbonyl)phenyl]urea (52). Compound **52** was prepared from **45** to give an off-white solid (46% yield), according to the procedure described for **46**, using piperazine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.40 (t, 3H, J = 7.1 Hz), 2.68 (br, 4H), 3.41 (br, 4H), 3.78 (t, 4H, J = 5.0 Hz), 3.94 (t, 4H, J = 5.0 Hz), 4.27 (q, 2H, J = 7.1 Hz), 6.66 (d, 1H, J = 3.5 Hz), 7.32 (d, 1H, J = 3.5 Hz), 7.33 (d, 2H, J = 8.6 Hz), 7.53 (d, 2H, J = 8.6 Hz), 7.56 (d, 2H, J = 8.6 Hz), 8.34 (d, 2H, J = 8.6 Hz), 8.98 (s, 1H), 9.01 (s, 1H). MS (ESI): m/z 555 [M + H]. HRMS calcd for $C_{30}H_{34}N_8O_3$ [M + H] 555.2827, obsd 555.2830. HPLC purity 95.2%.

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