Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

Trisubstituted Pyrimidines as Efficacious and Fast-Acting Antimalarials

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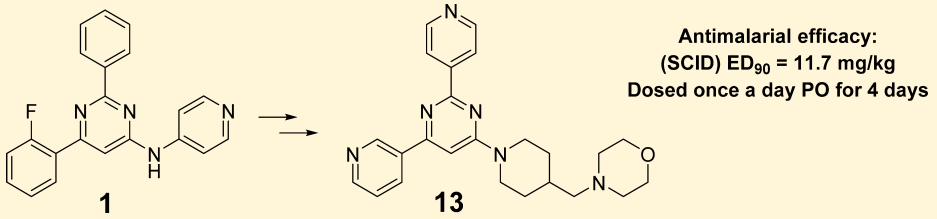
Supporting Information



ABSTRACT: In this paper we describe the optimization of a phenotypic hit against *Plasmodium falciparum*, based on a trisubstituted pyrimidine scaffold. This led to compounds with good pharmacokinetics and oral activity in a *P. berghei* mouse model of malaria. The most promising compound (**13**) showed a reduction in parasitemia of 96% when dosed at 30 mg/kg orally once a day for 4 days in the *P. berghei* mouse model of malaria. It also demonstrated a rapid rate of clearance of the erythrocytic stage of *P. falciparum* in the SCID mouse model with an ED_{90} of 11.7 mg/kg when dosed orally. Unfortunately, the compound is a potent inhibitor of cytochrome P450 enzymes, probably due to a 4-pyridyl substituent. Nevertheless, this is a lead molecule with a potentially useful antimalarial profile, which could either be further optimized or be used for target hunting.

INTRODUCTION

Malaria is a devastating parasitic disease causing widespread mortality and morbidity across many parts of the developing world. Human malaria is caused by five *Plasmodium* species: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*. *P. falciparum* causes the most mortality and is found in high levels in Africa, whereas *P. vivax* causes the most morbidity and is more commonly found across Asia and the Americas.[1] In 2013, there were an estimated 198 million cases of malaria worldwide and 584 000 deaths, of which 453 000 were of children under 5 years, with 90% of all malaria deaths in the African region.[2] Many medicines for the treatment of malaria such as chloroquine and pyrimethamine are failing due to increasing development of resistance. Furthermore, there are now cases of drug resistance to artemisinin-based combination therapies (ACTs), which are the mainstays for the World Health Organization (WHO) campaign against malaria.[3] Currently, primaquine is the only drug in general use for radical cure of malaria due to *P. vivax*, preventing relapse, but this medicine has a prolonged dosing schedule and is toxic to individuals with glucose 6-phosphate deficiency.[4] Therefore, new therapies for both treatment and prevention of this deadly disease across all of its life cycle stages are urgently needed. Efforts from

Received: January 7, 2016
Published: June 17, 2016

DOI: 10.1021/acs.jmedchem.6b00028
J. Med. Chem. 2016, 59, 6101−6120

academic groups and pharmaceutical companies to identify novel antimalarials are now beginning to bear fruit as novel therapies for the treatment of malaria are in clinical trials.[1] However, the discovery of potential new antimalarials remains vital, given the high attrition rates in clinical development,[5] the propensity of the parasite to develop resistance, and the need for additional indications (such as transmission blocking, chemoprevention, and radical cure of vivax malaria).[6] Here, we report the design, synthesis, and biological evaluation of fast-acting and highly efficacious antimalarials, based on trisubstituted pyrimidines, which were discovered using a whole cell-based screening approach.

RESULTS AND DISCUSSION

Project Initiation. A drug discovery program for the identification of novel antimalarials was initiated with the high throughput phenotypic screening (HTS) of an in-house library of protein kinase scaffolds (4731 compounds).[7] This effort identified multiple structurally diverse chemical series that blocked asexual blood stage parasite viability, as measured by a SYBR green assay.[8,9] In this paper, we describe a chemistry program based around one of these series, a trisubstituted pyrimidine, which displayed chemical tractability, nanomolar potency against *P. falciparum* cell line 3D7, and excellent selectivity over a mammalian cell line MRC-5 (Table 1). An initial example of this series was inactive against a panel of mammalian kinases up to a concentration of 10 μM.

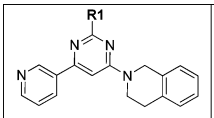
Table 1. Hit Series Identified from Phenotypic Screening of Kinase-like Library

Series ID	MMV02	
Compound ID	1	
EC_{50} vs. *P. falciparum* 3D7 (μM)	0.25	
EC_{50} vs. MRC5 (μM)	31	
clogP	3.2	
MWT	343	
No. of examples with EC_{50} <1 μM	3	

Lead Identification. The initial hit from the screen, **1**, was followed up by hit expansion through commercially available analogues. Systematic changes of functional groups at R^1, R^2, and R^3 were carried out to try to improve potency and physicochemical properties. Analogues of our original screening hit (**1**) were also identified from published data from GSK[10] and Novartis[9] (Figure 1). Following resynthesis and screening in-house, compound **2** (reported by GSK and Novartis) provided a suitable chemical start point for further synthetic modifications. However, due to poor solubility (5 μM), compound **2** was not progressed any further than assessment at the in vitro (cellular) level for potency and absorption, distribution, metabolism, excretion, and toxicology (ADMET). Analogue design was then directed toward improving potency and solubility and reducing the number of aromatic rings, which can have a beneficial impact on overall development characteristics including solubility.[11,12] Compound **2** has a high degree of planarity, so we sought further improvement by increasing the proportion of sp^3 to sp^2 carbon atoms, which is reported to increase the solubility.[13]

We were concerned about the inhibition of cytochrome P450 isoform CYP3A4, which we believed to be due to the 4-pyridyl group (see later for further discussion). Initial attempts to replace the 4-pyridyl functional group at R^1 resulted in a significant loss of antimalarial activity (Table 2). Removal of the

Table 2. Modifications at R^1 [a]

	R^1	*Pf* (3D7) EC_{50}(μM)	MRC5 EC_{50}(μM)
2		0.1	14
3		3.1	30
4		3.4	49
5		6.5	24

[a]All parasite assays were run in duplicate.

pyridine nitrogen at R^1 or simply moving the nitrogen from the 4- to the 3-position resulted in >30-fold drop in potency. In addition, replacing the 4-pyridyl group with a morpholine group reduced potency by almost 60-fold, highlighting the importance of the pyridine nitrogen and suggesting that the vector of the lone pair donor was also crucial for activity. We decided therefore to investigate variations at R^2 and R^3 for improvements in potency, which would render the interaction with the 4-pyridyl less critical.

Optimization of R^2. Removal of the tetrahydroisoquinoline (**2**) and replacement with an amino group (**6**) gave a 100-fold drop in activity, indicating the tetrahydroisoquinoline group has a significant effect on the potency. Replacement of the tetrahydroisoquinoline moiety of compound **2** with *N*-

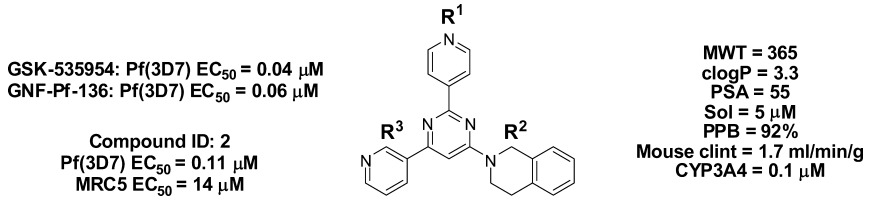
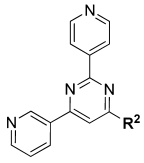
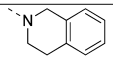
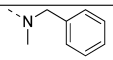
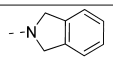
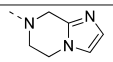
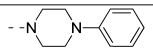
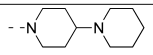
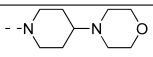
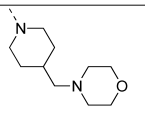
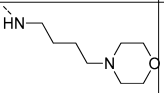
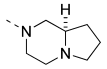


Figure 1. Published analogue compound **2**, codes TCMDC-125419 (GSK) and GNF-Pf-1034/GNF-Pf-1447 (Novartis).

DOI: 10.1021/acs.jmedchem.6b00028
J. Med. Chem. 2016, 59, 6101−6120

Table 3. Modifications at R^2 [a]

	R^2	Pf (3D7) EC_{50} (μM)	MRC5 EC_{50} (μM)	MWT	clogP[a]	Mouse microsomal Clint (ml/min/g)	Sol[b] (μM)
2		0.1	14	365	3.3	1.7	5
6		17	50	249	1.7	ND	ND
7		1.4	28	353	3.4	ND	ND
8		50	50	351	3.0	ND	ND
9		1.7	24	355	2.2	ND	ND
10		0.3	50	394	3.4	1.4	36
11		0.1	15	400	3.3	3.9	56
12		0.3	36	402	2.3	1.2	>248
13		0.3	50	416	2.6	3	106
14		0.3	ND	390	2.1	13	>100
15		0.3	14	358	2.6	7.0	>100

[a]clogP was calculated using StarDrop from Optibrium. Sol is solubility in water for the free base.

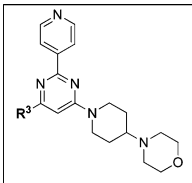
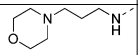
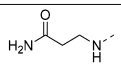
methylbenzylamine (**7**) resulted in a 10-fold loss of potency (Table 3), possibly suggesting that a degree of conformational restraint was necessary. Contracting the aliphatic ring size to a five-membered ring (**8**) led to a complete loss in activity. Replacing the phenyl ring in **2** with an imidazole (**9**) gave a 10-fold drop in activity (EC_{50} = 1.7 μM). Interestingly, activity was retained when the phenyl was attached to a piperazine rather than being directly fused onto the piperidine ring (**10**, EC_{50} = 0.3 μM), despite the different vector compared to compound **2**.

Further work was undertaken to remove an aromatic ring, with a key aim being to increase solubility and improve the potential for clinical development. Replacing the phenyl ring found in **10** with piperidine gave a compound equipotent to the starting point (**11**, EC_{50} = 0.1 μM). This compound had marginally improved aqueous solubility (56 μM, measured as the free base) and retained reasonably low microsomal turnover. Replacing the "terminal" piperidine with a morpholine gave a compound with similar activity (**12**, EC_{50} = 0.3 μM) but with a significantly increased solubility (>100 μM), reduced clogP, and low microsomal turnover. It was also possible to add a flexible linker between the piperidine and the morpholine (**13**) with only a minimal effect on potency (EC_{50} = 0.3 μM) and retaining low microsomal turnover but with a similar solubility (44 μM). It was possible to replace the piperidine of **13** with an alkyl linker to give **14**. This compound had the same activity as **13** (EC_{50} = 0.3 μM), but despite a lower clogP, showed a significantly higher microsomal turnover. Finally, a bicyclic aliphatic system, **15**, also showed similar activity (EC_{50} = 0.3 μM) and good solubility (>100 μM) but increased microsomal turnover. In summary, it is possible to reduce the number of aromatic rings and increase the proportion of sp^3 carbon atoms which improves solubility and clogP without compromising potency and microsomal turnover.

Optimization of R^3. Replacement of the planar aromatic 3-pyridyl unit at the R^3 position with aliphatic substituents was investigated to both reduce the aromatic ring count and increase the sp^3 nature.[13] Small aliphatic groups such as the cyclopropyl group of **16** were not tolerated and resulted in around a 30-fold drop in potency (Table 4). Furthermore, replacement of the 3-pyridyl by the flexible aminoalkylmorpho-

DOI: 10.1021/acs.jmedchem.6b00028
J. Med. Chem. 2016, 59, 6101−6120

Table 4. Modifications at R^3

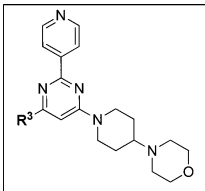
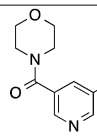
	R^3	Pf (3D7) EC_{50} (μM)	MRC5 EC_{50} (μM)	MWT	clogP
12		0.3	36	402	2.3
16		10	ND	365	2.7
17		32	ND	467	2.1
18		>50	ND	411	1.1
19		>50	ND	410	2.0
20		16	ND	420	3.0
21		4.3	ND	419	3.4
22		3.3	ND	419	3.4
23		4.3	ND	403	2.5

line (**17**) or aminoalkylamide (**18**) resulted in >90-fold drop in potency. In addition, the morpholine moiety **19** was completely inactive. Further examples are given in the Supporting Information. In summary, attempts to replace R^3 with an aliphatic group or heteroaromatics such as the oxazole (**20**) were unsuccessful. Attempts to replace the pyridyl nitrogen atom with groups such as 3-fluorophenyl (**21**) or 4-fluorophenyl (**22**) lost around 10-fold activity and led to an increase in clogP. Furthermore, the addition of another nitrogen atom into the pyridyl unit to afford the pyrimidine **23** was less well tolerated (10-fold loss in potency). In summary, despite extensive investigation, we were unable to find a suitable replacement for the 3-pyridyl moiety at R^3, and further changes were focused on different substitutions on the 3-pyridyl ring to improve activity and physicochemical properties (Table 5).

A variety of modifications were made at different positions around the 3-pyridyl ring. Small electron withdrawing and electron donating substituents *meta* to pyridyl nitrogen were tolerated (methoxy, **24**; nitrile, **25**; fluoro, **26**). However, the aminomethyl analogue **27** had a 10-fold loss in activity, and the morpholine amide **28** was essentially inactive.

Small functional groups *ortho* to the pyridine nitrogen such as amino (**29**) or methoxy (**30**) were tolerated, with only a 3- to 6-fold loss in activity compared to **12**. However, larger groups at this position on the 3-pyridyl moiety, such as the methylamide (**31**) or morpholine (**32**), reduced activity by >10-fold. Furthermore, moving the methoxy from the *meta*-position of the pyridine (**24**) to the *para*-position (**33**) caused a 20-fold reduction in potency compared to **12**. In summary, there appear to be limited opportunities for synthetic

Table 5. Modifications at R^3

	R^3	Pf (3D7) EC_{50} (μM)	MRC5 EC_{50} (μM)	MWT	clogP
12		0.3	36	402	2.3
24		0.1	ND	432	2.3
25		0.4	ND	427	2.2
26		0.5	ND	420	2.6
27		3.1	ND	431	1.4
28		>50	ND	515	1.8
29		1.1	ND	417	1.9
30		1.8	ND	432	2.3
31		28	ND	459	1.7
32		4.8	ND	487	2.5
33		19	ND	432	2.3

modification to enhance activity at the R^3 position, based on the pyridyl moiety.

In Vivo Efficacy. Compounds **12** and **13** were selected for in vivo pharmacokinetic (PK) and efficacy studies, based on their overall profile of properties. Both compounds displayed suitable predicted physicochemical properties consistent with that of an oral drug. In addition, **12** and **13** demonstrated submicromolar potency in vitro and good aqueous solubility, were reasonably stable when incubated with mouse liver microsomes, and displayed low plasma protein binding. Unfortunately, **13** displayed some binding to the hERG ion channel (Table 6).

In vivo PK studies with **12** showed rapid absorption after oral administration (10 mg/kg) but with limited exposure and a short half-life, whereas **13** displayed an improved half-life with a 7-fold increase in AUC. Subsequently, in vivo efficacy experiments were carried out and mice were subjected to oral dosing of compounds **12** and **13** up to 30 mg/kg once a day for

DOI: 10.1021/acs.jmedchem.6b00028
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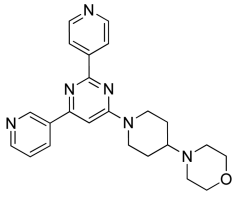
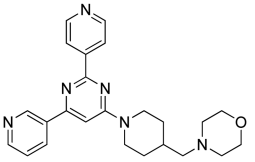
Table 6. In Vitro and in Vivo Profile of Key Compounds

		
Compound	**12**	**13**
Pf (3D7) EC_{50} (μM)	0.34	0.27
Pf (K1) EC_{50} (μM)[a]	ND	0.28
MRC5 EC_{50} (μM)	36	50
MWT	402	416
logP	2.3	2.5
PSA	67.3	67.3
Mouse microsomal Clint (ml/min/g)	1.2	3
Kinetic Solubility (μM)	>248	106
PPB (%)	59	78
CYP inhibition IC_{50} (μM)	1A2, 93; 2C9, 1.9; 2C19, 6.3; 2D6, 0.7; 3A4, 0.1.	1A2, >100; 2C9, 3.5; 2C19, 38; 2D6, 0.7; 3A4, 0.1.
hERG K^+ ion channel (μM)	ND	6.9
Intravenous PK (3 mg/kg)		
Clb (mL/min/kg)	39	N.D.
Vdss (L/kg)	2.7	N.D.
$T_{1/2}$ (h)	1.3	N.D.
Oral PK Parameters (10 mg/kg)		
C_{Max} (ng/mL)	264	1094
T_{Max} (h)	0.5	2
Oral AUC ($_{0\text{-}8}$) ng.min/mL	45,000	306,000
F (%)	18	ND
In vivo efficacy in Peters' test[b]	72% reduction in parasitaemia (4 x 30 mg/kg, qd, PO)	96% reduction in parasitaemia (4 x 30 mg/kg, qd, PO)

[a] *Pf*(K1) is a chloroquine and pyrimethamine resistant strain of *P. falciparum*. [b] Pharmacokinetic and efficacy studies were carried out using compound **12** as the HCl salt and compound **13** as the fumarate salt.

4 consecutive days using the *P. berghei* rodent model of infection (Peters' test, Table 6). Compound **13** displayed superior efficacy compared with **12** with a 96% reduction in parasitemia (compared to 72% for **12**), when dosed at 30 mg/kg, q.d., po. The early lead criteria, stipulated by MMV, required compounds to display both suppression of parasitemia and an ED_{50} < 50 mg/kg under this protocol.[14] However, we were unable to obtain complete cures in the rodent model for either compound **12** or **13**. For efficacy experiments with compound **12**, all mice were euthanized by day 14. For compound **13**, all mice were euthanized by day 11.

Compound **13** was also evaluated in vivo against *P. falciparum* parasites grown in the peripheral blood of NODscidIL2Rγ^{null} mice (SCID), engrafted with human erythrocytes.[15] Three days after infection, mice were dosed orally once a day with **13** for 4 days at concentrations up to 100 mg/kg (Figure 2a). The ED_{90} measured at day 7 = 11.7 mg/kg, and its equivalent estimated daily exposure in blood AUC_{ED90} = 1.4 μg·h/mL. In vivo there was a rapid reduction of parasitemia at doses of ≥20 mg/kg or >7.96 μg·h mL^{-1} day^{-1} in blood. With doses of ≥30 mg/kg, the parasites levels were reduced below detection limits within 2 days. The rate of parasite clearance in vivo was at least as fast as the artemisinins,[16] and only pyknotic parasites are observed in peripheral blood of mice 48 h after treatment at 100 mg/kg (Figure 2c). Interestingly, the in vitro parasite reduction ratio (PRR)

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J. Med. Chem. 2016, 59, 6101−6120

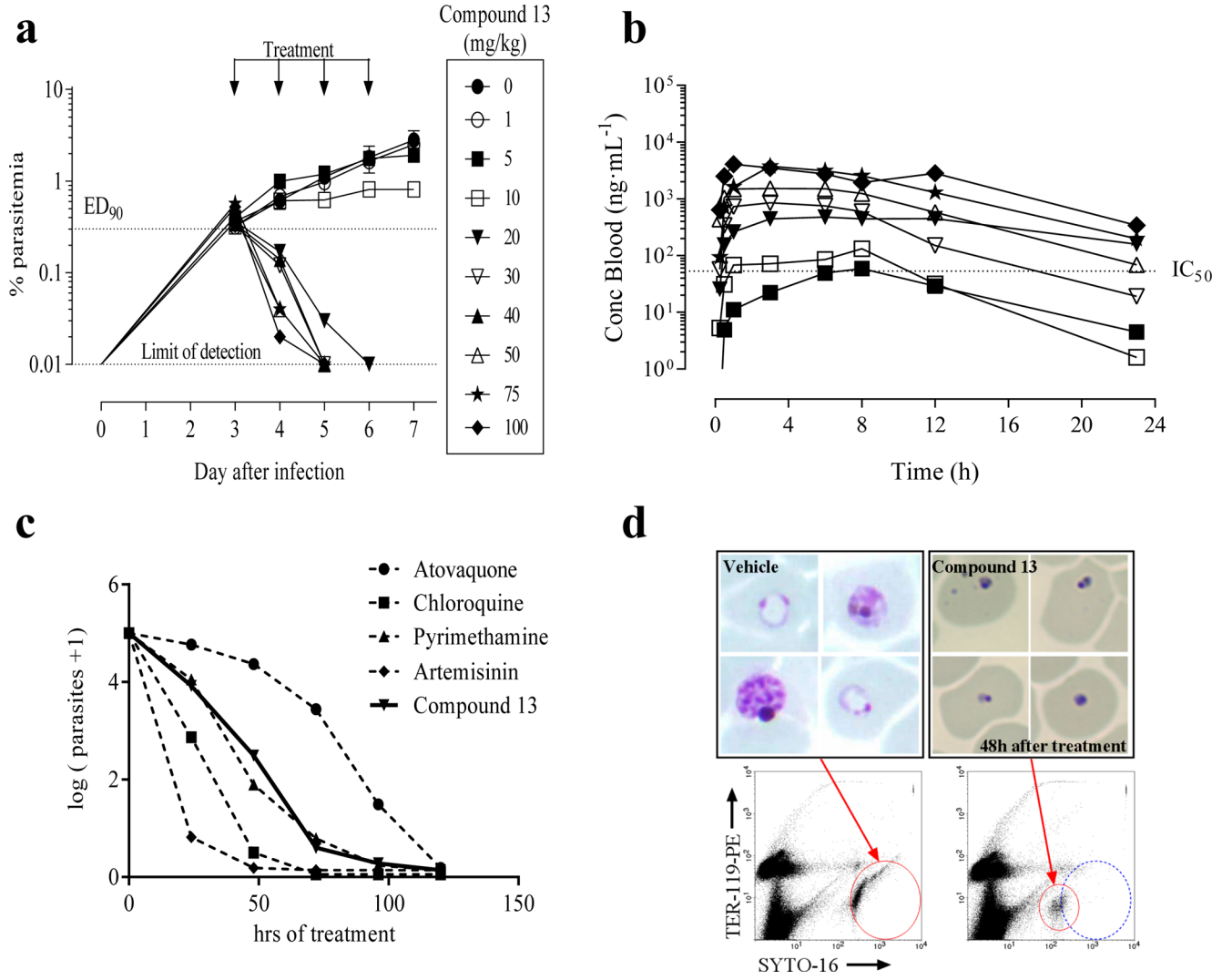


Figure 2. (a) In vivo efficacy data for compound **13** in *P. falciparum* infected SCID mice. (b) Levels of compound **13** in blood of the mice of the efficacy experiment during 23 h after the first oral dose. The symbols represent the same individuals depicted in plot a. (c) In vitro PRR data for compound **13** when parasites were treated at 10 × EC_{50}. Comparator data for other standard drugs are included for reference (data previously reported[17]). Compound **13** showed a similar rate of kill to pyrimethamine. (d) Comparison of morphology of parasitized human RBC in vehicle and compound **13** treated mice. Erythrocytes with only remnants of parasites showing nuclear condensation were seen following 2-day treatment with compound **13**. Compound dosed as the fumarate salt.

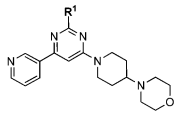
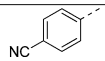
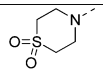
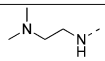
assay[17] identified **13** as a compound with a moderate rate of killing, displaying 99.9% clearance of parasites in 52 h, when tested at 10 × EC_{50} (Figure 2b). It is possible that the PRR assay would show a faster killing rate at higher concentrations of compound, more in-line with what is seen in vivo.

To assess the mode of action, given that the compound contained a potential heme binding moiety in the 4-pyridyl, the ability of compound **13** to block hemozoin (β-hematin) formation was also tested. It displayed relatively comparable activity to chloroquine in this assay (27 μM for **13** vs 6.6 μM for chloroquine). It was not known if the primary mode of action is through the same mechanism of action as chloroquine. However, when assayed against the chloroquine/pyrimethamine resistant (K1) lines, compound **13** displayed similar activity to sensitive cell lines, so it has a different profile to chloroquine.

Reducing Affinity for Human CYP Isoforms. Although the antimalarial properties of the compound series had been demonstrated in mouse models of malaria, further development of the series required compounds that had markedly reduced inhibition of the major CYP enzymes. Subsequent elaboration of **13** focused on reducing inhibition of human CYP isoforms 3A4 and 2D6. Previous work had not been successful in distinguishing the antimalarial activity and the inhibition of human CYP isoforms (Table 1), thought to be due to the 4-pyridyl group at the R^1 position. Therefore, two approaches were investigated to reduce CYP inhibition. One approach involved replacement of the 4-pyridyl unit with functional groups that could have similar steric and H-bond acceptor properties (Table 7). In parallel, the possibility of modifying the 4-pyridyl unit with the addition of functional groups adjacent to the pyridine nitrogen was also investigated, which could potentially reduce binding to human CYP isoforms while retaining suitable affinity for the unknown target of interest (Table 8). The R^2 and R^3 positions were fixed with piperidine-morpholine and 3-pyridyl, respectively, to use as a reference point for changes in activity and with the view that if it were possible to optimize R^1, this should also work with other R^2 and

DOI: 10.1021/acs.jmedchem.6b00028
J. Med. Chem. 2016, 59, 6101−6120

Table 7. Modifications at R^1

	R^1	Pf (3D7) EC_{50} (μM)	MRC5 EC_{50} (μM)	MWT	clogP
12		0.3	35.92	402	2.3
34		2.1	ND	426	3.1
35		5.3	ND	350	1.6
36		49	ND	458	1.3
37		24	ND	341	1.7
38		50	ND	423	1.6
39		30	ND	411	2.6

R^3 substituents (e.g., as found in **13**). The key molecules prepared are summarized in the main text. Additional molecules prepared are presented in the Supporting Information.

Optimization of R^1. The initial focus was on placing a hydrogen bond acceptor (HBA) at the 4-position of the phenyl ring to replace the 4-pyridyl moiety at the R^1 position (Table 7). Several nitrile derivatives were prepared. The 4-cyanophenyl (**34**) gave a 7-fold reduction in potency (EC_{50} = 2.1 μM) from **12** (EC_{50} = 0.3 μM). This would place the HBA further from the pyrimidine than the pyridine nitrogen in **12**. Therefore, it was decided to attach the nitrile directly onto the pyrimidine ring (**35**), which gave a similar level of potency (EC_{50} = 5.3 μM) to the 4-cyanophenyl analogue. Other HBAs such as sulfones (**36**) gave significantly reduced activity (EC_{50} = 49 μM). Direct attachment of a hydroxyl to the pyrimidine ring (**37**) also failed to increase activity (EC_{50} = 24 μM), although this may be in a different tautomeric form. Amide **38** was also inactive (EC_{50} = 50 μM). Finally, basic groups were investigated to determine if there was an interaction with an acidic group on the protein. None of these were active (e.g., **39**, EC_{50} = 30 μM).

The original 4-pyridyl moiety at R^1 was then revisited with a focus on reducing binding to the human CYP450 isoforms with close analogues incorporating blocking groups adjacent to the pyridine nitrogen, to reduce the interaction with the heme iron (Table 8). Addition of two methyl groups in the 3- and 5-positions significantly reduced CYP inhibition across all five CYPs investigated (**40**), which confirmed involvement of the parent 4-pyridyl moiety. However, there was a 5-fold drop in activity (EC_{50} = 1.5 μM). Interestingly having just one methyl group in the 3-position (**41**, EC_{50} = 17 μM) led to a further 10-fold drop in potency compared to disubstitution. Other groups in the 3-position which would alter the electronics of the pyridine nitrogen were also inactive (e.g., the CF_3 group **42**, EC_{50} = 50 μM). The effects of both electron-donating and electron-withdrawing substituents (**43** and **44**) were also investigated, where both gave a 5- to 10-fold reduction in potency compared to the substituted pyridine **12**. Changing the heterocycle to a pyrimidine, pyridone, or pyrazole (**45**–**47**) also led to a reduction in activity. Therefore, despite a variety of variations on the R^1 position, all modifications investigated led to a marked decrease in potency.

CONCLUDING REMARKS AND FUTURE WORK

Compounds **12** and **13** both display suitable physicochemical properties for an oral drug lead, good cellular activity in vitro against *P. falciparum* parasites, and good selectivity in a mammalian counterscreen. Compound **13** also demonstrated excellent oral efficacy in vivo with a 96% reduction in levels of parasitemia (*P. berghei*, 4 × 30 mg/kg, q.d., po) and a fast kill rate in the *P. falciparum* SCID mouse model. Compound **13** was also further profiled in the liver-stage schizont assay (EC_{50} > 10 μM),[18] and in a stage IV/V gametocyte assay (EC_{50} = 2.4 μM).[19] Initial infection with malaria occurs when *Plasmodium* sporozites injected by the mosquito invade the liver cells. The parasites then undergo a liver-stage life cycle that involves formation of liver schizonts. Compounds that can prevent liver schizont formation may have potential for chemoprevention. The data for compound **13** suggest that this is not likely to have chemopreventative activity. Blood-stage infection gives rise to the clinical symptoms of malaria. Some of the parasites involved in blood-stage infection differentiate into gametocytes, which are the form of the parasite that can infect a mosquito, completing the life cycle. Compounds that kill the gametocytes may be able to block transmission of the parasite to mosquitos. The data for compound **13** suggest that these compounds may have transmission blocking activity. Additional studies would be required to assess this in detail.

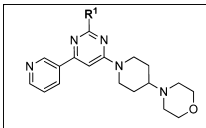
Unfortunately, further development is hampered by the potent inhibition of major CYP enzymes, where involvement of the 4-pyridyl group has been demonstrated. Focus has now moved toward the identification of the biological target of **13** to see if this information can be used to scaffold-hop to compounds that do not inhibit human cytochrome P450s. Given the rapid development of parasite drug resistance to known antimalarials, the identification of an essential and druggable target associated with the rapid clearance of *P. falciparum* parasites would be significant.

CHEMISTRY

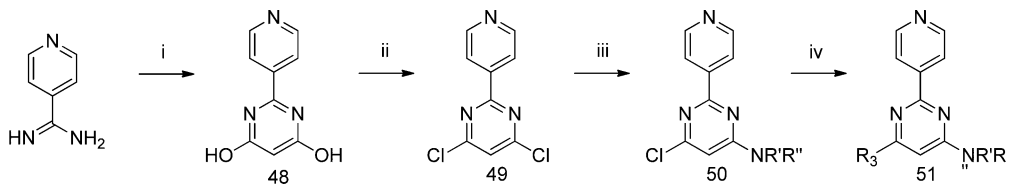
Synthesis of 4-pyridylpyrimidines via a modified literature procedure[20] was initially undertaken by condensation of 4-pyridylamidine with dimethyl malonate using sodium methoxide as a base and refluxing in methanol for up to 3 days to afford 2-(pyridin-4-yl)pyrimidine-4,6-diol **48** in 55% yield. However, by employing experiment design software Modde and transferring the process to a microwave reactor, we were able to rapidly optimize the reaction conditions, improving the reaction yield to 70% and shortening the reaction time from 3 days to 1 h (Scheme 1). Chlorination of diol **48** with phosphorus trichloride at 90 °C gave rise to 4,6-dichloro-2-(pyridin-4-yl)pyrimidine **49** with 58% yield. Nucleophilic displacement of one chlorine atom by an amine followed by a Suzuki cross-coupling reaction with a boronic acid or ester afforded pyrimidines **51**, allowing us to investigate substituents at the R^2 and R^3 positions.

DOI: 10.1021/acs.jmedchem.6b00028
J. Med. Chem. 2016, 59, 6101−6120

Table 8. Modifications at R^1

	R^1	*Pf* (3D7) EC_{50} (μM)	MRC5 EC_{50} (μM)	MWT	clogP	CYP inhibition IC_{50} (μM)
12		0.3	36	402	2.3	**1A2** 93 **2C9** 1.9 **2C19** 6.3 **2D6** 0.7 **3A4** 0.1
40		1.5	ND	430	3.1	**1A2** >100 **2C9** 82 **2C19** 50 **2D6** 50 **3A4** 40
41		17	37	416	2.7	ND
42		50	ND	470	3.4	ND
43		1.6	ND	416	2.7	ND
44		2.8	ND	420	2.6	ND
45		21	ND	418	2.1	ND
46		4.1	ND	405	2.4	ND
47		4.5	ND	403	2.5	ND

Scheme 1[a]



[a](i) Dimethyl malonate (DMM), NaOMe, MeOH, reflux, 3 days, 55%; or DMM, NaOMe, *N*-methylpyrrolidinone, microwave, 1 h, 150 °C, 70%; (ii) $POCl_3$, 90°C, 58%; (iii) amine, DIPEA, THF, rt ; (iv) boronic ester/acid, K_3PO_4, $Pd(PPh_3)_4$, DMF/water, microwave, 120 °C, 20 min.

The synthetic route outlined in Scheme 1 is not amenable to explore the influence of changes at the R^1 position on antimalarial activity. Therefore, a number of synthetic routes that allowed the introduction of a diverse array of substituents

DOI: 10.1021/acs.jmedchem.6b00028
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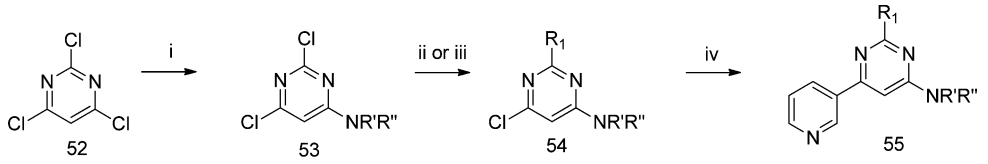
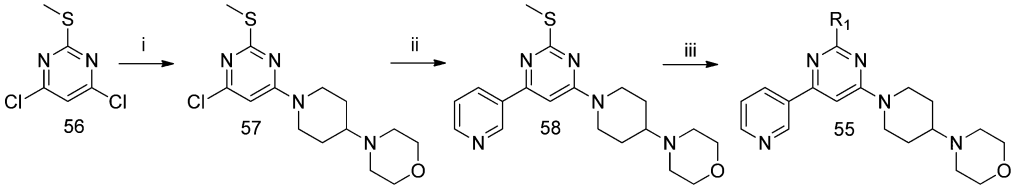
Scheme 2[a]



[a](i) Amine, Et_3N, ethanol, −5 °C, 4 h; (ii) boronic acid/ester, 2 M aq Na_2CO_3, $Pd(PPh_3)_4$, 1,4-dioxane/water, microwave at 120 °C, 20 min; (iii) amine, Et_3N, acetonitrile, 40−70°C; (iv) 3-pyridyl boronic acid, K_3PO_4, $Pd(PPh_3)_4$,DMF/water 3/1, microwave at 120 °C, 20 min.

Scheme 3[a]



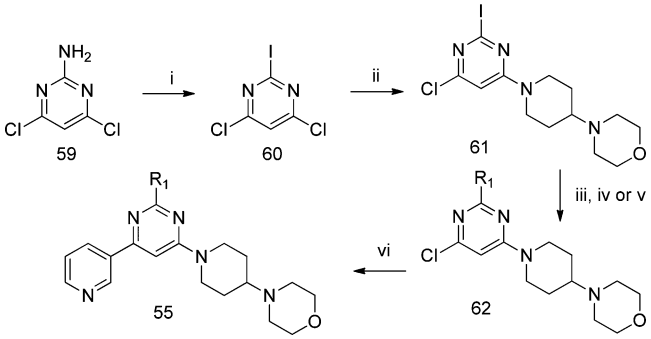
[a](i) Amine, Et_3N, ethanol, rt, 16 h, 56%; (ii) 3-pyridylboronic acid, K_3PO_4, $Pd(PPh_3)_4$, 1,4-dioxane/water 3/1, microwave at 130 °C, 20 min, 96%; (iii) boronic acid, thiophene-2-carbonyloxycopper, $Pd(PPh_3)_4$, 1,4-dioxane or THF, microwave at 130 °C, 1 h or 85 °C, 18 h.

at C-2 position on the pyrimidine ring were explored. First, starting from commercially available 2,4,6-trichloropyrimidine **52**, nucleophilic displacement with the corresponding amine (1 equiv) at −5 °C in ethanol gave rise to **53**, with substitution at the 4-position as the major product, together with substitution at the 2-position as the minor product (Scheme 2).

The two reaction products could be easily separated by column chromatography. Suzuki cross-coupling reaction at the 2-position allowed the introduction of aromatic R^1 substituents using commercially available boronic esters or acids. Alternatively, amino derivatives at C-2 were prepared by heating **53** in acetonitrile in the presence of the corresponding amine. Finally, the desired trisubstituted pyrimidines **55** were obtained by Suzuki cross-coupling with 3-pyridylboronic acid. An alternative route allowing the introduction of the R^1 substituent at C-2 as the last step is shown in Scheme 3. Starting from commercially available 4,6-dichloro-2-methylsulfanylpyrimidine **56**, reaction with 4-(4-piperidyl)morpholine in acetonitrile at room temperature gave rise to **57** in 56% yield. As above, a Suzuki cross-coupling with 3-pyridylboronic acid led to **58** in excellent yield. Finally, the introduction of the R^1 substituent was carried out following the palladium-catalyzed, copper(I) thiophene-2-carboxylate (CuTC) mediated coupling of boronic acids with heteroaromatic thioethers to yield compounds of type **55**, reported by Liebeskind and Srogl.[21] However, this reaction is limited to boronic acids and the more commercially accessible boronic esters led to low yields or failed.

To expand the diversity of substituents at R^1 allowing a comprehensive SAR study, we developed the synthetic route outlined in Scheme 4. Iodination of commercially available 2-aminopyrimidine **59** was performed in good yield using *tert*-butyl nitrate and diiodomethane as previously described.[22] Subsequent selective displacement of one of the chlorine atoms on intermediate **60** with amines such as 4-(4-piperidyl)-morpholine was carried out to afford substituted pyrimidines as exemplified by **61**. Intermediate **61** proved to be a very versatile synthon, allowing the introduction of a diverse array of R^1 groups by a variety of synthetic methods. Pyrimidines bearing alkyl substituents were prepared by Sonogashira cross-coupling with a terminal alkyne followed by reduction of the resulting alkene. Aromatic and heteroaromatic substituents were

Scheme 4[a]



[a](i) CH_2I_2, *t*-BuONO, acetonitrile, 80 °C, 3 h 30 min, 64%; (ii) amine, Et_3N, ethanol, 0 °C, 3 h; (iii) acetylene, CuI, Et_3N, $Pd(PPh_3)_2Cl_2$, acetonitrile, rt, 18 h; (iv) amine, DIPEA, NMP, microwave at 200 °C, 15 min; (v) boronic acid/ester, 2 M aq Na_2CO_3, $Pd(PPh_3)_2Cl_2$, DME, microwave at 200 °C, 20 min; (vi) 3-pyridylboronic acid, K_3PO_4, $Pd(PPh_3)_4$, DMF, microwave at 120 °C, 20 min.

introduced at C-2 by coupling with boronic acids or esters with good selectivity, and nucleophilic displacements of iodine with amines and copper cyanide were also selective. The final step to obtain trisubstituted pyrimidine **55** from intermediate **62** was by Suzuki cross-coupling with 3-pyridylboronic acid.

EXPERIMENTAL SECTION

General. Reactions using microwave irradiation were carried out in a Biotage Initiator microwave. Normal phase TLC was carried out on precoated silica plates (Kieselgel 60 F_{254}, BDH) with visualization via UV light (UV 254/365 nm) and/or ninhydrin solution. Flash chromatography was performed using Combiflash Companion Rf (Teledyne ISCO) and prepacked silica gel columns purchased from Grace Davison Discovery Science or SiliCycle. Mass-directed preparative HPLC separations were performed using a Waters HPLC (2545 binary gradient pumps, 515 HPLC make-up pump, 2767 sample manager) connected to a Waters 2998 photodiode array and a Waters 3100 mass detector. Preparative HPLC separations were performed with a Gilson HPLC (321 pumps, 819 injection module, 215 liquid handler/injector) connected to a Gilson 155 UV/vis detector. On both intruments, HPLC chromatographic separations were conducted using Waters XBridge C18 columns, 19 mm × 100

DOI: 10.1021/acs.jmedchem.6b00028
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mm, 5 μm particle size, using 0.1% ammonia in water (solvent A) and acetonitrile (solvent B) as mobile phase. ^{1}H NMR and ^{19}F NMR spectra were recorded on a Bruker Avance DPX 500 spectrometer (^{1}H at 500.1 MHz, ^{13}C at 125 MHz, ^{19}F at 470.5 MHz) or a Bruker Avance DPX 300 (^{1}H at 300 MHz). Chemical shifts (δ) are expressed in ppm recorded using the residual solvent as the internal reference in all cases. Signal splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), or a combination thereof. Coupling constants (J) are quoted to the nearest 0.5 Hz. Low resolution electrospray (ES) mass spectra were recorded on a Bruker MicroTof mass spectrometer, run in positive mode. High resolution mass spectrometry (HRMS) was performed using a Bruker MicroTof mass spectrometer. LCMS analysis and chromatographic separation were conducted with a Bruker MicrOTOf mass spectrometer or an Agilent Technologies 1200 series HPLC connected to an Agilent Technologies 6130 quadrupole LC/MS, where both instruments were connected to an Agilent diode array detector. The column used was a Waters XBridge column (50 mm × 2.1 mm, 3.5 μm particle size) and the compounds were eluted with a gradient of 5−95% acetonitrile/water + 0.1% ammonia. All compounds for in vitro and in vivo experiments displayed >95% purity by LCMS. Unless otherwise stated herein reactions have not been optimized. Solvents and reagents were purchased from commercial suppliers and used without further purification. Dry solvents were purchased in Sure/Seal bottles stored over molecular sieves.

Synthetic Routes. See Schemes 1−4.

Preparation of Compounds. 2-(2,6-Di(pyridine-3-yl)-pyrimidin-4-yl)-1,2,3,4-tetrahydroisoquinoline (3). To a solution of 2,4,6-trichloropyrimidine (**52**) (1 g, 5.45 mmol) in ethanol (12 mL) at 0 °C, a solution of 1,2,3,4-tetrahydroisoquinoline (0.68 mL, 5.45 mmol) in ethanol (5 mL) was added dropwise followed by triethylamine (1.14 mL, 8.19 mmol). Reaction mixture was stirred at 0 °C for 1.5 h. Solvents were removed under vacuum, and the reaction crude was partitioned between DCM (150 mL) and a saturated aqueous solution of $NaHCO_3$ (2 × 100 mL). The organic phase was dried over $MgSO_4$, filtered, and solvents were removed under reduced pressure. The product was purified by column chromatography (25 g silica cartridge) using (A) hexane and (B) ethyl acetate as eluents and the following gradient: 3 min hold to 100% A, 10 min ramp to 40% B, 1 min hold to 40% B. Fractions containing pure product were pooled together and solvents were removed to obtain 2-(2,6-dichloropyrimidin-4-yl)-1,2,3,4-tetrahydroisoquinoline as a yellow solid (0.98 g, 64% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.22 (m, 4H), 6.49 (s, 1H), 4.76 (broad peak, 2H), 3.81 (broad peak, 4H), 3.01−2.99 (m, 2H); LRMS (ES^+) m/z 281 $[M + H]^+$.

To a stirred solution of 2-(2,6-dichloropyrimidin-4-yl)-1,2,3,4-tetrahydroisoquinoline (0.15 g, 0.54 mmol) and 3-pyridylboronic acid (0.15 g, 1.18 mmol) in 1,4-dioxane (4.5 mL), a solution of potassium phosphate (0.34 g, 1.61 mmol) in water (1.5 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then $Pd(PPh_3)_4$ (0.018 g, 0.02 mmol) was added. The reaction was heated at 120 °C under microwave irradiation for 30 min. The reaction crude was partitioned between DCM (2 × 50 mL) and saturated aqueous solution of $NaHCO_3$ (10 mL). The organics phase was dried over $MgSO_4$ before concentration to dryness. The product was purified by column chromatography (12 g silica cartridge) using (A) DCM and (B) 10% MeoH in DCM as eluents and the following gradient: 3 min hold to 100% A, 15 min ramp to 100% B, 3 min hold to 100% B. The fractions containing product were pooled together and solvents were removed to obtain **3** as an off-white solid (100 mg, 51% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (dd, 1H, J = 0.8, 2.1 Hz), 9.31 (dd, 1H, J = 0.7, 2.2 Hz), 8.82−8.79 (m, 1H), 8.72−8.70 (m, 2H), 8.49−8.47 (m, 1H), 7.47−7.41 (m, 2H), 7.29−7.24 (m, 4H), 6.92 (s, 1H), 4.95 (broad m, 2H), 4.07 (broad m, 4H), 3.07−3.04 (m, 2H); LRMS (ES^+) m/z 366 $[M + H]^+$.

4-(4-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-6-(pyridine-3-yl)-pyrimidin-2-yl)morpholine (5). To a solution of 2,4,6-trichloropyrimidine (**52**) (0.63 mL, 5.5 mmol) in ethanol (12 mL) at 0 °C, a solution of 1,2,3,4-tetrahydroisoquinoline (0.68 mL, 5.45 mmol) in ethanol (5 mL) was added dropwise followed by triethylamine (1.14 mL, 8.19 mmol). The white suspension was stirred at 0 °C for 3 h and then was allowed to reach room temperature. Morpholine (0.48 mL, 5.5 mmol) and acetonitrile (20 mL) were added to the reaction mixture. The clear suspension was stirred at 40 °C overnight. Solvents were removed under vacuum, and the reaction crude was partitioned between DCM (100 mL) and water (25 mL). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (25 mL), dried over $MgSO_4$, filtered, and solvents were removed under reduced pressure. The product was purified by column chromatography (24 g silica cartridge) using (A) hexane amd (B) ethyl acetate as eluents and the following gradient: 3 min hold to 100% A, 18 min ramp to 30% B, 2 min hold to 30% B. Fractions containing product were pooled together and solvents were removed to obtain 4-(4-chloro-6-(3,4-dihydroisoquinolin-2(1*H*)-yl)pyrimidin-2-yl)morpholine as a white wax (1.25 g, 69% yield, 88% purity by LCMS) that was used for the next step without further purification.

To a stirred solution of 4-(4-chloro-6-(3,4-dihydroisoquinolin-2(1*H*)-yl)pyrimidin-2-yl)morpholine (0.15 g, 0.45 mmol) and 3-pyridylboronic acid (0.17 g, 1.4 mmol) in DMF (6 mL), a solution of potassium phosphate (0.30 g, 1.4 mmol) in water (2 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then $Pd(PPh_3)_4$ (0.016 g, 0.01 mmol) was added. The reaction was heated at 120 °C under microwave irradiation for 30 min. The reaction crude was filtered through Celite and partitioned between DCM (2 × 50 mL) and saturated aqueous solution of $NaHCO_3$ (10 mL). The organics phase was dried over $MgSO_4$ before concentration to dryness. The product was purified by column chromatography (12 g silica cartridge) using (A) hexane and (B) ethyl acetate as eluents and the following gradient: 3 min hold to 100% A, 15 min ramp to 80% B, 2 min ramp to 100% B, 3 min hold to 100% B. The fractions containing product, first eluting peak, were pooled together and solvents were removed to obtain **5** as yellow solid (34 mg, 20% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (bs, 1H), 8.66−8.65 (m, 1H), 8.312−8.29 (m, 1H), 7.38−7.36 (m, 1H), 7.23−7.18 (m, 4H), 6.38 (s, 1H), 4.79 (broad peak, 2H), 3.93−3.87 (m, 6H), 3.81−3.79 (m, 4H), 2.97 (t, 2H, J = 5.9 Hz); LRMS (ES^+) m/z 374 $[M + H]^+$.

6-(Pyridyl-3yl)-2-(pyridin-4-yl)pyrimidin-4-amine (6). In a sealed tube a solution of 4,6-dichloro-2-(pyridin-4-yl)pyrimidine (**49**) (0.13 g, 0.58 mmol) and ammonium hydroxide (2 mL) in methanol (2 mL) was heated at 80 °C for 5h. Solvents were removed under reduced pressure, and the residue was partitioned between water (10 mL) and DCM (2 × 25 mL). The organic phases were combined, dried over magnesium sulfate, and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using (A) DCM and (B) 20% MeOH in DCM as eluents and the following gradient: 2 min hold at 100% A, 18 min ramp to 100% B, 3 min hold at 100% B. The fractions containing product were pooled together and solvents were removed to obtain 6-chloro-2-(pyridin-4-yl)pyrimidin-4-amine as white solid (69 mg, 39% yield, 99% purity by LCMS). Product was used in the next step without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74−8.72 (m, 2H), 8.10−8.08 (m, 2H), 7.50 (bs, 2H), 6.51 (m, 1H); LRMS (ES^+) m/z 207 $[M + H]^+$.

To a stirred solution of 6-chloro-2-(pyridin-4-yl)pyrimidin-4-amine (69 mg, 0.33 mmol) and 3-pyridylboronic acid (91 mg, 0.66 mmol) in DMF (3 mL), a solution of potassium phosphate (140 mg, 0.66 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) was added. The reaction was heated at 120 °C under microwave irradiation for 30 min. Reaction crude was filtered through Celite, quenched with water (10 mL), and extracted with DCM (2 × 25 mL). The organic phases were combined, dried over magnesium sulfate, and solvents were removed under reduced pressure. The product was purified by column chromatography (4 g silica cartridge) using (A) DCM and (B) 20% MeOH in DCM as eluents and the following gradient: 3 min hold at 100% A, 18 min ramp to 50% B, 3 min hold at 50% B. The fractions containing product were pooled

DOI: 10.1021/acs.jmedchem.6b00028
J. Med. Chem. 2016, 59, 6101−6120

together and solvents were removed to obtain **6** as off-white solid (24 mg, 29% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76−8.72 (m, 3H), 8.50−8.47 (m, 1H), 8.31−8.29(m, 2H), 7.59 (dd, 2H, J = 4.8, 7.4 Hz), 7.29 (m, 1H), 7.02 (m, 1H); LRMS (ES$^+$) m/z 250 [M + H]$^+$.

***N*-Benzyl-*N*-methyl-6-(pyridine-3-yl)-2-(pyridin-4-yl)-pyrimidin-4-amine (7).** **7** was prepared in an analogous four-step procedure as that of compound **12**: To a stirred solution of *N*-benzyl-6-chloro-*N*-methyl-2-(pyridin-4-yl)pyrimidin-4-amine (0.18 g, 0.58 mmol) and 3-pyridylboronic acid (0.21 g, 1.74 mmol) in DMF (3 mL), a solution of potassium phosphate (0.36 g, 1.74 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then Pd(PPh$_3$)$_4$ (0.02 g, 0.014 mmol) was added. The reaction was heated at 120 °C under microwave irradiation for 30 min. Reaction crude was filtered through Celite, quenched with water (10 mL), and extracted with DCM (2 × 25 mL). The organic phases were combined, dried over magnesium sulfate, and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using (A) DCM and (B) 20% MeOH in DCM as eluents and the following gradient: 3 min hold at 100% A, 18 min ramp to 50% B, 3 min hold at 50% B. The fractions containing product were pooled together and solvents were removed to obtain **7** as a white solid (115 mg, 56% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.27 (s, 1H), 8.74−8.73 (m, 2H), 8.70−8.69 (m, 1H), 8.42−8.41 (m, 1H), 8.37−8.35 (m, 2H), 7.43−7.28 (m, 6H), 6.82 (s, 1H), 4.99 (bs, 2H), 3.20 (bs, 3H); LRMS (ES$^+$) m/z 354 [M + H]$^+$.

2-(6-(Pyridin-4-yl)-2-(pyridine-4-yl)pyrimidin-4-yl)-isoindoline (8). **8** was prepared in an analogous four-step procedure as that of compound **12**: To a stirred solution of 2-(6-chloro-2-(pyridin-4-yl)pyrimidin-4-yl)isoindoline (0.21 g, 0.68 mmol) and 3-pyridylboronic acid (2.50 g, 2.04 mmol) in DMF (3 mL), a solution of potassium phosphate (0.63 g, 2.04 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then Pd(PPh$_3$)$_4$ (0.03 g, 0.02 mmol) was added. The reaction was heated at 120 °C under microwave irradiation for 30 min. Reaction crude was filtered through Celite, quenched with water (10 mL), and extracted with DCM (2 × 25 mL). The organic phases were combined, dried over magnesium sulfate, and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using (A) DCM and (B) 20% MeOH in DCM as eluents and the following gradient: 3 min hold at 100% A, 15 min ramp to 100% B, 3 min hold at 100% B. The fractions containing product were pooled together and solvents were removed to obtain **8** as off-white solid (90 mg, 38% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.35 (d, 1H, J = 1.7 Hz), 8.78−8.73 (m, 2H), 8.74 (dd, 1H, J = 1.5, 4.8 Hz), 8.53−8.50 (m, 1H), 8.44−8.43 (m, 2H), 7.47 (ddd, 1H, J = 0.7, 4.8, 8.0 Hz), 7.43−7.38 (m, 4H), 6.83 (s, 1H), 5.16 (s, 2H), 4.90 (s, 2H); LRMS (ES$^+$) m/z 352 [M + H]$^+$.

7-(6-(Pyridine-4-yl)-2-(pyridine-4-yl)pyrimidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine (9). **9** was prepared in an analogous four-step procedure as that of compound **12**: To a stirred solution of 7-(6-chloro-2-(pyridine-4-yl)pyrimidin-4-yl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine (0.09 g, 0.29 mmol) and 3-pyridylboronic acid (0.71 g, 0.58 mmol) in DMF (3 mL), a solution of potassium phosphate (0.18 g, 0.86 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then Pd(PPh$_3$)$_4$ (0.01 g, 0.008 mmol) was added. The reaction was heated at 120 °C under microwave irradiation for 30 min. Reaction crude was filtered through Celite, quenched with water (10 mL), and extracted with DCM (2 × 25 mL). The organic phases were combined, dried over magnesium sulfate, and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using (A) DCM and (B) 20% MeOH in DCM as eluents and the following gradient: 3 min hold at 100% A, 15 min ramp to 100% B, 3 min hold at 100% B. The fractions containing product were pooled together and solvents were removed to obtain **9** as an off-white solid (79 mg, 77% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.30 (d, 1H, J = 1.7 Hz), 8.75−8.74 (m, 2H), 8.72 (dd, 1H, J = 1.6, 4.8 Hz), 8.43−8.40 (m, 1H), 8.33−8.32 (m, 2H), 7.44 (ddd, 1H, J = 0.7, 4.8, 8.0 Hz), 7.09 (s, 1H), 6.98 (s, 1H), 6.92 (s, 1H), 4.97 (s, 2H), 4.93(t, 2H, J = 5.3 Hz), 4.20−4.18 (m, 2H); LRMS (ES$^+$) m/z 356 [M + H]$^+$.

4-(4-Phenylpiperazin-1-yl)-6-(pyridin-3-yl)-2-(pyridin-4-yl)-pyrimidine (10). **10** was prepared in an analogous four-step procedure as that of compound **12**: To a stirred solution of 4-chloro-6-(4-phenylpiperazin-1-yl)-2-(pyridin-4-yl)pyrimidine (0.18 g, 0.53 mmol) and 3-pyridylboronic acid (0.21 g, 1.69 mmol) in DMF (3 mL), a solution of potassium phosphate (0.35 g, 1.69 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then Pd(PPh$_3$)$_4$ (0.02 g, 0.014 mmol) was added. The reaction was heated at 120 °C under microwave irradiation for 30 min. Reaction crude was filtered through Celite, quenched with water (10 mL), and extracted with DCM (2 × 25 mL). The organic phases were combined, dried over magnesium sulfate, and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using (A) DCM and (B) 20% MeOH in DCM as eluents and the following gradient: 3 min hold at 100% A, 18 min ramp to 30% B, 3 min hold at 30% B. The fractions containing product were pooled together and solvents were removed to obtain **10** as off-white solid (28 mg, 13% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.30 (s, 1H), 8.77−8.74 (m, 3H), 8.47−8.45 (m, 1H), 8.37−8.36 (m, 2H), 7.46 (dd, 1H, J = 4.8, 7.7 Hz), 7.33−7.31 (m, 2H), 7.01−6.92 (s, 4H), 4.02 (broad peak, 4H), 3.37−3.35 (m, 4H); LRMS (ES$^+$) m/z 395 [M + H]$^+$.

1′-(6-(Pyridin-3-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)-1,4′-bipiperidine (11). **11** was prepared in an analogous four-step procedure as that of compound **12**: To a stirred solution of 1′-(6-chloro-2-(pyridin-4-yl)pyrimidin-4-yl)-1,4′-bipiperidine (0.25 g, 0.71 mmol) and 3-pyridylboronic acid (0.17 g, 1.43 mmol) in DMF (9 mL), a solution of potassium phosphate (0.45 g, 2.14 mmol) in water (3 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then Pd(PPh$_3$)$_4$ (0.02 g, 0.014 mmol) was added. The reaction was heated at 120 °C under microwave irradiation for 30 min. Reaction crude was filtered through Celite, quenched with water (20 mL), and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over magnesium sulfate, and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using (A) DCM and (B) 20% MeOH in DCM as eluents and the following gradient: 3 min hold at 100% A, 18 min ramp to 100% B, 3 min hold at 100% B. The fractions containing product were pooled together and solvents were removed to obtain **11** as an off-white solid (261 mg, 91% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.21 (d, 1H, J = 1.8 Hz), 8.68−8.67 (m, 2H), 8.64 (dd, 1H, J = 1.6, 4.8 Hz), 8.36−8.34 (m, 1H), 8.27−8.26 (m, 2H), 7.36 (dd, 1H, J = 4.9, 7.8 Hz), 6.83 (s, 1H), 4.61 (broad peak, 2H), 3.95−3.90 (m, 2H), 2.59−2.49 (m, 5H), 1.96−1.93 (m, 2H), 1.57−1.49 (m, 6H), 1.40−1.39(m, 2H); LRMS (ES$^+$) m/z 401 [M + H]$^+$.

4-(1-(6-(Pyridin-3-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)-piperidin-4-yl)morpholine (12). Scheme 1 (Four-Step Procedure). Step 1: 2-(Pyridin-4-yl)pyrimidine-4,6-diol (48). A mixture of 4-amidinopyridine hydrochloride (0.5 g, 3.17 mmol) and *N*-methyl-2-pyrolidone (10 mL) was prepared at rt and dimethylmalonate (0.363 mL, 419 mg, 3.17 mmol) added followed by sodium methoxide (686 mg, 12.69 mmol) and the mixture heated in a microwave at 150 °C for 1 h. The mixture was then concentrated under reduced pressure, diluted with water (10 mL), and acidified to pH 6 with concentrated acetic acid. The resulting precipitate was then filtered and dried in vacuo to afford compound **48** (420 mg, 2.22 mmol, 70%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.10 (bs, 2H), 8.76−8.75 (m, 2H), 8.02−8.03 (m, 2H), 5.56 (s, 1H); LRMS (ES$^+$) m/z 190 [M + H]$^+$.

Step 2: 4,6-Dichloro-2-(pyridin-4-yl)pyrimidine (49). A stirred solution of 2-(pyridin-4-yl)pyrimidine-4,6-diol (0.62 g, 3.28 mmol) in phosphorus oxychloride (6 mL) was heated at 90 °C for 3 h. The

DOI: 10.1021/acs.jmedchem.6b00028
J. Med. Chem. 2016, 59, 6101−6120

reaction mixture was slowly added to ice−water, and 2.5 M NaOH was added to adjust to pH 7. The white precipitate was filtered. The filtrate was extracted with ethyl acetate (2 × 50 mL), and the organic phases were combined, dried over magnesium sulfate, and solvents were removed under reduced pressure. Precipitate and extracted product were combined to obtain **49** as a brown solid (421 mg, 58% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 90%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.81−8.80 (m, 2H), 8.27−8.26 (m, 2H), 7.41 (s, 1H); LRMS (ES$^+$) m/z 225 [M + H]$^+$.

Step 3: 4-(1-(6-Chloro-2-(pyridin-4-yl)pyrimidin-4-yl)-piperidin-4-yl)morpholine. To a stirred solution of 4,6-dichloro-2-(pyridin-4-yl)pyrimidine (0.13 g, 0.58 mmol) in anhydrous THF (5 mL), 4-morpholinopiperidine (0.11 g, 0.63 mmol) and diisopropylethylamine (0.20 mL, 1.15 mmol) were added at room temperature, and the reaction mixture was stirred at room temperature overnight. Water (10 mL) was added, and the product was extracted with DCM (2 × 50 mL), the organic phases were combined, dried over magnesium sulfate, and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using (A) DCM and (B) 10% MeOH in DCM as eluents and the following gradient: 3 min hold at 100% A, 18 min ramp to 50% B, 3 min hold at 50% B. The fractions containing product were pooled together and solvents were removed to obtain 4-(1-(6-chloro-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine as white solid (151 mg, 73% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 97%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74−8.72 (m, 2H), 8.14−8.13 (m, 2H), 7.03 (s, 1H), 4.58 (broad peak, 2H), 3.57−3.55 (m, 4H), 3.06−3.02 (m, 2H), 2.48−2.46 (m, 4H), 1.90−1.87 (m, 2H), 1.39 (dddd, 2H, J = 4.2, 12.5, 12.6, 12.6 Hz); LRMS (ES$^+$) m/z 360 [M + H]$^+$.

Step 4. To a stirred solution of 4-[1-[6-chloro-2-(4-pyridyl)-pyrimidin-4-yl]-4-piperidyl]morpholine (**3x**) (0.141 g, 0.39 mmol) and 3-pyridylboronic acid (0.098 g, 0.78 mmol) in DMF (3 mL), a solution of potassium phosphate (0.249 g, 1.17 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then $Pd(PPh_3)_4$ (0.018 g, 0.016 mmol) was added. The reaction was heated at 120 °C under microwave irradiation for 20 min. Reaction crude was diluted with methanol (10 mL) and applied to a SCX 5 g column, and product was eluted with 2 M NH_3 in MeOH. Solvents were removed. The product was further purified by preparative HPLC. The fractions containing product were pooled together, and solvents were removed to obtain compound **12** as off-white solid (38 mg, 24% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28−9.27 (m, 1H), 8.76−8.75 (m, 2H), 8.72 (dd, 1H, J = 1.7, 4.8 Hz), 8.45−8.42 (m, 1H), 8.34−8.33 (m, 2H), 7.44 (ddd, 1H, J = 0.7, 4.8, 7.9 Hz), 6.93 (s, 1H), 4.65 (bs, 2H), 3.74−3.72 (m, 4H), 3.12−3.06 (m, 2H), 2.60−2.52 (m, 5H), 2.04−2.01 (m, 2H), 1.59 (ddd, 2H, J = 4.3, 12.3, 24.1 Hz); LRMS (ES$^+$) m/z 403 [M + H]$^+$. HRMS (ES$^+$) calculated for $C_{23}H_{27}N_6O$ m/z [M + H]$^+$ 403.2241. Measured m/z [M + H]$^+$ 403.2260.

4-((1-(6-(Pyridin-3-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)-piperidin-4-yl)methyl)morpholine Fumarate (13). 13 was prepared in an analogous four-step procedure to that of compound **12**: A mixture of 4-((1-(6-chloro-2-(pyridin-4-yl)pyrimidin-4-yl)-piperidin-4-yl)methyl)morpholine (312 mg, 0.83 mmol) in DMF (4 mL) was prepared at rt, and to it were added 3-pyridylboronic acid (205 mg, 1.70 mmol), potassium phosphate (354 mg, 1.70 mmol) in water (1 mL), and Pd tetrakis (48 mg, 0.04 mmol). The mixture was then heated in a microwave at 130 °C for 1 h. The mixture was then diluted with DCM (10 mL) and filtered through a Celite column. Filtrate was then purified by SCX-2 column, column washed with methanol (2 × 10 mL) and then flushed with 7 M ammonia in methanol (2 × 10 mL), and the ammonia/methanol filtrate concentrated under reduced pressure. Mixture was then purified by column (0−10% 7 M ammonia in methanol/dichloromethane) to afford **13** as an off-white solid (276 mg, 0.66 mmol). A sample of **13** (free base) (100 mg, 0.24 mmol) was suspended in ethanol (20.0 mL) and refluxed for 5 min until dissolution occurred. Fumaric acid (13.9 mg, 0.12 mmol) was dissolved in ethanol (5 mL) and added to the mixture and stirred at rt for a further 24 h. The mixture was then concentrated under reduced pressure and triturated with ethyl acetate and the resulting precipitate filtered, washed with ethyl acetate (2 × 5 mL), and dried by vacuum filtration to afford compound **13** (82 mg, 0.15 mmol, 21% yield over two steps). Purity by LCMS (UV chromatogram, 190−450 nm) > 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (1H, d, J = 1.6 Hz), 8.74 (2H, d, J = 6.0 Hz), 8.71 (1H, dd, J = 1.3, 4.7 Hz), 8.67−8.64 (1H, m), 8.33 (2H, d, J = 6.0 Hz), 7.57 (1H, dd, J = 4.8, 8.0 Hz), 7.49 (1H, s), 6.60 (1H, s), 4.73−4.73 (2H, m), 3.59 (4H, dd, J = 4.0, 4.0 Hz), 3.04 (2H, t, J = 12.5 Hz), 2.35 (4H, s), 2.16 (2H, d, J = 7.3 Hz), 1.95−1.89 (1H, m), 1.86 (2H, d, J = 13.0 Hz), 1.17−1.09 (2H, m); LRMS (ES$^+$) m/z 417 [M + H]$^+$

***N*-(4-Morpholinobutyl)-6-(pyridin-3-yl)-2-(pyridin-4-yl)-pyrimidin-4-amine (14). 14** was prepared in an analogous four-step procedure to that of compound **12**: A mixture of 6-chloro-*N*-(4-morpholinobutyl)-2-(pyridin-4-yl)pyrimidin-4-amine (187 mg, 0.54 mmol) in DMF (4 mL) was prepared at rt and 3-pyridylboronic acid (132, 1.08 mmol) added followed by potassium phosphate (228 mg, 1.08 mmol) in water (2 mL). Pd tetrakis (31 mg, 0.03 mmol) was added and the mixture heated in a microwave to 130 °C for 1 h. The mixture was diluted with dichloromethane (10 mL) and filtered through an SCX-2 column, washed with methanol (2 × 10 mL), and flushed with 7 M ammonia in methanol (2 × 10 mL) and filtrate concentrated under reduced pressure. The mixture was then purified by mass directed autoprep to afford **14** (161 mg, 0.41 mmol, 77%) as a colorless solid. Purity by LCMS (UV chromatogram, 190−450 nm) > 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (d, 1H, J = 1.8 Hz), 8.75 (dd, 2H, J = 1.6, 4.5 Hz), 8.72 (dd, 1H, J = 1.6, 4.8 Hz), 8.45 (dt, 1H, J = 2.0, 9.9 Hz), 8.32 (d, 2H, J = 8.3 Hz), 7.45 (dd, 1H, J = 3.1, 7.3 Hz), 6.70 (s, 1H), 6.04 (brs, 1H), 3.78 (t, 4H, J = 4.4 Hz), 3.52 (brs, 2H), 2.49 (brs, 4H), 2.43 (t, 2H, J = 7.1 Hz), 1.80 (p, 2H, J = 6.8 Hz), 1.69 (p, 2H, J = 7.1 Hz); LRMS (ES$^+$) m/z 389 [M + H]$^+$.

(*R*)-2-(6-(Pyridin-3-yl)-2-(pyridine-4-yl)pyrimidin-4-yl)-octahydropyrrolo[1,2-*a*]pyrazine (15). 15 was prepared in an analogous four-step procedure as that of compound **12**: To a stirred solution of (*R*)-2-(6-chloro-2-(pyridin-4-yl)pyrimidin-4-yl)octahydro-pyrrolo[1,2-*a*]pyrazine (0.14 g, 0.44 mmol) and 3-pyridylboronic acid (0.16 g, 1.31 mmol) in DMF (4.5 mL), a solution of potassium phosphate (0.28 g, 1.31 mmol) in water (1.5 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then $Pd(PPh_3)_4$ (0.015 g, 0.013 mmol) was added. The reaction was heated at 120 °C under microwave irradiation for 30 min. Reaction crude was filtered through Celite, quenched with water (20 mL), and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over magnesium sulfate, and solvents were removed under reduced pressure. The product was purified by column chromatography (12 g silica cartridge) using (A) DCM and (B) 20% MeOH in DCM as eluents and the following gradient: 3 min hold at 100% A, 18 min ramp to 45% B, 3 min hold at 45% B. The fractions containing product were pooled together and solvents were removed to obtain **15** as white solid (119 mg, 75% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.69−8.65 (m, 3H), 8.37−8.35 (m, 1H), 8.28−8.27 (m, 2H), 7.37 (dd, 1H, J = 4.8, 7.8 Hz), 6.84 (s, 1H), 4.56 (broad peak, 2H), 3.16−3.09 (m, 3H), 2.78−2.74 (m, 1H), 2.27−2.22 (m, 1H), 2.18−2.13 (m, 1), 2.04−1.98 (m, 1H) 1.94−1.82 (m, 2H), 1.78−1.70 (m, 1H), 1.54−1.45 (m, 1H); LRMS (ES$^+$) m/z 359 [M + H]$^+$.

4-(1-(6-Cyclopropyl-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (16). 16 was prepared in an analogous four-step procedure to that of compound **12**: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol), cyclopropylboronic acid (0.012 g, 0.014 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 30 min. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2 g column eluting with MeOH and then 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% MeCN, basic, to afford **16** as a white solid (15 mg, 28% yield).

DOI: 10.1021/acs.jmedchem.6b00028
J. Med. Chem. 2016, 59, 6101−6120

Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, 2H, J = 5.5 Hz), 8.19 (d, 2H, J = 5.65 Hz), 6.42 (s, 1H), 4.59 (bs, 2H), 3.86−3.74 (broad peak, 4H), 2.96 (m, 2H), 2.76−2.51 (broad peak, 5H), 2.07−1.98 (broad peak, 2H), 1.88 (m, 1H), 1.65−1.52 (broad peak, 2H), 1.19 (m, 2H), 0.98 (m, 2H); LRMS (ES^+) m/z 366 $[M + H]^+$.

6-(4-Morpholinopiperidin-1-yl)-*N*-(3-morpholinopropyl)-2-(pyridin-4-yl)pyrimidin-4-amine (17). To a mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14 mmol) in anhydrous NMP (1 mL) was added 3-morpholino-propan-1-amine (60 mg, 0.41 mmol), and the mixture was heated at 200 °C under microwave irradiation for 10 min. The cooled reaction mixture was purified by mass directed HPLC 5−95% MeCN, basic, to afford **17** as a yellow solid (38 mg, 55% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69- 8.65 (m, 2H), 8.18−8.16 (m, 2H), 5.61 (bs, 1H), 5.43 (s, 1H), 4.50−4.45 (m, 2H), 3.80−3.70 (m, 8H), 3.44−3.38 (m, 2H), 2.90 (m, 2H), 2.62−2.44 (m, 11H), 1.97−1.94 (m, 2H), 1.87−1.80 (m, 2H), 1.58−1.48 (m, 2H); LRMS (ES^+) m/z 468 $[M + H]^+$.

3-((6-(4-Morpholinopiperidin-1-yl)-2-(pyridin-4-yl)-pyrimidin-4-yl)amino)propanamide (18). A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14mmol), *N*,*N*-diisopropylethylamine (0.072ml, 0.41mmol), 3-aminopropanamide hydrochloride (0.052 g, 0.41mmol) in anhydrous NMP (1 mL) was heated at 200 °C under microwave irradiation for 10 min. The cooled reaction mixture was purified by mass directed HPLC 5−95% MeCN, basic, to afford **18** as a yellow solid (16 mg, 26% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 8.67−8.64 (m, 2H), 8.15−8.12 (m, 2H), 7.33 (bs, 1H), 6.84−6.75 (broad peaks, 2H), 5.7 (s, 1H), 4.41−4.32 (m, 2H), 3.48−3.47 (m, 6H), 2.83 (m, 2H), 2.52−2.34 (m, 7H), 1.88−1.82 (m, 2H), 1.40−1.30 (m, 2H); LRMS (ES^+) m/z 412 $[M + H]^+$.

4-(1-(6-Morpholino-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (19). To a mixture of 4-[1-[6-chloro-2-(4-pyridyl)-pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14 mmol) in anhydrous NMP (1 mL) was added morpholine (36 mg, 0.41 mmol), and the mixture was heated at 200 °C under microwave irradiation for 10 min. The cooled reaction mixture was purified by mass directed HPLC 5−95% MeCN, basic, to afford **19** as a white solid (30 mg, 57% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69−8.67 (m, 2H), 8.20−8.18 (m, 2H), 5.61 (s, 1H), 4.55−4.49 (m, 2H), 3.83−3.80 (m, 4H), 3.68−3.71 (broad peak, 4H), 3.66−3.63, (m, 4H), 2.92 (m, 2H), 2.62−2.57 (broad peak, 5H), 2.00−1.93 (m, 2H), 1.62−1.52 (m, 2H); LRMS (ES^+) m/z 411 $[M + H]^+$.

4-(1-(6-(3,5-Dimethylisoxazol-4-yl)-2-(pyridin-4-yl)-pyrimidin-4-yl)piperidin-4-yl)morpholine (20). **20** was prepared in an analogous four-step procedure to that of compound **51**: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]-morpholine (0.050 g, 0.14 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol), 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (0.093 g, 0.41 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 30 min. The cooled reaction mixture was filtered through a Celite cartridge (2.5 g), washing the cartridge with DCM. The filtrate was partitioned between saturated $NaHC0_3$ (5 mL) and DCM (10 mL). The DCM extract was evaporated to dryness. The residue was dissolved in MeOH and purified by SCX 2 g column eluting with MeOH and then 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% MeCN, basic, to afford **20** as a white solid (36 mg, 61% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75−8.73 (m, 2H), 8.25−8.23 (m, 2H), 6.51 (s, 1H), 4.61 (bs, 2H), 3.92−3.67 (broad peak, 4H), 3.05 (m, 2H), 2.75−2.55 (m, 8H), 2.53 (s, 3H), 2.16−2.00 (broad peak, 2H), 1,72−1.49 (broad peak, 2H); LRMS (ES^+) m/z 421 $[M + H]^+$.

4-(1-(6-(3-Fluorophenyl)-2-(pyridin-4-yl)pyrimidin-4-yl)-piperidin-4-yl)morpholine (21). **21** was prepared in an analogous four-step procedure to that of compound **12**: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol), (3-fluorophenyl)boronic acid (0.058 g, 0.41 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 30 min. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2 g column eluting with MeOH and then 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% MeCN, basic, to afford **21** as a white solid (47 mg, 76% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76−8.74 (m, 2H), 8.35−8.33 (m, 2H), 7.88−7.83 (m, 2H), 7.49−7.44 (m, 1H), 7.2−7.16 (m, 1H), 6.90 (s, 1H), 4.68 (bs, 2H), 3.85−3.73 (broad peak, 4H), 3.06 (m, 2H), 2.76−2.59 (broad peak, 5H), 2.14−2.04 (m, 2H), 1.69−1.54 (m, 2H); LRMS (ES^+) m/z 420 $[M + H]^+$.

4-(1-(6-(4-Fluorophenyl)-2-(pyridin-4-yl)pyrimidin-4-yl)-piperidin-4-yl)morpholine (22). **22** was prepared in an analogous four-step procedure to that of compound **12**: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.1389 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol), (4-fluorophenyl)boronic acid (0.058 g, 0.41 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 30 min. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2 g column eluting with MeOH and then 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% MeCN, basic, to afford **22** as a white solid (38 mg, 61% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, 2H, J = 5.35 Hz), 8.35−8.32 (m, 2H), 8.14−8.09 (m, 2H), 7.21−7.16 (m, 2H), 6.87 (s, 1H), 4.67 (broad peak, 2H), 3.84−3.7 (broad peak, 4H), 3.05 (m, 2H), 2.71−2.55 (broad peak, 5H), 2.10−2.00 (m, 2H), 1.67−1.52 (m, 2H); LRMS (ES^+) m/z 420 $[M + H]^+$.

4-(1-(2-(Pyridin-4-yl)[4,5′-bipyrimidin]-6-yl)piperidin-4-yl)-morpholine (23). **23** was prepared in an analogous four-step procedure to that of compound **12**: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (0.085 g, 0.41 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 30 min. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2 g column eluting with MeOH and then 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% MeCN, basic, to afford **23** as a white solid (26 mg, 44% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 2H), 9.32 (s, 1H), 8.78−8.75 (m, 2H), 8.33−8.31 (m, 2H), 6.92 (s, 1H) 4.70 (bs, 2H), 3.99−3.66 (broad peak, 4H), 3.11 (m, 2H), 2.82−2.52 (broad peak, 5H), 2.19−2.01 (broad peak, 2H), 1.77−1.49 (broad peak, 2H); LRMS (ES^+) m/z 404 $[M + H]^+$.

4-(1-(6-(5-Methoxypyridin-3-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (24). **24** was prepared in an analogous four-step procedure to that of compound **12**: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol), (5-methoxy-3-pyridyl)boronic acid (0.063 g, 0.41 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 30 min. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2 g column eluting with MeOH and then 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% MeCN, basic, to afford **24** as a white solid (38 mg, 60% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (d, 1H, J = 1.7

DOI: 10.1021/acs.jmedchem.6b00028
J. Med. Chem. 2016, 59, 6101−6120

Hz), 8.76−8.74 (m, 2H), 8.41 (d, 1H, J = 2.85 Hz), 8.34−8.32 (m, 2H), 8.00−7.98 (m, 1H), 6.93 (s, IH), 4.71 (broad peak, 2H), 3.98 (s, 3H), 3.86−3.74 (broad peak, 4H), 3.13−3.04 (m, 2H), 2.76−2..04 (broad peak, 5H), 2.16−2.04 (broad peak, 2H), 1.7−1.56 (broad peak, 2H); LRMS (ES^+) m/z 433 $[M + H]^+$.

5-(6-(4-Morpholinopiperidin-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)nicotinonitrile (25). **25** was prepared in an analogous four-step procedure to that of compound **12**: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol), (3-cyanophenyl)boronic acid (0.061 g, 0.41 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 60 min. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2 g column eluting with MeOH and then 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% MeCN, basic, to afford **25** as a white solid (14 mg, 22% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 97%. ^1H NMR (500 MHz, $CDCl_3$) δ 9.45 (d, 1H, J = 2.09 Hz), 8.97 (d, 1H, J = 1.94 Hz), 8.79−8.72 (m, 3H), 8.34−8.29 (m, 2H), 6.94 (s, 1H), 4.69 (broad peak, 2H), 3.84−3.72 (broad peak, 4H), 3.12 (m, 2H), 2.70−2.58 (broad peak, 5H), 2.15−2.03 (m, 2H), 1.71−1.54 (broad peak, 2H); LRMS (ES^+) m/z 428 $[M + H]^+$.

4-(1-(6-(5-Fluoropyridin-3-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (26). **26** was prepared in an analogous four-step procedure to that of compound **12**: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol), (5-fluoropyridin-3-yl)boronic acid (0.058 g, 0.41 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 30 min. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2 g column eluting with MeOH and then 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% MeCN, basic, to afford **26** as a yellow solid (13 mg, 21% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^1H NMR (500 MHz, $CDCl_3$) δ 9.07 (m, 1H), 8.76 (m, 2H), 8.58 (d, 1H, J = 2.8 Hz), 8.34 (m, 2H), 8.22−8.19 (m, 1H), 6.94 (s, IH), 4.67 (bs, 2H), 3.76−3.74 (m, 4H), 3.13−3.07 (m, 2H), 2.64−2.62 (m, 5H), 2.07−2.04 (m, 2H), 1.64−1.56 (m, 2H); LRMS (ES^+) m/z 421 $[M + H]^+$.

5-(6-(4-Morpholinopiperidin-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)pyridin-3-yl)methanamine (27). **27** was prepared in an analogous four-step procedure to that of compound **12**: A solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinaldehyde (0.100 g, 0.43 mmol) in ammonia (7 M in MeOH, 2 mL) was stirred at room temperature overnight. Sodium borohydride (0.035 g, 0.92 mmol) was added and the reaction mixture stirred at room temperature under argon for 5 h. Water (1 mL) was added and the reaction mixture evaporated to dryness. The residue was dissolved in MeOH and purified by SCX 2 g column eluted MeOH and then 2 M NH_3 in MeOH. The fractions containing product were evaporated to dryness to give impure (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methanamine (0.090 g) as a brown gum. A mixture of impure (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-methanamine (0.090 g, 0.38 mmol), 4-[1-[6-chloro-2-(4-pyridyl)-pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 30 min. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2 g column eluting with MeOH and then 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% MeCN, basic, to afford **27** as a white solid (13 mg, 20% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 95%. ^1H NMR (500 MHz, $CDCl_3$) δ 9.16 (d, 1H, J = 1.9 Hz), 8.77−8.74 (m, 2H), 8.34 (d, 1H, J = 1.85 Hz), 8.47 (m, 1H), 8.35−8.33 (m, 2H), 6.95 (s, 1H), 4,65 (bs, 2H) 4.04 (s, 2H), 3.76−3.70 (m, 4H), 3.09 (m, 2H), 2.62−2.56 (m, 5H), 2.07−1.99 (m, 2H), 1.65−1.54 (m, 2H); LRMS (ES^+) m/z 432 $[M + H]^+$.

5-(6-(4-Morpholinopiperidin-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)pyridin-3-yl)methanone (28). **28** was prepared in an analogous four-step procedure to that of compound **12**: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol), morpholino(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)methanone (0.132 g, 0.41 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 30 min. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2 g column eluting with MeOH and then 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% MeCN, basic, to afford **28** as a light brown solid (52 mg, 68% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^1H NMR (500 MHz, $CDCl_3$) δ 9.35 (d, 1H, J = 2.11 Hz), 8.77−8.73 (m, 3H), 8.51 (m, 1H), 8.33−8.30 (m, 2H), 6.95 (s, 1H), 4.70 (bs, 2H), 3.92−3.64 (broad peaks, 12H), 3.09 (m, 2H), 2.77−2.55 (broad peak, 5H), 2.17−2.03 (broad peak, 2H), 1.73−1.53, (broad peak, 2H); LRMS (ES^+) m/z 516 $[M + H]^+$.

5-(6-(4-Morpholinopiperidin-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)pyridin-2-amine (29). A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (0.091 g, 0.41 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 30 min. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2 g column eluting with MeOH and then picolinamide, 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% MeCN, basic, to afford **29** as a white solid (42 mg, 68% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 96%. ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 8.92 (d, 1H, J = 2.05 Hz), 8.74−8.72 (m, 2H), 8.32−8.28 (m, 3H), 7.23 (s, 1H), 6.54 (d, 1H, J = 8.75 Hz), 6.48 (bs, 2H), 4.70 (bs, 2H), 3.59−3.55 (m, 4H), 3.04−2.97 (m, 2H), 2.55−2.48 (m, 5H), 1.94−1.88 (m, 2H), 1.45−1.36 (m, 2H); LRMS (ES^+) m/z 418 $[M + H]^+$.

4-(1-(6-(6-Methoxypyridin-3-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (30). **30** was prepared in an analogous four-step procedure to that of compound **12**: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol), (6-methoxypyridin-3-yl)boronic acid (0.063 g, 0.41 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 30 min. The cooled reaction mixture was filtered through a Celite cartridge (2.5 g). The cartridge was washed with DCM. The filtrate was partitioned between saturated $NaHCO_3$ (5 mL) and DCM (10 mL). The DCM extract was evaporated to dryness. The residue was dissolved in MeOH and purified by SCX 2 g column eluting with MeOH and then 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% basic to afford impure product. The sample was dissolved in DMF and purified by mass directed HPLC 25−75% MeCN, basic, to afford **30** as a white solid (17 mg, 26% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 96%. ^1H NMR (500 MHz, $CDCl_3$) δ 8.9 (m, 1H), 8.75−8.73 (m, 2H), 8.34−8.31 (m, 3H), 6.88−6.85 (m, 1H), 6.84 (s, 1H), 4.67 (broad peak, 2H), 4.01 (s, 3H), 3.87−3.79 (broad peak, 4H), 3.06 (m, 2H), 2.76−2.58 (broad peak, 5H), 2.14−2.08 (broad peak 2H), 1.69−1.55 (broad peak 2H); LRMS (ES^+) m/z 433 $[M + H]^+$.

***N*-Methyl-5-(6-(4-morpholinopiperidin-1-yl)-2-(pyridin-4-yl)-pyrimidin-4-yl)picolinamide (31).** **31** was prepared in an analogous four-step procedure to that of compound **12**: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g,

DOI: 10.1021/acs.jmedchem.6b00028
J. Med. Chem. 2016, 59, 6101−6120

0.14 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol), *N*-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide (0.109 g, 0.41 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 30 min. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2 g column eluting with MeOH and then 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% MeCN, basic, to afford **31** as a white solid (22 mg, 32% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (m, 1H), 8.77 (bs, 2H), 8.53−8.49 (m, 1H), 8.36−8.30 (m, 3H), 8.10−8.04 (m, 1H), 6.95 (s, 1H), 4.72 (bs, 2H), 3.96−3.67 (broad peak, 4H), 3.013−3.04 (m, 5H), 2.75−2.60 (broad peak, 5H), 2.16−2.03 (broad peak, 2H), 1.75−1.55 (broad peak, 2H); LRMS (ES^+) *m*/*z* 460 $[M + H]^+$.

4-(5-(6-(4-Morpholinopiperidin-1-yl)-2-(pyridin-4-yl)-pyrimidin-4-yl)pyridin-2-yl)morpholine (32). **32** was prepared in an analogous four-step procedure to that of compound **12**: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol), 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (0.121 g, 0.41 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 30 min. The cooled reaction mixture was filtered through a Celite cartridge (2.5 g), washing the cartridge with DCM. The filtrate was partitioned between saturated $NaHC0_3$ (5 mL) and DCM (10 mL). The DCM extract was evaporated to dryness. The residue was dissolved in MeOH and purified by SCX 2 g column eluting with MeOH and then 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% MeCN, basic, to afford impure product. The sample was dissolved in DMF and purified by mass directed HPLC 25−75%, basic, to afford **32** as a white solid (40 mg, 56% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 95%. ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.12−9.09 (m, 1H), 8.72 (d, 2H, *J* = 5.78 Hz), 8.48−8.42 (m, 1H), 8.30 (d, 2H, *J* = 5.93 Hz), 7.3 (s, 1H), 6.95 (d, 1H, *J* = 9.08 Hz), 4.65 (bs, 2H), 3.78−3.50 (m, 12H), 3.01 (m, 2H), 2.58−2.38 (m, 5H), 1.97−1.84 (m, 2H), 1.50−1.29 (m, 2H); LRMS (ES^+) *m*/*z* 488 $[M + H]^+$.

4-(1-(6-(4-Methoxypyridin-3-yl)-2-(pyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (33). **33** was prepared in an analogous four-step procedure to that of compound **12**: A mixture of 4-[1-[6-chloro-2-(4-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.050 g, 0.14 mmol), potassium phosphate (0.088 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol), (4-methoxypyridin-3-yl)boronic acid (0.068 g, 0.41 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) was heated at 120 °C under microwave irradiation for 30 min. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in MeOH/DCM and purified by SCX 2 g column eluting with MeOH and then 2 M NH_3 in MeOH. The fraction containing product was evaporated to dryness. The residue was dissolved in DMF and purified by mass directed HPLC 5−95% MeCN, basic, to afford **33** as a white solid (46 mg, 72% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.75−8.71 (m, 2H), 8.56 (d, 1H, *J* = 5.75 Hz), 8.32−8.29 (m, 2H), 7.13 (s, 1H), 6.94 (d, 1H, *J* = 5.80 Hz), 4.65 (bs, 2H), 3.97 (s, 3H), 3.85−3.76 (broad peak, 4H), 3.04 (m, 2H), 2.72−2.65 (broad peak, 5H), 2.15−2.02 (m, 2H), 1.67−1.54 (m, 2H); LRMS (ES^+) *m*/*z* 433 $[M + H]^+$.

4-(4-(4-Morpholinopiperidin-1-yl)-6-(pyridin-3-yl)pyrimidin-2-yl)benzonitrile (34). **34** was prepared in an analogous three-step procedure to that of compound **43**: In a sealed 5 mL microwave vial, a solution of 4-[1-[2-methylsulfanyl-6-(3-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.075 g, 0.20 mmol) in THF (4 mL) was degassed by bubbling argon through for 5 min. (4-Cyanophenyl)-boronic acid (0.030 g, 0.20 mmol), thiophene-2-carbonyloxycopper (0.058 g, 0.30 mmol), and $Pd(PPh_3)_4$ (0.023 g,0.02 mmol) were added at room temperature. The reaction was heated in the sealed tube at 85 °C for 18 h. Reaction was filtered through Celite and partitioned between DCM (10 mL) and NH_3 aq (5 mL). The organic phase was dried over magnesium sulfate, and solvents were removed under reduced pressure. The product was purified by mass directed autopreparative HPLC under basic conditions. The fractions containing product were pooled together and solvents were removed to obtain **34** as off-white solid (12 mg, 14% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (d, 1H, *J* = 1.7 Hz), 8.72 (dd, 1H, *J* = 1.6z, 4.8 Hz), 8.64−8.61 (m, 2H), 8.44−8.42 (m, 1H), 7.78−7.76 (m, 2H), 7.45 (ddd, 1H, *J* = 0.7, 4.8, 7.9 Hz), 6.92(s, 1H), 4.74−4.61 (m, 2H), 3.79−3.72 (m, 4H), 3.49 (d, 2H, *J* = 5.2 Hz), 3.11−3.06 (m, 2H), 2.69−2.52 (m, 5H), 2.08−2.03 (m, 2H), 1.63−1.54 (m, 2H); LRMS (ES^+) *m*/*z* 427 $[M + H]^+$.

4-(4-Morpholinopiperidin-1-yl)-6-(pyridin-3-yl)pyrimidine-2-carbonitrile (35). In a stirred sealed tube a solution of 4-[1-(6-chloro-2-iodo-pyrimidin-4-yl)-4-piperidyl]morpholine (0.29 g, 0.72 mmol) and copper cyanide (0.077 g, 0.86 mmol) in NMP (3 mL) was heated at 120 °C for 5 h. Reaction crude was applied to a SCX cartridge (5 g), and the product was diluted with a solution of 2 N NH_3 in methanol. The product was further purified by column chromatography (12 g silica cartridge) using (A) DCM, (B) 10% MeOH in DCM as eluents and the following gradient: 1 min hold at 100% A, 10 min ramp to 50% B, and 3 min hold at 50% B. The fractions containing product were pooled together and solvents were removed to obtain 4-chloro-6-(4-morpholinopiperidin-1-yl)-pyrimidine-2-carbonitrile as an off-white solid (139 mg, 62% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (s, 1H), 3.73−3.71 (m, 4H), 3.06−3.01 (m, 2H), 2.56−2.48 (m, 5H), 1.99−1.96 (m, 2H), 1.55−1.47 (m, 2H); LRMS (ES^+) *m*/*z* 308 $[M + H]^+$.

To a stirred solution of 6-chloro-4-(4-morpholino-1-piperidyl)-1,6-dihydropyrimidine-2-carbonitrile (0.128 g, 0.41 mmol) and 3-pyridylboronic acid (0.103 g, 0.83 mmol) in DME (4 mL), an aqueous solution of sodium carbonate (2 M, 0.26 g, 1.24 mmol) and $PdCl_2(PPh_3)_2$ (0.014 g, 0.02 mmol) were added. The reaction was heated at 120 °C for 20 min under microwave irradiation. The reaction crude was diluted with methanol (5 mL) and applied to a SCX column (5 g), and the product was eluted with 2 M NH_3 in MeOH. The product was further purified by preparative HLPC under acidic conditions. The fractions containing product were pooled together and solvents were removed to obtain **35** as off-white solid (47 mg, 31% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14−9.13 (m, 1H), 8.72 (dd, 1H, *J* = 1.7, 4.8 Hz), 8.36−8.34 (m, 1H), 7.45 (ddd, 1H, *J* = 0.8, 4.8, 8.0 Hz), 6.97 (s, 1H), 4.59−4.56 (m, 2H), 3.76−3.74 (m, 4H), 3.10−3.05 (m, 2H), 2.63−2.57 (m, 5H), 2.04−2.02 (m, 2H), 1.60−1.52 (m, 2H); LRMS (ES^+) *m*/*z* 351 $[M + H]^+$.

1-(4-(4-Morpholinopiperidin-1-yl)-6-(pyridine-3-yl)-pyrimidin-2-yl)thiomorpholine 1,1-Dioxide (36). **36** was prepared in an analogous three-step procedure to that of compound **74**: A solution of 4-[1-(6-chloro-2-iodo-pyrimidin-4-yl)-4-piperidyl]-morpholine (0.15 g, 0.37 mmol), thiomorpholine 1,1-dioxide (0.06 mg, 0.40 mmol), and DIPEA (0.13 mL, 040 mmol) in NMP (2 mL) was heated at 200 °C for 15 min under microwaved irradiation. Reaction crude was diluted with MeOH (5 mL) and applied to a SCX cartridge (5 g), and the product was diluted with a solution of 2 N NH_3 in methanol. Solvents were removed under reduced pressure and the product was further purified by column chromatography (12 g silica cartridge) using (A) DCM, (B) 10% MeOH in DCM as eluents and the following gradient: 1 min hold at 100% A, 18 min ramp to 50% B, and 3 min hold at 50% B. The fractions containing product were pooled together and solvents were removed to obtain 1-(4-chloro-6-(4-morpholinopiperidin-1-yl)pyrimidin-2-yl)thiomorpholine 1,1-dioxide as an off-white solid (149 mg, 98%, 91% purity by LCMS). The product was used for the next step without further purification.

To a stirred solution of 1-(4-chloro-6-(4-morpholinopiperidin-1-yl)pyrimidin-2-yl)thiomorpholine 1,1-dioxide (0.15 g, 0.36 mmol) and 3-pyridylboronic acid (0.09 g, 0.76 mmol) in DMF (3 mL), $Pd(PPh_3)_4$ (0.015 g, 0.01 mmol) and an aqueous solution of potassium carbonate

DOI: 10.1021/acs.jmedchem.6b00028
J. Med. Chem. 2016, 59, 6101−6120

(2 M, 0.5 mL) were added. The reaction was heated at 120 °C for 20 min under microwave irradiation. The reaction crude was diluted with methanol (10 mL) and applied to a SCX column (2 g), and the product was eluted with 2 M NH_3 in MeOH. The product was further purified by preparative HLPC under basic conditions. The fractions containing product were pooled together, and solvents were removed to obtain **36** as off-white solid (67 mg, 41% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.13 (dd, 1H, J = 0.7, 2.2 Hz), 8.66 (dd, 1H, J = 1.7, 4.8 Hz), 8.22−8.20 (m, 1H), 7.37 (ddd, 1H, J = 0.8, 4.8, 8.0 Hz), 6.42 (s, 1H), 4.45−4.40 (m, 6H), 3.73−3.71 (m, 4H), 3.07−3.05 (m, 4H), 2.53−2.93 (m, 2H), 2.58−2.56 (m, 4H), 2.52−2.47 (m, 1H), 1.97−1.94 (m, 2H), 1.55−1.47 (m, 2H); LRMS (ES$^+$) m/z 459 [M + H]$^+$.

4-(4-Morpholinopiperidin-1yl)-6-(pyridin-3-yl)pyrimidin-2-ol (37). To a stirred solution of 4-[1-(2,6-dichloropyrimidin-4-yl)-4-piperidyl]morpholine (0.60 g, 1.89 mmol) in THF (10 mL) in a 20 mL microwave vial, a solution of NaOH (1M, 9.8 mL) was added at room temperature. The reaction mixture was heated 150 °C for 1 h under microwave irradiation. The reaction crude was washed with ethyl acetate (2 × 100 mL). The pH of the aqueous layer was adjusted to pH 6 with 10% HCl, and then MeOH (40 mL) added. The water/methanol mixture was applied onto an SCX column (20 g) and the compound was eluted from the column with 2 M NH_3 in methanol. Solvents were removed under reduced pressure to obtain 4-chloro-6-(4-morpholinopiperidin-1-yl)pyrimidin-2-ol as a white solid (256 mg, 45% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 86%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (s, 1H), 4.26 (broad peak, 2H), 3.69 (broad peak, 4H), 2.94−2.89 (m, 2H), 2.51−2.40 (m, 5H), 1.90−1.87 (m, 2H), 1.46−1.40 (m, 2H); LRMS (ES$^+$) m/z 299 [M + H]$^+$.

To a stirred suspension of 4-chloro-6-(4-morpholinopiperidin-1-yl)pyrimidin-2-ol (0.26 g, 0.86 mmol) and 3-pyridylboronic acid (0.32 g, 2.57 mmol) in DMF (3 mL), a solution of potassium phosphate (0.55 g, 2.57 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then $Pd(PPh_3)_4$ (0.049 g, 0.04 mmol) was added. The reaction was heated at 130 °C under microwave irradiation for 20 min. Reaction was filtered through Celite and partitioned between DCM (50 mL) and a saturated aqueous solution of $NaHCO_3$ (15 mL). The organics phase was dried over $MgSO_4$ before concentration to dryness. The crude was then purified by column chromatography (12 g silica cartridge) using (A) DCM and (B) MeOH as eluents and the following gradient: 1 min hold at 100% A, 20 min ramp to 20% B, 5 min hold to 10% B. The fractions containing product were pooled together and solvents were removed to obtain **37** as a white solid (50 mg, 17% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (bs, 1H), 9.07 (d, 1H, J = 2.0 Hz), 8.77 (dd, 1H, J = 1.5, 4.8 Hz), 8.28−8.25 (m, 1H), 7.61 (dd, 1H, J = 4.8, 8.0 Hz), 6.58(s, 1H), 4.84−4.32 (broad peak, 2H), 3.65−3.63 (m, 4H), 3.02 (broad peak, 2H), 2.54 (broad peak, 5H), 1.93−1.91 (m, 2H), 1.45−1.33 (m, 2H); LRMS (ES$^+$) m/z 342 [M + H]$^+$.

4(4-(4-Morpholinopiperidin-1-yl)-6-(pyridine-3-yl)-pyrimidin-2yl)piperazine-2-one (38). **38** was prepared in an analogous three-step procedure to that of compound **74**: A solution of 4-[1-(6-chloro-2-iodo-pyrimidin-4-yl)-4-piperidyl]morpholine (0.15 g, 0.37 mmol), piperazine-2-one (0. 04 mg, 0.40 mmol), and DIPEA (0.13 mL, 0.40 mmol) in NMP (2 mL) was heated at 200 °C for 15 min under microwave irradiation. Reaction crude was diluted with MeOH (5 mL) and applied to a SCX cartridge (5 g), and the product was diluted with a solution of 2 N NH_3 in methanol. Solvents were removed under reduced pressure, and the product was further purified by column chromatography (12 g silica cartridge) using (A) DCM, (B) 10% MeOH in DCM as eluents and the following gradient: 1 min hold at 100% A, 18 min ramp to 50% B, and 3 min hold at 50% B. The fractions containing product were pooled together and solvents were removed to obtain 4-chloro-*N*-(2-morpholinoethyl)-6-(4-morpholinopiperidin-1-yl)pyrimidin-2-amine as an off-white solid (159 mg, quantitiative yield, 83% purity by LCMS). The product was used for the next step without further purification. To a stirred solution of 4-chloro-*N*-(2-morpholinoethyl)-6-(4-morpholinopiperidin-1-yl)-pyrimidin-2-amine (0.16 g, 0.41 mmol) and 3-pyridylboronic acid (0.10 g, 0.82 mmol) in DMF (3 mL), $Pd(PPh_3)_4$ (0.015 g, 0.01 mmol) and an aqueous solution of potassium carbonate (2 M, 0.5 mL) were added. The reaction was heated at 120 °C for 20 min under microwave irradiation. The reaction crude was diluted with methanol (10 mL) and applied to a SCX column (2 g), and the product was eluted with 2 M NH_3 in MeOH. The product was further purified by preparative HLPC under basic conditions. The fractions containing product were pooled together and solvents were removed to obtain **38** as off-white solid (70 mg, 40% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (dd, 1H, J = 0.7, 2.2 Hz), 8.67 (dd, 1H, J = 1.7, 4.8 Hz), 8.31−8.29 (m, 1H), 7.38 (ddd, 1H, J = 0.8, 4.8, 8.0 Hz), 6.47 (bs, 1H), 6.41 (s,1H), 4.52−4.49 (m, 4H), 4.16−4.13 (m, 2H), 3.16−3.74 (m, 4H), 3.53−3.50 (m, 2H), 2.99−2.94 (m, 2H), 2.60−2.59 (m, 4H), 2.54−2.48 (m, 1H), 1.98−1.95 (m, 2H), 1.57−1.49 (m, 2H); LRMS (ES$^+$) m/z 425 [M + H]$^+$.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(4-(4-morpholinopiperidin-1-yl)-6-(pyridine-3-yl)pyrimidin-2-yl)ethane-1,2-diamine (39).** **39** was prepared in an analogous three-step procedure to that of compound **5**: To a stirred suspension of N^1-(4-chloro-6-(4-morpholinopiperidin-1-yl)pyrimidin-2-yl)-N^2,N^2-dimethylethane-1,2-diamine (0.04 g, 0.11 mmol) and 3-pyridylboronic acid (0.41 g, 0.33 mmol) in DMF (3 mL), a solution of potassium phosphate (0.07 g, 0.33 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then $Pd(PPh_3)_4$ (0.004 g, 0.003 mmol) was added. The reaction was heated at 130 °C under microwave irradiation for 20 min. Reaction was filtered through Celite and partitioned between DCM (10 mL) and a saturated aqueous solution of $NaHCO_3$ (5 mL). The organics phase was dried over $MgSO_4$ before concentration to dryness. The crude was then purified by preparative mass directed autopreparative HPLC (method: 5−95 basic). The fractions containing product were pooled together and solvents were removed to obtain **39** as a white solid (18 mg, 39% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.63 (dd, 1H, J = 1.6, 4.8 Hz), 8.24 (d, 1H, J = 7.9 Hz), 7.35 (dd, 1H, J = 4.8, 7.9 Hz), 6.32 (s, 1H), 4.51−4.48 (m, 2H), 3.73−3.55 (m, 4H), 3.55−3.52 (m, 2H), 2.90 (t, 1H, J = 12.7 Hz), 2.58−2.54 (m, 4H), 2.53−2.51 (m, 2H), 2.49−2.44 (m, 1H), 2.27 (s, 6H), 1.94−1.91 (m, 2H), 1.54−1.45 (m, 2H); LRMS (ES$^+$) m/z 412 [M + H]$^+$.

4-(1-(2-(2,6-Dimethylpyridin-4-yl)-6-(pyridin-3-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (40). To a stirred solution of 4-[1-[6-chloro-2-(2,6-dimethyl-4-pyridyl)pyrimidin-4-yl]-4-piperidyl]-morpholine (0.042 g, 0.11 mmol) and 3-pyridylboronic acid (0.040 g, 0.32 mmol) in DMF (3 mL), a solution of potassium phosphate (0.069 g, 0.32 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then $Pd(PPh_3)_4$ (0.006 g, 0.005 mmol) was added. The reaction was heated at 130 °C under microwave irradiation for 20 min. The reaction crude was partitioned between DCM (15 mL) and saturated aqueous solution of $NaHCO_3$ (5 mL). The organics phase was dried over $MgSO_4$ before concentration to dryness. The crude was then purified by preparative HLPC. The fractions containing product were pooled together and solvents were removed to obtain **40** as off-white solid (8 mg, 17% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27−9.26 (m, 1H), 8.72 (dd, 1H, J = 1.6, 4.8 Hz), 8.45−8.42 (m, 1H), 8.03 (bs, 2H), 7.46 (ddd, 1H, J = 0.6, 4.8, 8.0 Hz), 6.93 (s, 1H), 4.69 (broad m, 2H), 3.78 (broad m, 4H), 3.12−3.06 (m, 2H), 2.67−2.61 (m, 11H), 2.09−2.07 (m, 2H), 1.67−1.57 (m, 2H); LRMS (ES$^+$) m/z 431 [M + H]$^+$.

4-(1-(2-(2-Methylpyridin-4-yl)-6-(pyridin-3-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (41). **41** was prepared in an analogous three-step procedure to that of compound **43**: In a sealed 5 mL microwave vial, a solution of 4-[1-[2-methylsulfanyl-6-(3-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.07 g, 0.20 mmol) in THF (4 mL) was degassed by bubbling argon through for 5 min. (2-Methyl-4-pyridyl)boronic acid (0.03 g, 0.20 mmol), thiophene-2-carbonyloxycopper (0.06 g, 0.30 mmol), and $Pd(PPh_3)_4$ (0.02 g, 0.02 mmol) were added at room temperature. The reaction was heated in a sealed tube at 85 °C for 18 h. The reaction crude was filtered through Celite and partitioned between DCM (10 mL) and ammonium

DOI: 10.1021/acs.jmedchem.6b00028
J. Med. Chem. 2016, 59, 6101−6120

hydroxide (5 mL). The organic phase was dried over magnesium sulfate, and solvents were removed under reduced pressure. The product was purified by mass directed autopreparative HPLC under basic conditions (5−95 prep basic). The fractions containing product were pooled together and solvents were removed to obtain **41** as white solid (9 mg, 10% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 97%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (d, 1H, J = 2.0 Hz), 8.72−8.71 (m, 1H), 8.62 (d, 1H, J = 5.2 Hz), 8.45−8.42 (m, 1H), 8.19 (s, 1H), 8.13 (d, 1H, J = 5.1 Hz), 7.44 (dd, 1H, J = 4.8, 7.9 Hz), 6.92 (s, 1H), 4.67−4.66 (m, 2H), 3.75−3.73 (m, 4H), 3.10−3.04 (m, 2H), 2.67 (s, 3H), 2.61−2.54 (m, 5H), 2.05−2.00 (m, 2H), 1.63−1.55 (m, 2H); LRMS (ES$^+$) m/z 417 [M + H]$^+$.

4-(1-(6-(Pyridine-3-yl)-2-(2-(trifluoromethyl)pyridine-4-yl)-pyrimidin-4-yl)piperidin-4-yl)morpholine (42). **42** was prepared in an analogous three-step procedure to that of compound **63**: To a solution of 4-[1-(6-chloro-2-iodo-pyrimidin-4-yl)-4-piperidyl]-morpholine (0.15 g, 0.37 mmol) and (2-(trifluoromethyl)pyridine-4yl)boronic acid (0.07 mg, 0.37) in DME (3 mL) in a 5 mL sealed microwave tube, $Pd(PPh_3)_2Cl_2$ (0.01 g, 0.02 mmol) and an aqueous 2 M Na_2CO_3 solution (0.55 mL) were added. The reaction was heated at 120 °C for 20 min under microwave irradiation. The reaction mixture was diluted with methanol (10 mL) and applied to a SCX column (5 g), and the product was eluted with 2 M NH_3 in MeOH. Solvents were removed under reduced pressure and the product was further purified by column chromatography (12 g silica cartridge) using (A) DCM, (B) 10% MeOH in DCM as eluents and the following gradient: 1 min hold at 100% A, 18 min ramp to 50% B, and 3 min hold at 50% B. The fractions containing product were pooled together and solvents were removed to obtain 4-(1-(6-chloro-2-(2-(trifluoromethyl)pyridine-4-yl)pyrimidin-4-yl)piperidin-4-yl)-morpholine as an off-white solid (100 mg, 64% yield, 77% purity by LCMS). The product was used for the next step without further purification. To a stirred solution of 4-(1-(6-chloro-2-(2-(trifluoromethyl)pyridine-4-yl)pyrimidin-4-yl)piperidin-4-yl)-morpholine (0.10 g, 0.23 mmol) and 3-pyridylboronic acid (0.057 g, 0.46 mmol) in DME (3 mL), $Pd(PPh_3)_4$ (0.015 g, 0.01 mmol) and an aqueous solution of potassium phosphate (2M, 0.5 mL) were added. The reaction was heated at 120 °C for 20 min under microwave irradiation. The reaction crude was diluted with methanol (5 mL) and applied to a SCX column (1 g), and the product was eluted with 2 M NH_3 in MeOH. The product was further purified by preparative HLPC under basic conditions. The fractions containing product were pooled together and solvents were removed to obtain **42** as off-white solid (69 mg, 63% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (d, 1H, J = 1.5 Hz), 8.87−8.86 (m, 1H), 8.74 (dd, 1H, J = 1.2, 4.6 Hz), 8.74−8.71 (m, 1H), 8.55 (dd, 1H, J = 1.1, 5.0 Hz), 8.45−8.43 (m, 2H), 7.47 (dd, 1H, J = 5.1, 7.7 Hz), 6.97 (s, 1H), 4.69−4.61 (m, 2H), 3.75−3.73 (m, 4H), 3.15−3.10 (m, 2H), 2.61−2.55 (m, 5H), 2.07−2.04 (m, 2H), 1.64−1.56 (m, 2H); LRMS (ES$^+$) m/z 471 [M + H]$^+$.

4-(1-(2-(3-Methylpyridin-4-yl)-6-(pyridin-3-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (43). In a sealed 5 mL microwave vial, a solution of 4-[1-[2-methylsulfanyl-6-(3-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.10 g, 0.26 mmol) in 1,4-dioxane (4 mL) was degassed by bubbling argon through for 5 min. (3-Methyl-4-pyridyl)boronic acid (0.073 g, 0.54 mmol), thiophene-2-carbonyloxycopper (0.102 g, 0.54 mmol), and $Pd(PPh_3)_4$ (0.031 g, 0.03 mmol) were added at room temperature. The reaction was heated under microwave irradiation at 130 °C for 1 h. The reaction crude was applied to a SCX column (2 g), and the product was eluted with 2 M NH_3 in MeOH. Solvents were removed, and the product was purified by mass directed autopreparative HPLC under basic conditions. The fractions containing product were pooled together and solvents were removed to obtain **43** as off-white solid (31 mg, 26% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26−9.21 (m, 1H), 8.72−8.71 (m, 1H), 8.69−8.52 (m, 2H), 8.39−8.37 (m, 1H), 7.87 (d, 1H, J = 4.5 Hz), 7.43 (dd, 1H, J = 4.8, 7.8 Hz), 6.91(s, 1H), 4.62−4.59 (m, 2H), 3.80−3.72 (m, 4H), 3.10−3.04 (m, 2H), 2.66 (s, 3H), 2.64−2.52 (m, 5H), 2.06−2.03 (m, 2H), 1.65−1.55 (m, 2H); LRMS (ES$^+$) m/z 417 [M + H]$^+$.

4-(1-(2-(3-Fluoropyridin-4-yl)-6-(pyridin-3-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (44). **44** was prepared in an analogous three-step procedure to that of compound **43**: In a sealed 5 mL microwave vial, a solution of 4-[1-[2-methylsulfanyl-6-(3-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.10 g, 0.26 mmol) in 1,4-dioxane (4 mL) was degassed by bubbling argon through for 5 min. (3-Fluoro-4-pyridyl)boronic acid (0.076 g, 0.54 mmol), thiophene-2-carbonyloxycopper (0.102 g, 0.54 mmol), and $Pd(PPh_3)_4$ (0.031 g, 0.03 mmol) were added at room temperature. The reaction was heated under microwave irradiation at 130 °C for 1 h. The reaction crude was applied to a SCX column (2 g), and the product was eluted with 2 M NH_3 in MeOH. Solvents were removed and the product was purified by mass directed autopreparative HPLC under basic conditions. The fractions containing product were pooled together and solvents were removed to obtain **44** as off-white solid (10 mg, 9% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32−9.31 (m, 1H), 8.58−8.51 (m, 1H), 8.96−8.52 (m, 2H), 8.55−8.54 (m, 1H), 8.49−8.47 (m, 1H), 8.10−8.08 (m, 1H), 7.51−7.47 (m, 1H), 7.00 (s, 1H), 4.88−4.84 (m, 2H), 3.41−3.38 (m, 2H), 4.03−3.99 (m, 2H), 3.42−3.36 (m, 3H), 3.08−2.95 (m, 4H), 2.47−2.45 (m, 2H), 2.00−1.91 (m, 2H); LRMS (ES$^+$) m/z 421 [M + H]$^+$.

4-(4-(4-Morpholinopiperidin-1-yl)-6-(pyridin-3-yl)pyrimidin-2-yl)pyridine-2-ol (45). **45** was prepared in an analogous three-step procedure to that of compound **43**: In a sealed vial, a solution of 4-[1-[2-methylsulfanyl-6-(3-pyridyl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.15 g, 0.40 mmol) in THF (8 mL) was degassed by bubbling argon through for 5 min. 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-pyridin-2-ol (0.09 g,0.40 mmol), thiophene-2-carbonyloxycopper (0.12 g, 0.61 mmol), and $Pd(PPh_3)_4$ (0.05 g, 0.04 mmol) were added at room temperature. The reaction was heated in a sealed tube at 85 °C for 16 h. The reaction crude was applied to a SCX column (2 g), and the product was eluted with 2 M NH_3 in MeOH. Solvents were removed under reduced pressured, and the product was purified by mass directed autopreparative HPLC under basic conditions (5−95 prep basic). The fractions containing product were pooled together and solvents were removed to obtain the product as white solid (10 mg, 6% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >97%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.73 (bs, 1H), 9.43−9.42 (m, 1H), 8.70−8.69 (m, 1H), 8.61−8.60 (m, 1H), 7.56 (dd, 1H, J = 4.8, 8.0 Hz), 7.49 (s, 1H), 7.48 (d, 1H, J = 6.8 Hz), 7.32 (s, 1H), 7.13 (d, 1H, J = 6.9 Hz), 4.70−4.67 (m, 2H), 3.57−3.55 (m, 4H), 3.06−3.01 (m, 2H), 1.92−1.90 (m, 2H), 1.44−1.36 (m, 2H); LRMS (ES$^+$) m/z 419 [M + H]$^+$.

4-(1-(2-(1-Methyl-1*H*-pyrazol-4-yl)-6-(pyridin-3-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (46). **46** was prepared in an analogous three-step procedure to that of compound **40**: To a stirred solution of 4-[1-[6-chloro-2-(1-methylpyrazol-4-yl)pyrimidin-4-yl]-4-piperidyl]morpholine (0.070 g, 0.19 mmol) and 3-pyridylboronic acid (0.071 g, 0.58 mmol) in DMF (3 mL), a solution of potassium phosphate (0.122 g, 0.58 mmol) in water (1 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then $Pd(PPh_3)_4$ (0.011 g, 0.010 mmol) was added. The reaction was heated at 130 °C under microwave irradiation for 20 min. Reaction was filtered through Celite and partitioned between DCM (15 mL) and a saturated aqueous solution of $NaHCO_3$ (5 mL). The organics phase was dried over $MgSO_4$ before concentration to dryness. The crude was then purified by preparative HLPC. The fractions containing product were pooled together and solvents were removed to obtain **46** as off-white solid (27 mg, 35% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 96%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (m, 1H), 8.70−8.69 (m, 1H), 8.38−8.36 (m, 1H), 8.17 (s, 1H), 8.10 (s, 1H), 7.43−7.40 (m, 1H), 6.74 (s, 1H), 4.66−4.60 (m, 2H), 3.97 (m, 3H), 3.79−3.68 (m, 4H), 3.03−2.97 (m, 2H), 2.62−2.56 (m, 5H), 2.05−1.95 (m, 2H), 1.58−1.54 (m, 2H); LRMS (ES$^+$) m/z 406 [M + H]$^+$.

4-(1-(6-(Pyridin-3-yl)-[2,4′-bipyrimidin]-4-yl)piperidin-4-yl)-morpholine (47). **47** was prepared in an analogous three-step procedure to that of compound **43**: In a sealed 5 mL microwave vial, a solution of 4-[1-[2-methylsulfanyl-6-(3-pyridyl)pyrimidin-4-yl]-4-

DOI: 10.1021/acs.jmedchem.6b00028
J. Med. Chem. 2016, 59, 6101−6120

piperidyl]morpholine (0.075 g, 0.20 mmol) in THF (4 mL) was degassed by bubbling argon through for 5 min. Pyrimidin-4-ylboronic acid (0.037 g, 0.30 mmol), thiophene-2-carbonyloxycopper (0.058 g, 0.30 mmol), and $Pd(PPh_3)_4$ (0.023 g,0.02 mmol) were added at room temperature. The reaction was heated in the sealed tube at 85 °C for 18 h. Reaction was filtered through Celite and partitioned between DCM (10 mL) and NH_3 aq (5 mL). The organic phase was dried over magnesium sulfate, and solvents were removed under reduced pressure. The product was purified by the product was purified by mass directed autopreparative HPLC under basic conditions. The fractions containing product were pooled together and solvents were removed to obtain **47** as off-white solid (10 mg, 12% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (d, 1H, J = 1.3 Hz), 9.23 (dd, 1H, J = 0.7, 2.3 Hz), 8.93 (d, 1H, J = 5.2 Hz), 8.72 (dd, 1H, J = 1.6, 4.8 Hz), 8.46−8.43 (m, 2H), 7.45 (ddd, 1H, J = 0.8, 4.8, 8.0 Hz), 7.00 (s, 1H), 4.77−4.75 (m, 2H), 3.82−3.70 (m, 4H), 3.14−3.09 (m, 2H), 3.67−2.55 (m, 5H), 2.11−2.01 (m, 2H), 1.62−1.61 (m, 2H); LRMS (ES^+) m/z 404 $[M + H]^+$.

Scheme 2 (General Procedure for Intermediates). 4-(1-(6-Chloro-2-(2,6-dimethylpyridin-4-yl)pyrimidin-4-yl)piperidin-4-yl)morpholine (54). To a solution of 2,4,6-trichloropyrimidine (**52**) (10 g, 54.52 mmol) in ethanol (125 mL) at −5 °C (salt−ice bath), a solution of 4-(4-piperidyl)morpholine (9.28 g, 54.52 mmol) in ethanol (100 mL) was added dropwise followed by *N*,*N*-diethylethanamine (8.27 g, 81.78 mmol). Reaction mixture was stirred at −5 °C for 4 h. A white precipitate was formed. Solvents were removed under vacuum, and the reaction crude was partitioned between DCM (300 mL) and a saturated aqueous solution of $NaHCO_3$ (2 × 200 mL). The organic phase was dried over $MgSO_4$, filtered, and solvents were removed under reduced pressure. The product was purified by column chromatography (330 g silica cartridge) using (A) DCM and (B) 5% MeOH in DCM as eluents and the following gradient: 2 min hold to 100% A, 20 min ramp to 50% B, 3 min hold to 50% B. Fractions containing pure product were pooled together and solvents were removed to obtain intermediate 4-(1-(2,6-dichloropyrimidin-4-yl)-piperidin-4-yl)morpholine as a white solid (5.6 g). Column fractions that contained a mixture of the desired product and a side product resulting from substitution at C-2 were pooled together and solvents removed under vacuum. The mixture was suspended in methanol, and DCM was added to obtain a clear solution that was left standing at −20 °C. The precipitate was filtered and dried to obtain 4-(1-(2,6-dichloropyrimidin-4-yl)piperidin-4-yl)morpholine as a white solid (1.7 g). Both product fractions were mixed together (7.3 g, 42% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (s, 1H), 4.41 (broad peak, 2H), 3.72 (broad peak, 4H), 2.01−2.97 (m, 2H), 2.55−2.47 (m, 5H), 1.97−1.94 (m, 2H), 1.54−1.46 (m, 2H); LRMS (ES^+) m/z 317 $[M + H]^+$.

To a stirred solution of 4-[1-(2,6-dichloropyrimidin-4-yl)-4-piperidyl]morpholine (0.20 g, 0.63 mmol) and 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.16 g,0.69 mmol) in 1,4-dioxane (6 mL), a solution sodium carbonate (0.20 g, 1.89 mmol) in water (2 mL) was added. The reaction mixture was degassed by bubbling argon through for 5 min, and then $Pd(PPh_3)_4$ (0.036 g,0.03 mmol) was added. The reaction was heated at 120 °C under microwave irradiation for 1 h. The reaction crude filtered through Celite and partitioned between DCM (15 mL) and saturated aqueous solution of $NaHCO_3$ (5 mL). The organics phase was dried over $MgSO_4$ before concentration to dryness. The product was purified by column chromatography (4 g silica cartridge) using (A) DCM and (B) 10%MeOH in DCM as eluents and the following gradient: 1 min hold at 100% A, 18 min ramp to 40% B, 5 min hold at 40% B. The fractions containing product were pooled together and solvents were removed to obtain **54** as an off-white solid (42 mg, 15% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 88%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.81 (s, 2H), 6.47 (s, 1H), 4.64 (broad peak, 2H), 3.71−3.69 (m, 4H), 3.02−2.97 (m, 2H), 2.58 (s, 6H), 2.56−2.43(m, 5H), 1.98−1.86 (m, 2H), 1.55−1.47 (m, 2H); LRMS (ES^+) m/z 388 $[M + H]^+$.

Scheme 3 (General Procedure for Intermediates). 4-(1-(2-(Methylthio)-6-(pyridin-3-yl)pyrimidin-4-yl)piperidin-4-yl)-morpholine (58). To a stirred solution of 4-(4-piperidyl)morpholine (4.36 g, 25.63 mmol) in ethanol (50 mL), a solution of 4,6-dichloro-2-methylsulfanylpyrimidine (**56**) (5.00 g, 25.63 mmol) in ethanol (50 mL) was added dropwise at room temperature. *N*,*N*-Diethylethanamine (3. 89 g, 38.45 mmol) was then added, and the reaction mixture was stirred at room temperature for 3 h. A white precipitate was formed. Solvents were removed under reduced pressured, and the reaction crude was purified by filtration through a silica plug. First, impurities were removed with a mixture 1/1 of petroleum ether and ethyl acetate, and then the product eluted with methanol. The fractions containing product were pooled together and methanol was removed to obtain 4-[1-(6-chloro-2-methylsulfanyl-pyrimidin-4-yl)-4-piperidyl]morpholine (**57**) as off-white solid (7.17 g, 84% yield). Purity by LCMS (UV chromatogram, 190−450 nm) >98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (s, 1H), 4.37 (broad peak, 2H), 3.76 (broad peak, 4H), 2.95−2.90 (m, 2H), 2.69−2.53 (m, 5H), 2.47 (s, 3H), 1.98−1.96 (m, 2H), 1.54−1.48 (m, 2H); LRMS (ES^+) m/z 329 $[M + H]^+$.

A solution of **57** (4.00 g, 12.16 mmol) and 3-pyridylboronic acid (2.99 g, 24.3 mmol) in 1,4-dioxane (60 mL) was divided equally into four 20 mL microwave vials. A solution of K_3PO_4 (5.16 g, 24.32 mmol) in water (20 mL) was prepared, and an amount of 5 mL was added to each reaction vial. The reaction mixtures were degassed by bubbling argon through for 5 min. Then, $Pd(PPh_3)_4$ (0.70 mg, 0.61 mmol) was added and the reaction mixtures were heated under microwave irradiation at 130 °C for 30 min. The contents of the three vials were pooled together, and the reaction was filtered through Celite and partitioned between DCM (2 × 200 mL) and a saturated aqueous solution of $NaHCO_3$ (20 mL). The product was purified by column chromatography (120 g silica cartridge) using (A) DCM and (B) 10% MeOH in DCM as eluents and the following gradient: 1 min hold at 100% A, 20 min ramp to 50% B, 10 min hold at 50% B. The fractions containing product were pooled together and the solvents removed to obtain a dark color solid. The solid was dissolved in methanol (50 mL) and 3-mercaptopropyl ethyl sulfide silica (2 g, 60−200 μM, Phosphonics SPM-32) was added. The stirred suspension was heated at 50 °C overnight. The silica was filtered and washed with methanol (100 mL). Methanol was removed under reduced pressure to obtain the **58** as an off-white solid (2.24 g, 50% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (dd, 1H, J = 0.6, 2.2 Hz), 8.66 (dd, 1H, J = 1.7, 4.8), 8.32−8.29 (m, 1H), 7.37 (ddd, 1H, J = 0.7, 4.8, 7.9 Hz), 6.61 (s, 1H), 4.49−4.51 (m, 2H), 3.73−3.71 (m, 4H), 3.00−2.94 (m, 2H), 2.58−2.56 (m, 7H), 2.53−2.46(m, 1H), 1.97−1.95 (m, 2H), 1.52 (ddd, 2H, J = 4.3, 12.3, 24.2 Hz); LRMS (ES^+) m/z 372 $[M + H]^+$.

Scheme 4 (General Procedure for Intermediates). 4,6-Dichloro-2-iodopyrimidine (60). To a stirred solution 4,6-dichloropyrimidin-2-amine (4.23 g, 25.8 mmol) and diiodomethane (6.91 g, 25.8 mmol) in anhydrous acetonitrile (36 mL) was added *tert*-butyl nitrite (11.97 g, 116.1 mmol) at room temperature under nitrogen. The reaction mixture was heated at 80 °C for 3 h and 30 min. The reaction crude was concentrated under reduced pressure and purified by column chromatography (80 g silica cartridge) using (A) Hex, (B) ethyl acetate as eluents and the following gradient: 5 min hold at 100% A, 10 min ramp to 20% B, 1 min hold at 20% B. Fractions containing product were pooled together and solvents removed under reduced pressure to obtain **12** as an off-white solid (4.49 g, 63% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (m, 1H).

4-(1-(6-Chloro-2-iodopyrimidin-4-yl)piperidin-4-yl)-morpholine (61). To a stirred solution of 4,6-dichloro-2-iodopyrimidine (**60**) (6.14 g, 22.33 mmol) in ethanol (120 mL), a solution of 4-(4-piperidyl)morpholine (3.80 g, 22.33 mmol) in 7 mL of ethanol was added in an ice bath. *N*,*N*-Diethylethanamine (6.78 g, 66.98 mmol) was then added, and the reaction was stirred for 3 h at 0 °C. Solvents were removed under reduced pressure, and the reaction was partitioned between a saturated aqueous solution of $NaHCO_3$ (50 mL) and DCM (150 mL). Solvents were removed under vacuum, and

DOI: 10.1021/acs.jmedchem.6b00028
J. Med. Chem. 2016, 59, 6101−6120

reaction crude was purified by column chromatography (80 g silica cartridge) using (A) Hex, (B) ethyl acetate as eluents and the following gradient: 1 min hold at 100% A, 25 min ramp to 100% B, 15 min hold at 100% B. Fractions containing product were pooled together and solvents removed under reduced pressure to obtain **61** as yellow solid (7 g, 77% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (s, 1H), 3.72−3.70 (m, 4H), 2.97−2.93 (m, 2H), 2.55−2.53 (m, 4H), 2.50−2.45 (m, 1H), 1.95−1.92 (m, 2H), 1.52−1.43 (m, 2H); LRMS (ES^+) m/z 409 $[M + H]^+$.

4-Chloro-6-(4-morpholinopiperidin-1-yl)pyrimidine-2-carbonitrile (62). In a stirred sealed tube a solution of 4-[1-(6-chloro-2-iodo-pyrimidin-4-yl)-4-piperidyl]morpholine (**61**) (0.29 g, 0.72 mmol) and copper cyanide (0.077 g, 0.86 mmol) in NMP (3 mL) was heated at 120 °C for 5 h. Reaction crude was applied to a SCX cartridge (5 g), and the product was diluted with a solution of 2 N NH_3 in methanol. The product was further purified by column chromatography (12 g silica cartridge) using (A) DCM, (B) 10% MeOH in DCM as eluents and the following gradient: 1 min hold at 100% A, 10 min ramp to 50% B, and 3 min hold at 50% B. The fractions containing product were pooled together and solvents were removed to obtain 4-chloro-6-(4-morpholinopiperidin-1-yl)pyrimidine-2-carbonitrile (**62**) as an off-white solid (139 mg, 62% yield). Purity by LCMS (UV chromatogram, 190−450 nm) 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (s, 1H), 3.73−3.71 (m, 4H), 3.06−3.01 (m, 2H), 2.56−2.48 (m, 5H), 1.99−1.96 (m, 2H), 1.55−1.47 (m, 2H); LRMS (ES^+) m/z 308 $[M + H]^+$.

Biology Materials and Methods. This information is in the Supporting Information.

Ethical Statements. In vivo antimalarial efficacy studies in *P. berghei* carried out at the Swiss Tropical and Public Health Institute (Basel, Switzerland) adhere to local and national regulations of laboratory animal welfare in Switzerland (awarded permission no. 1731). Protocols are regularly reviewed and revised following approval by the local authority (Veterinäramt Basel Stadt).

In vivo antimalarial efficacy studies using *P. falciparum* in SCID mice carried out at GSK were approved by the Diseases of the Developing World Ethical Committee on Animal Research and carried out in accordance with European Directive 2010/63/EU and the GSK Policy on the Care, Welfare and Treatment of Animals. The animal studies were performed at DDW Laboratory Animal Science facilities accredited by AAALAC. The human biological samples were sourced ethically, and their research use was in accord with the terms of the informed consents.

Mouse pharmacokinetics were carried out at the University of Dundee. All regulated procedures on living animals were carried out under the authority of a license issued by the Home Office under the Animals (Scientific Procedures) Act 1986, as amended in 2012 (and in compliance with EU Directive EU/2010/63). License applications will have been approved by the University's Ethical Review Committee (ERC) before submission to the Home Office. The ERC has a general remit to develop and oversee policy on all aspects of the use of animals on University premises and is a subcommittee of the University Court, its highest governing body.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.6b00028.

Synthetic details for all compounds, supplementary data tables, additional information on ADMET and pharmacology (PDF)

Molecular formula strings (CSV)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge Medicines for Malaria for financial support. The University of Dundee also acknowledges support from the Wellcome Trust (Grant 100476 and a Principal Research Fellowship to A.H.F.). This work is partially funded by the MSD Scottish Life Sciences Fund. As part of an ongoing contribution to Scottish life sciences, Merck Sharp & Dohme (MSD) Ltd. (known as Merck & Co., Inc., Kenilworth, NJ, U.S., in the United States and Canada) has given substantial monetary funding to the Scottish Funding Council (SFC) for distribution via the Scottish Universities Life Sciences Alliance (SULSA) to develop and deliver a high quality drug discovery research and training program. All aspects of the program have been geared toward attaining the highest value in terms of scientific discovery, training, and impact. The opinions expressed in this research are those of the authors and do not necessarily represent those of MSD or its affiliates. We thank Jolanda Kamber for assistance in performing the in vivo (Pb) antimalarial assays. We thank L. D. Shultz and The Jackson Laboratory for providing access to nonobese diabetic scid IL2Rγc^{null} mice through their collaboration with GSK Tres Cantos Medicines Development Campus.

■ ABBREVIATIONS USED

ACT, artemisinin-based combination therapy; MMV, Medicines for Malaria Venture; PRR, parasite reduction ratio; SCX, strong cation exchange; SCID, nonobese diabetic scid IL2Rγc^{null}; WHO, World Health Organization

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