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Original article

Synthesis and biological activity of imidazopyridine anticoccidial agents: Part I

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Abstract

Coccidiosis is the major cause of morbidity and mortality in the poultry industry. Protozoan parasites of the genus *Eimeria* invade the intestinal lining of the avian host causing tissue pathology, poor weight gain, and in some cases mortality. Resistance to current anticoccidials has prompted the search for new therapeutic agents with potent in vitro and in vivo activity against *Eimeria*. Antiparasitic activity is due to inhibition of a parasite specific cGMP-dependent protein kinase (PKG). In this study, we present the synthesis and biological activity of imidazo[1,2-*a*]pyridine anticoccidial agents. From this series, several compounds showed subnanomolar in vitro activity and commercial levels of in vivo activity. However, the potential genotoxicity of these compounds precludes them from further development.

Keywords: Coccidiosis; Antiparasitic; Antiprotozoal; Kinase; Imidazopyridine

1. Introduction

Coccidiosis is a parasitic disease which is the major cause of morbidity and mortality in the poultry industry. It is a disease of the avian intestinal lining due to invasion by protozoan parasites of the genus *Eimeria* [1]. Some of the most significant *Eimeria* species in poultry are *Eimeria tenella*, *Eimeria acervulina*, *Eimeria necartrix*, *Eimeria brunetti* and *Eimeria maxima*. Over 35 billion chickens are raised annually worldwide, and all major poultry operations use anticoccidial agents prophylactically. Resistance to current coccidiostats is becoming widespread, and new broad spectrum drugs directed at novel biochemical targets are needed. Genetic studies in *Toxoplasma gondii*, a protozoan parasite closely related to *Eimeria*, demonstrate that cGMP-dependent protein kinase (PKG) is essential for survival and represents a desirable therapeutic target [2]. It was reported recently that inhibition of a novel PKG, isolated from these parasites, stops the parasite proliferation by blocking parasite invasion [2,3]. High throughput screening of known kinase inhibitors resulted in the discovery of imidazopyridine analogs as PKG inhibitors and broad spectrum anticoccidial agents [4]. Herein, we report PKG inhibition, synthesis, evaluation, optimization and in vivo anticoccidial activities of such compounds with diversity introduced at the imidazopyridine 2- and 3-positions. Future publications will explore modifications introduced elsewhere on the imidazopyridine scaffold.

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2. Results and discussion

2.1. Chemistry

Introduction of diversity on the amino group of the pyrimidine 2-position was accomplished as shown in Scheme 1. First, 2-mercapto-4-methylpyrimidine hydrochloride was refluxed with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) to give thiomethyl ether **1** [5]. Upon treatment with lithium diisopropylamide (LDA), the anion of **1** reacted with methyl 4-fluorobenzoate to yield **2**, which exists as a mixture of ketone and enol tautomers [6]. Subsequent bromination with tetra-*n*-butylammonium tribromide gave α-bromoketone **3**, which cyclized with (2-aminopyridin-4-yl)methanol to give imidazopyridine **4** [7]. Treatment of alcohol **4** with methanesulfonyl chloride and triethylamine afforded methanesulfonate ester **5**, which upon treatment with dimethylamine and diisopropylethylamine gave benzylic dimethylamine **6**. Treatment of sulfide **6** with hydrogen peroxide, acetic acid, and sodium tungsate dihydrate, followed by sulfur dioxide to back-reduce any tertiary amine N-oxide [8], gave sulfone **7**. The desired 2-NHR-substituted pyrimidines (**8a–dd**) were ultimately prepared by heating sulfone **7** with an excess of appropriate alkylamine, benzylamine, or arylamine [6].

Carbonyl- and sulfonyl-bearing substituents were also installed on the amino group at the pyrimidine 2-position as shown in Scheme 2 below. Treatment of sulfone **7** with ammonia afforded 2-aminopyrimidine **8ee** [9], which was then treated with appropriate acid chloride in pyridine to give amides **9a–f** [10], or sulfonyl chloride in pyridine to give sulfonamides **9g–i** [11]. Alternatively, treatment of 2-aminopyrimidine **8ee** with formic acid and acetic anhydride gave formamide **9j** [12], while reaction of **8ee** with *t*-butyl isocyanate and sodium hydride gave urea **9k** [13]. Likewise, treating **8ee** with methyl chloroformate and triethylamine yielded carbamate **9l** [14].

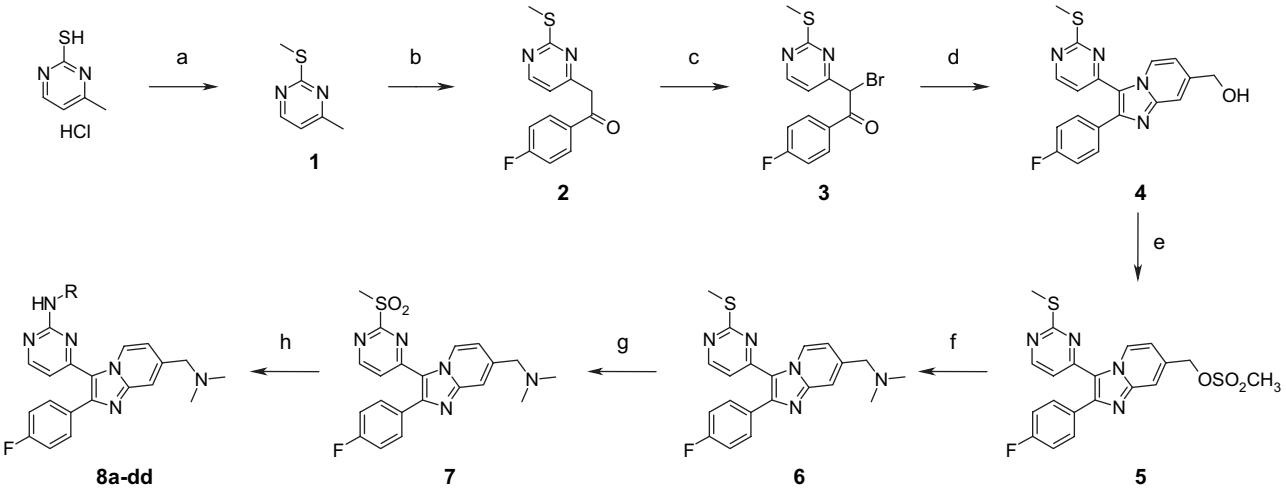
In addition, functionality was introduced at the pyrimidine 5-position, including methyl (**17**), cyano (**22**), fluoro (**25**), and bromo (**26**). The 5-methylpyrimidine (**17**) was synthesized as shown below in Scheme 3. Bromination of methyl 4-fluorobenzoylacetate with tetra-*n*-butylammonium tribromide gave bromide **10**, which was treated with (2-aminopyridin-4-yl)-methanol to yield imidazopyridine **11** [7]. Esterification of alcohol **11** with methanesulfonyl chloride and triethylamine afforded methanesulfonate ester **12**, which upon treatment with dimethylamine and diisopropylethylamine produced tertiary amine **13**. The methyl ester of **13** was then converted to the corresponding Weinreb amide (**14**) with *N*,*O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride [15]. Treatment of Weinreb amide **14** with ethylmagnesium bromide gave ethyl ketone **15** [15], which then reacted with DMFDMA to yield enone **16** [16]. Subsequent treatment of enone **16** with guanidine hydrochloride and sodium methoxide yielded 2-amino-5-methylpyrimidine **17** [16].

5-Cyanopyrimidine (**22**) was synthesized in a similar fashion, as shown in Scheme 4. Treatment of Weinreb amide **14** with methylmagnesium bromide gave methyl ketone **18** [15], which reacted with bromine in acetic acid to give α-bromoketone **19** [17]. Subsequent nucleophilic displacement with sodium cyanide afforded α-cyanoketone **20** [17]. Reaction of ketone **20** with DMFDMA yielded enone **21** [16], which upon treatment with guanidine hydrochloride and sodium methoxide afforded 2-amino-5-cyanopyrimidine **22** [16].

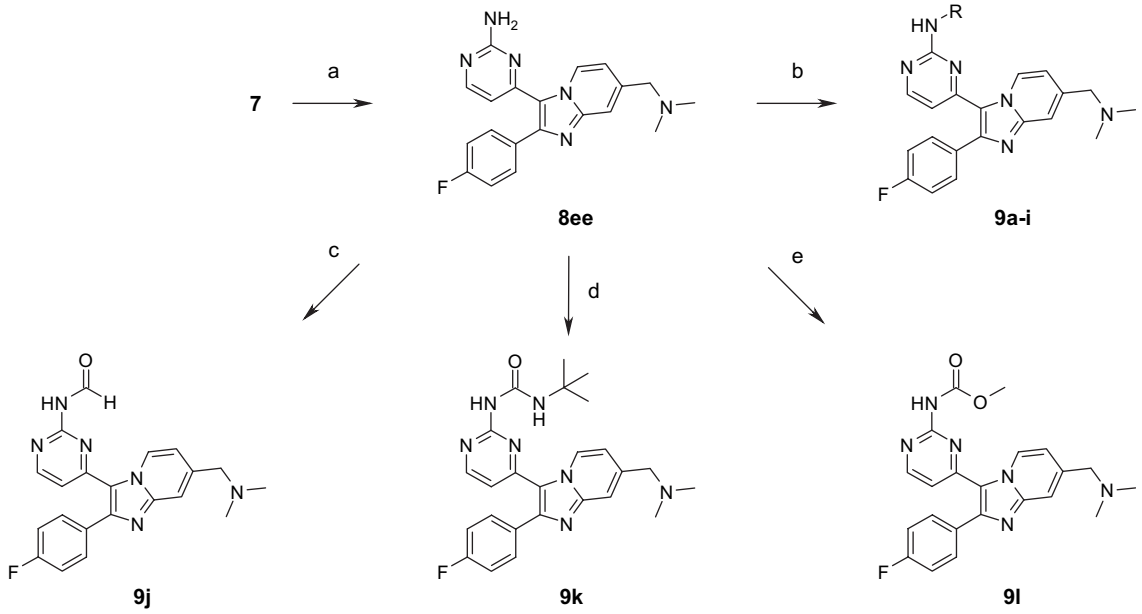
Scheme 5 shows the synthesis of the 5-fluoropyrimidine (**25**). Treatment of ketone **18** with DMFDMA gave enone **23** [16], which was fluorinated by *N*-fluorobenzenesulfonimide to give 2-fluoroenone **24** [18]. Subsequent reaction with guanidine hydrochloride and sodium methoxide afforded 2-amino-5-fluoropyrimidine **25** [16].

Scheme 6 shows the synthesis of 5-bromopyrimidine **26** via treatment of 2-aminopyrimidine **8ee** with *N*-bromosuccinimide [19].

In addition, several modifications were made at the 2-aryl ring. Substitutes for the 4-fluorophenyl ring included 3-bromo-4-fluorophenyl (**34a**), 4-fluoro-3-methylphenyl (**34b**), 4-chlorophenyl (**34c**), 2,4-difluorophenyl (**34d**), and 2,4,6-trifluorophenyl (**43**). Scheme 7 shows the synthesis of compounds

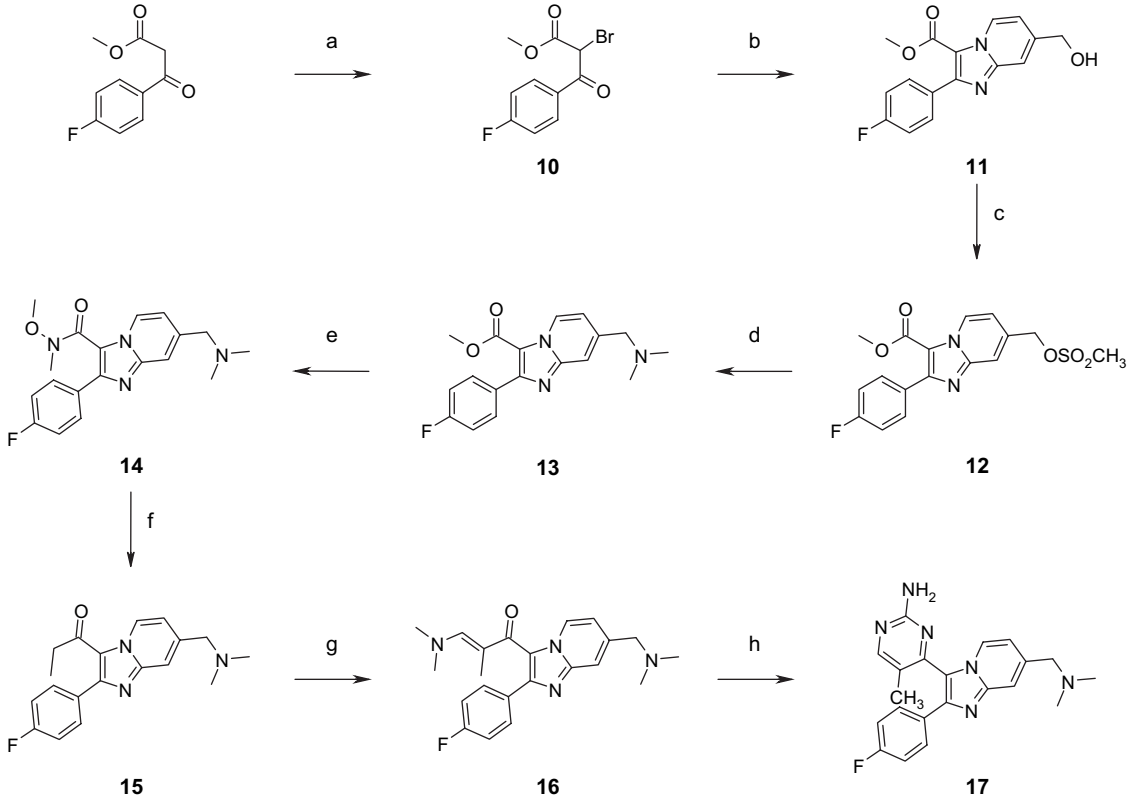


Scheme 1. Reagents: (a) DMFDMA; (b) LDA, methyl 4-fluorobenzoate; (c) *n*-Bu_4NBr_3; (d) (2-aminopyridin-4-yl)methanol; (e) CH_3SO_2Cl, Et_3N; (f) $HNMe_2$, *i*-Pr_2NEt; (g) (i) 30% H_2O_2, AcOH, Na_2WO_4-$2H_2O$; (ii) SO_2; (h) H_2NR where R is defined in Table 1.

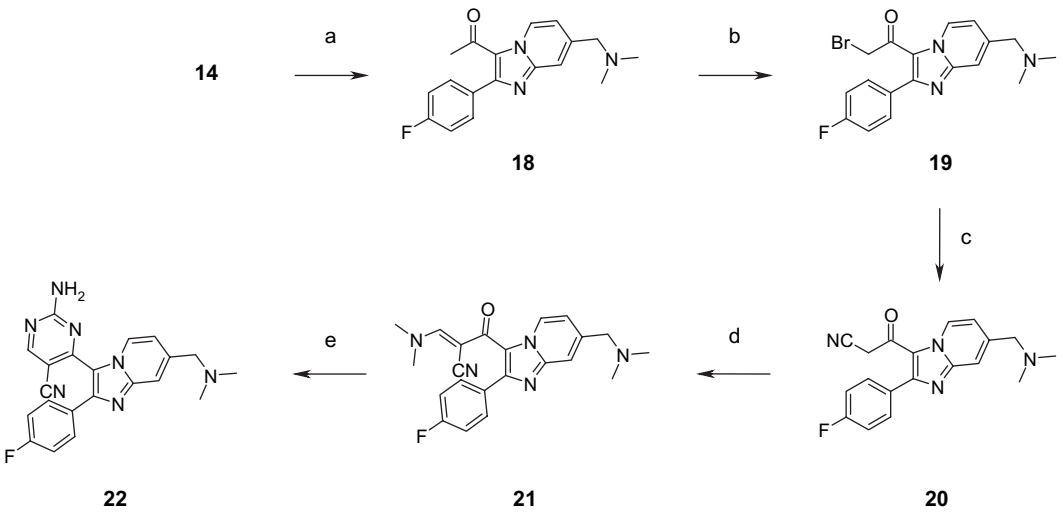


Scheme 2. Reagents: (a) NH_3; (b) RC(=O)Cl or RSO_2Cl, pyridine where R is defined in Table 2; (c) HCO_2H, Ac_2O; (d) $(CH_3)_3CN{=}C{=}O$, NaH; (e) $ClCO_2CH_3$, Et_3N.

34a–d. Esterification of both 3-bromo-4-fluorobenzoic acid and 4-fluoro-3-methylbenzoic acid with methanol and catalytic sulfuric acid gave the corresponding methyl esters **27a** and **27b**. Subsequent treatment of these two esters, along with the commercially available esters methyl 4-chlorobenzoate and ethyl 2,4-difluorobenzoate, with the anion of 4-methyl-2-(methylmercapto)pyrimidine (**1**) gave **28a–d**, which also exist as ketone/enol mixtures [6]. This was followed by bromination with tetra-*n*-butylammonium tribromide to give bromides **29a–d**, which were then cyclized with (2-aminopyridin-4-yl)-methanol to give imidazopyridines **30a–d** [7]. Subsequent oxidation with OXONE® gave sulfones **31a–d**, which were



Scheme 3. Reagents: (a) *n*-Bu_4NBr_3; (b) (2-aminopyridin-4-yl)methanol; (c) CH_3SO_2Cl, Et_3N; (d) $HNMe_2$, *i*-Pr_2NEt; (e) Me(MeO)NH–HCl, *i*-PrMgCl; (f) CH_3CH_2MgBr; (g) DMFDMA; (h) guanidine–HCl, NaOMe.



Scheme 4. Reagents: (a) CH_3MgBr; (b) Br_2, HOAc; (c) NaCN; (d) DMFDMA; (e) guanidine–HCl, NaOMe.

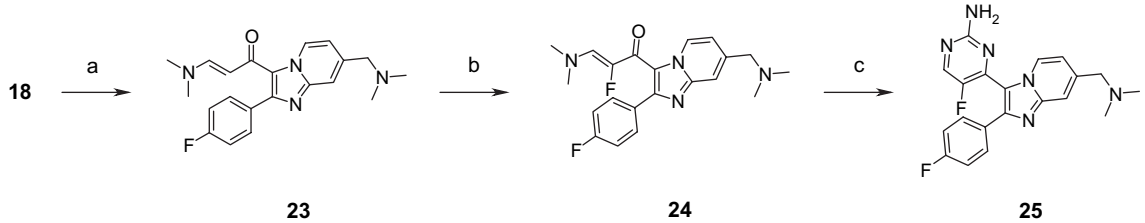
then treated with ammonia to give 2-aminopyrimidines **32a–d** [6]. Benzylic oxidation with manganese(IV) oxide yielded aldehydes **33a–d**, which was followed by reductive amination with dimethylamine and sodium triacetoxyborohydride to ultimately yield benzylic amines **34a–d**.

The 2-(2,4,6-trifluorophenyl)imidazopyridine (**43**) was prepared by a slightly different pathway, in which the pyrimidine ring was constructed after the 7-(dimethylaminomethyl)imidazopyridine scaffold was assembled, shown in Scheme 8. Ethyl hydrogen malonate was treated with 2 equivalents *n*-BuLi, and then with 2,4,6-tifluorobenzoyl chloride to yield 1,3-ketoester **35** [20]. Subsequent bromination with tetra-*n*-butylammonium tribromide gave bromide **36**, which was cyclized with (2-aminopyridin-4-yl)methanol to yield imidazopyridine **37** [7]. Functionalization of the imidazopyridine 7-position then occurred via esterification with methanesulfonyl chloride and triethylamine to methanesulfonate ester **38** followed by treatment with dimethylamine and diisopropylethylamine to give tertiary amine **39**. Ethyl ester **39** was then treated with *N*,*O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride to yield Weinreb amide **40**, which was then converted to methyl ketone **41** with methylmagnesium bromide [15]. Methyl ketone **41** then reacted with DMFDMA to give enone **42**, which was subsequently treated with guanidine hydrochloride and sodium methoxide to ultimately yield 2-aminopyrimidine **43** [16].

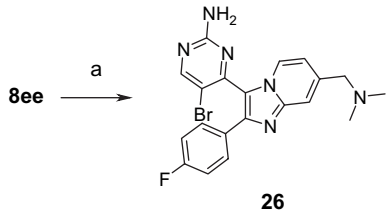
2.2. Biology

The title compounds were tested for in vitro efficacy using the Ten_K (*Ten*ella *K*inase) assay, and in vivo efficacy in the ExMAC (*Ex*panded *M*ini-*A*ssay *C*occidiosis) assay. The Ten_K assay measures inhibition of *E. tenella* PKG enzyme activity, and is reported as the amount of compound required to inhibit activity by 50% (IC_{50}, in nM). The ExMAC assay measures antiparasitic activity after administration of compound to infected chickens (ppm in feed). Birds are infected with *E. tenella* (E_t), *E. acervulina* (E_a), *Eimeria mitis* (E_{mi}), and *E. maxima* (E_{ma}), and efficacy is reported using a score of 0 through 4 based on percent of oocyte reduction relative to an untreated control. Treatments that provide 100% reduction of oocyte production are scored with a '4', those with 80–99% reduction are scored '3', those with 50–79% reduction are scored '2', and those with <50% reduction are scored '0'. Details of these procedures were published in early work [3]. In some cases, not all 4 species of *Eimeria* were tested.

The data presented in Table 1 summarizes the effect of substitution at the pyrimidine 2-NH-group on both in vitro and in vivo efficacies. Regarding in vitro activity, it is seen that alkyl, benzyl, aryl, and carbonyl-bearing functionality are all well tolerated at the pyrimidine 2-position. However, the sulfonamides showed distinctly weaker potency, possibly due to

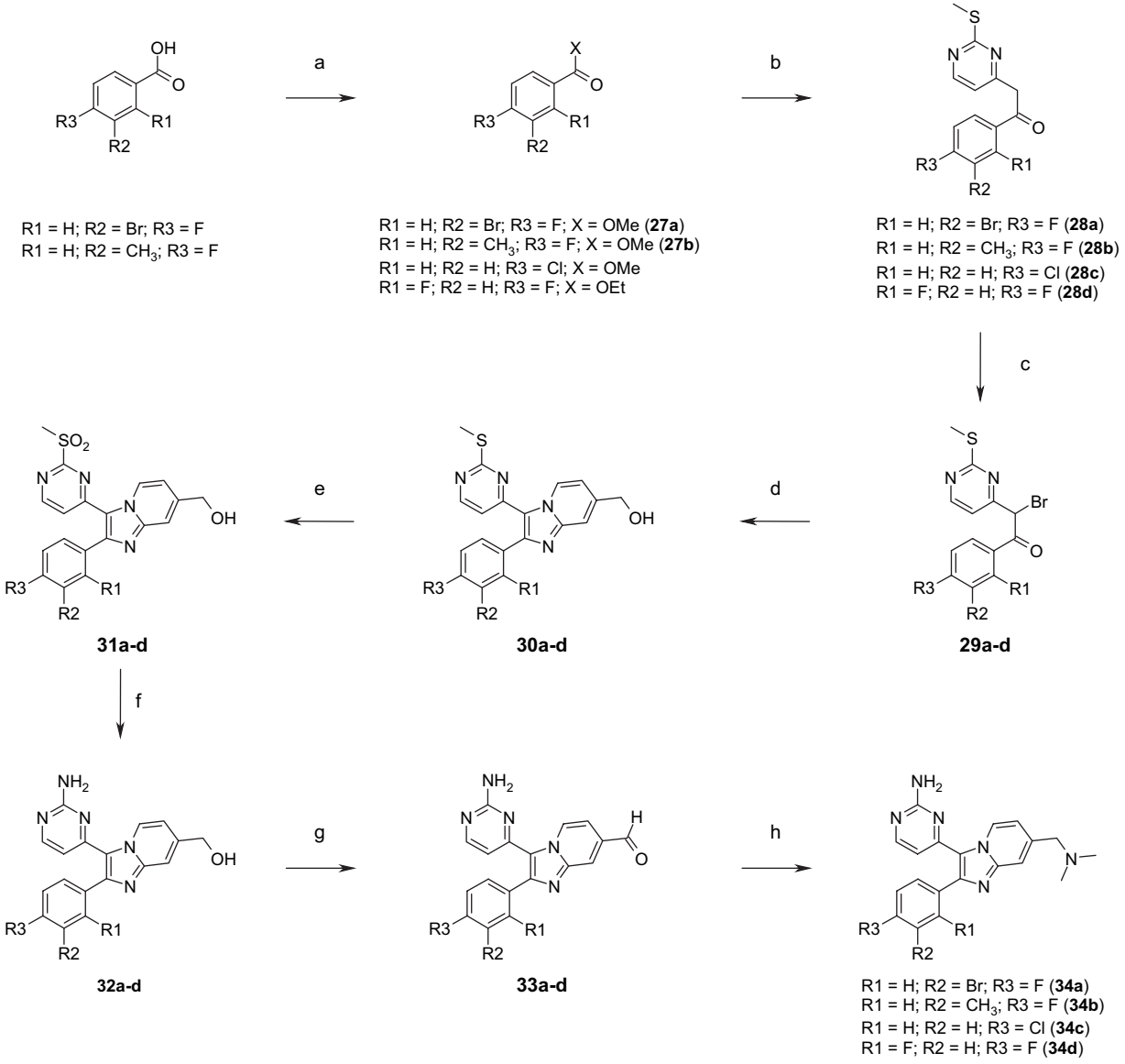


Scheme 5. Reagents: (a) DMFDMA; (b) $(PhSO_2)_2NF$; (c) guanidine–HCl, NaOMe.

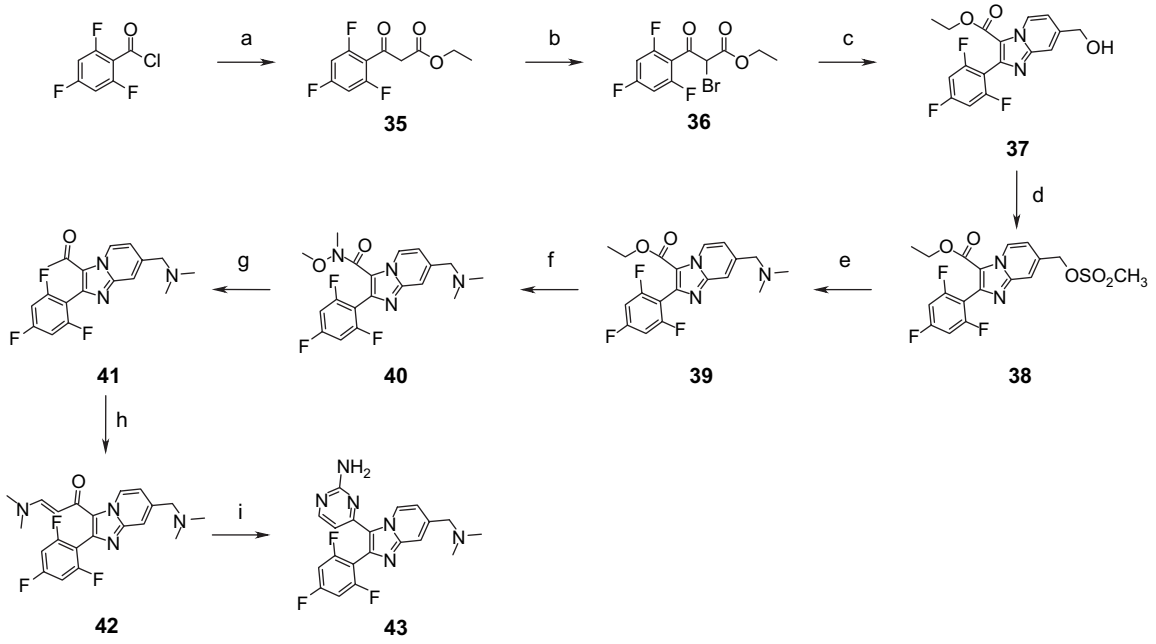


Scheme 6. Reagents: (a) *N*-bromosuccinimide.

deprotonation of the sulfonamide −NH under the assay conditions. Efficacy in vivo, however, varied more significantly with NH-substitution. The NH-alkylpyrimidines generally showed good in vivo potency, as 8 out of 14 showed activity against all 4 species of *Eimeria* at 25 ppm, and 3 of these showed such activity at 12.5 ppm. It is noted that activity was often slightly better with 2-NH-cycloalkylpyrimidines than the corresponding isomeric NH-*n*-alkylpyrimidines, with potency being the lowest in the *n*-hexyl analog, where alkyl chain length reached 6 carbons. The NH-benzylpyrimidines, on the other hand, generally showed weaker in vivo activity, with only 2 examples out of 15 showing activity against all 4 species of *Eimeria* at 25 ppm, and none of these showing the same spectrum of activity at 12.5 ppm. One NH-aryl compound (pyridin-2-yl) from this series showed significant in vivo activity. All 6 amides tested showed activity against all 4 species of *Eimeria* at 25 ppm, and 2 of these showed such activity at 12.5 ppm. The three sulfonamides showed significantly weaker in vivo activity, which again may be due to deprotonation of the sulfonamide −NH under the assay condition. Between the formamide, urea, and carbamate, the formamide showed the most promising activity; however, pH stability studies (not shown) suggested that the formamide group could be hydrolyzed to the active 2-aminopyrimidine at pH < 2.5.



Scheme 7. Reagents: (a) MeOH, H_2SO_4; (b) LDA, **1**; (c) *n*-Bu_4NBr_3; (d) (2-aminopyridin-4-yl)methanol; (e) OXONE®; (f) NH_3; (g) MnO_2; (h) $HNMe_2$, $NaB(OAc)_3H$.



Scheme 8. Reagents: (a) *n*-BuLi, ethyl hydrogen malonate; (b) *n*-Bu_4NBr_3; (c) (2-aminopyridin-4-yl)methanol; (d) CH_3SO_2Cl, Et_3N; (e) $HNMe_2$, *i*-Pr_2NEt; (f) Me(MeO)NH-HCl, *i*-PrMgCl; (g) CH_3MgBr; (h) DMFDMA; (i) guanidine–HCl, NaOMe.

The data presented in Table 2 summarizes the effect of introducing a substituent at the pyrimidine 5-position on both in vitro and in vivo efficacies. Here it is seen that only hydrogen and fluorine at the pyrimidine 5-position are well tolerated. Other compounds bearing sterically larger groups are considerably less potent in both assays. It is possible that when such a large group is present at the pyrimidine 5-position, it forces conformational rigidity that prohibits the 3-aryl ring from rotating out of an orthogonal position relative to the imidazopyridine core. This may, in turn, adversely affect PKG binding affinity.

The data presented in Table 3 summarizes the effect of substitution on the aryl ring at the imidazopyridine 2-position on biological activity. All analogs showed subnanomolar in vitro potency, suggesting some degree of tolerance of small substituents on the 2-aryl ring. In vivo potency was also found to be consistently strong in all compounds except in 4-chlorophenyl, suggesting that fluorine at the phenyl 4-position is important for bioavailability. It is noted that the 2,4-difluorophenyl analog is the most active compound in this series, showing activity against all 3 species of *Eimeria* tested down to 6.25 ppm, while the 2,4,6-trifluorophenyl analog shows weaker activity than either the 4-fluorphenyl or 2,4-difluorophenyl analogs.

3. Conclusion

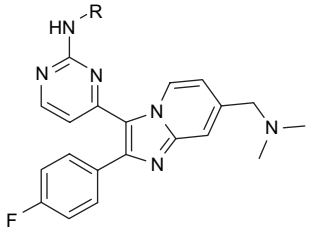
We have prepared several 2-aryl-3-(2-aminopyrimidin-4-yl) imidazopyridines with varying substitution on the 2-aryl and 3-aryl rings that have potent anticoccidial activity. We have found that there is tolerance of alkyl groups, carbonyl groups, and to a lesser extent, benzyl and aryl groups at the pyrimidine 2-NHR-position as long as this pyrimidine amino group remains protonated at physiological pH. There is less tolerance, however, for bulky substituents at the pyrimidine 5-position, which perhaps induce a conformational change on the molecule that is detrimental for PKG binding. We have also found there to be some freedom to vary substitution on the 2-aryl ring, as long as a fluorine remains at the 4-position of this ring, with both 4-fluoro-3-methylphenyl and 2,4-difluorophenyl being optimal. Overall, there are 14 compounds presented that show activity against all tested species of *Eimeria* at 12.5 ppm (**8c**, **8d**, **8f**, **8g**, **8h**, **8k**, **9b**, **9c**, **9e**, **9j**, **9k**, **8ee**, **34b**, and **34d**). Of these, compound **8ee** was strongly considered for further studies. However, the potential genotoxicity of this compound and others in this series precluded them from further development [4a].

4. Experimental section

4.1. General

Reactions were monitored by thin-layer chromatography (TLC) on precoated EMD silica gel (60 F_{254}) plates (250 μm thickness) and visualized using UV light (254 nm), or by LCMS using a ThermoFinnigan AQA spectrometer with UV detection (254 nm). Flash chromatography purification was performed using Isco RediSep cartridges on an Isco OptiX10 or Companion automated flash chromatography system, or using EMD silica gel (230–400 mesh). HPLC purification was conducted on a Varian Dynamax HPLC Guard Column, 21.4 mm, Compression Module Microsorb Guard-8 C-18 (P/N R00083221G). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 MHz spectrometer; the values of chemical shifts (δ) are given in ppm relative to the central peak of the solvent, and the values of coupling constants (J) are given in hertz (Hz). Mass spectra were recorded on a ThermoFinnigan

Table 1
Biological activity of 3-(2-NHR)pyrimidin-4-yl)imidazopyridines



Compound	R	Ten_K IC_{50} (nM)[a]	ExMAC dose (ppm)	ExMAC rating			
				E_t	E_a	E_{mi}	E_{ma}
8a	CH_2CH_3	0.23; 0.28	25	3	3	3	3
			12.5	3	3	0	3
			6.25	0	0	0	3
8b	CH_2CH_2OH	2.9; 0.3	25	3	3	3	3
			12.5	2	0	0	3
			6.25	0	0	0	2
8c	*c*-Pr	0.08; 0.25	25	3	3	3	3
			12.5	3	3	2	3
			6.25	0	3	0	3
8d	$CH_2CH_2CH_3$	0.13	12.5	3	3	3	3
8e	$CH_2CH_2OCH_3$	0.47; 0.25	25	3	3	0	3
			12.5	3	3	0	3
			6.25	0	0	0	2
8f	$CH_2CH_2CH_2OH$	0.33; 0.34	12.5	3	3	3	3
			6.25	3	0	0	3
8g	CH_2–*c*-Pr	0.064;	25	3	3	3	3
		0.25	12.5	3	3	3	3
			6.25	0	3	0	3
8h	*c*-Bu	0.22; 0.3	25	3	3	3	3
			12.5	3	3	2	3
			6.25	3	0	0	2
8i	$CH_2CH_2CH_2CH_3$	2.14	50	0	0	0	0
8j	$CH_2CH_2CH_2OCH_3$	0.52; 0.25	25	3	3	0	2
8k	*c*-Pentyl	0.102;	12.5	3	3	3	3
		0.55	6.25	3	3	2	0
8l	$CH_2CH_2CH_2CH_2CH_3$	0.1; 0.28	25	0	3	2	3
8m	*c*-Hexyl	0.12; 0.3	25	3	2	3	3
			12.5	3	0	2	3
			6.25	3	0	0	3
8n	$CH_2CH_2CH_2CH_2CH_2CH_3$	0.13; 0.3	25	3	0	0	0
8o	CH_2–2-F–Ph	0.087	25	3	0	3	3
8p	CH_2–2-F–3-F–Ph	0.12; 0.3	25	0	0	0	0
8q	CH_2–2-F–4-F–Ph	0.15; 0.27	25	0	0	0	3
8r	CH_2–2-F–5-F–Ph	0.026; 0.25	25	0	0	0	3
8s	CH_2–2-F–6-F–Ph	0.06; 0.3	25	2	0	3	3
			12.5	0	0	0	3
			6.25	0	0	0	2
8t	CH_2–2-Cl–Ph	0.056; 0.55	25	2	0	0	3
8u	CH_2–2-CH_3–Ph	0.08; 0.28	25	0	0	0	2
8v	CH_2–3-F–Ph	0.09; 0.3	25	2	3	2	3
			12.5	0	2	0	3
			6.25	0	0	0	0

Table 1 (*continued*)

Compound	R	Ten_K IC_{50} (nM)[a]	ExMAC dose (ppm)	ExMAC rating			
				E_t	E_a	E_{mi}	E_{ma}
8w	CH_2–3-F–4-F–Ph	0.06	25	0	0	0	0
8x	CH_2–3-F–5-F–Ph	0.11; 0.3	25	3	3	0	3
			12.5	0	0	0	0
8y	CH_2–3-Cl–Ph	0.18; 0.3	25	0	0	0	3
8z	CH_2–3-CH_3–Ph	0.083; 0.29	25	3	0	0	0
8aa	CH_2–4-F–Ph	0.066;	25	3	3	3	3
		0.29	12.5	0	0	0	0
8bb	CH_2–4-Cl–Ph	0.24; 0.3	25	0	0	0	0
8cc	CH_2–4-CH_3–Ph	0.121; 0.55	25	0	2	0	3
8dd	Pyridin-2-yl	0.4; 0.45	25	3	0	3	3
			12.5	3	0	3	2
9a	C(=O)CH_2CH_3	0.73; 0.3	25	3	3	3	3
			12.5	3	0	0	3
			6.25	0	0	0	2
9b	C(=O)–*c*-Pr	1.03; 0.42	25	3	3	3	2
			12.5	3	3	3	3
			6.25	2	3	0	0
9c	C(=O)$CH_2CH_2CH_3$	0.63	12.5	3	3	3	3
			6.25	0	0	0	3
9d	C(=O)–*c*-Bu	0.27; 0.42	25	3	3	3	3
			12.5	3	0	3	3
			6.25	3	0	0	0
9e	C(=O)$CH_2CH_2CH_2CH_3$	0.25; 0.42	25	3	3	3	3
			12.5	2	2	2	3
			6.25	0	3	0	3
9f	C(=O)–*c*-pentyl	0.21; 0.3	25	3	3	3	3
			12.5	3	0	3	3
			6.25	0	0	0	3
9g	SO_2CH_3	40	25	2	2	0	0
9h	SO_2CH_2Ph	40% Inhibition at 100 nM	25	0	0	0	0
9i	SO_2Ph	9.4; 0.25	25	0	0	0	0
9j	C(=O)H	0.66; 0.45	12.5	3	3	2	3
			6.25	3	3	0	3
9k	C(=O)$NC(CH_3)_3$	4.39	12.5	3	3	3	3
9l	CO_2CH_3	0.8; 0.45	25	3	3	0	3
			12.5	3	3	0	3

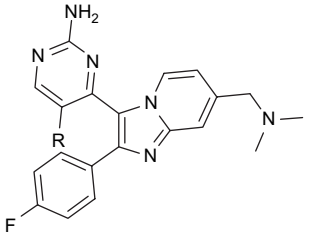
[a] In cases where a compound was tested more than once, all values obtained are reported.

AQA spectrometer. HPLC traces were recorded on an Agilent 1100 or Hewlett Packard 1050 instrument with a Phenomenex Aqua C18 125A 5 μm column, 4.6 mm i.d. × 50 mm length. All compounds tested biologically were found to be ≥90% pure by HPLC at 254 nM.

*4.1.1. 4-Methyl-2-methylsulfanylpyrimidine (**1**)*

A mixture of toluene (12 L), 4-methylpyrimidine-2-thiol hydrochloride (900 g, 5.53 mol), diisopropylethylamine (1.07 kg, 8.30 mol), and DMFDMA (1.61 kg, 12.7 mol) was heated to reflux for 3.5 h, and then was concentrated under reduced pressure. The residue was then treated with EtOAc (2 L), H_2O (2 L), and enough 10% (w/v) aqueous $NaHSO_4$ solution to reach a pH of 4.5. The aqueous layer was extracted with additional EtOAc (2 ×2 L). All organic extracts were combined, dried over Na_2SO_4, and concentrated under reduced pressure to yield ~1 L of a red oil, which was then purified by vacuum distillation at <1 mm Hg. Yield of **1**: 704 g (91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.49 (s, 3H), 6.75 (d, $J = 5.2$ Hz, 1H), 8.29 (d, $J = 5.2$ Hz, 1H). MS (ESI+) 141.1.

Table 2
Biological activity of 3-(2-NH_2-5-R-pyrimidin-4-yl)imidazopyridines

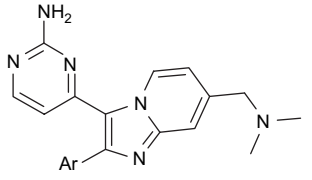


Compound	R	Ten_K IC_{50} (nM)	ExMAC dose (ppm)	ExMAC rating			
				E_t	E_a	E_{mi}	E_{ma}
8ee	H	0.11	25	3	3	3	3
			12.5	3	3	3	3
			6.25	3	3	0	0
17	CH_3	10.35	25	3	3	0	
			12.5	0	0	3	
			6.25	2	0	0	
22	CN	1.6	25	0	0	0	0
25	F	0.26	25	3	4	2	4
			1.25	3	4	0	0
			6.25	3	2	0	0
26	Br	5.8	25	2	0	0	2

4.1.2. 1-(4-Fluorophenyl)-2-(2-methylsulfanylpyrimidin-4-yl) ethanone and 1-(4-fluorophenyl)-2-(2-methylsulfanylpyrimidin-4-yl)ethenol (**2**)

A solution of 4-methylpyrimidine **1** (1.00 g, 7.13 mmol) in THF (15 mL) was stirred at −78 °C in a CO_2/IPA bath, and charged with LDA (7.5 mL of a 2.0 M solution in heptane/THF/ethylbenzene, 15 mmol). After stirring for 1 h at <−75 °C, the reaction was treated with a cooled solution of methyl 4-fluorobenzoate (1.21 g, 7.85 mmol) in THF (10 mL) dropwise over 15 min, during which reaction temperature was maintained at <−55 °C. The reaction was allowed to warm to room temperature while stirring for 12 h, and was then diluted with a saturated aqueous NH_4Cl solution (50 mL), and extracted with EtOAc (3 × 50 mL). Organic extracts were pooled, dried over Na_2SO_4, and concentrated under reduced pressure to give 2.15 g of crude solid, which was triturated with pentane (50 mL) and filtered. Yield of **2**: 809 mg (43%) as a 1.7:1.0 mixture of enol:ketone tautomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ enol tautomer: 2.60 (s, 3H), 5.91 (s, 1H), 6.63 (d, $J = 5.4$ Hz, 1H), 7.10–7.18 (m, 2H), 7.78–7.86 (m, 2H), 8.29 (d, $J = 5.4$ Hz, 1H); ketone tautomer: 2.51 (s, 3H), 4.34 (s, 2H), 6.97 (d, $J = 5.0$ Hz, 1H), 7.10–7.18 (m, 2H), 8.03–8.11 (m, 2H), 8.45 (d, $J = 5.0$ Hz, 1H). MS (ESI+) 263.

Table 3
Biological activity of 2-arylimidazopyridines



Compound	Ar	Ten_K IC_{50} (nM)	ExMAC dose (ppm)	ExMAC rating			
				E_t	E_a	E_{mi}	E_{ma}
8ee	4-F–Ph	0.11	25	3	3	3	3
			12.5	3	3	3	3
			6.25	3	3	0	0
34a	3-Br–4-F–Ph	0.16	25	3	3	0	3
34b	3-CH_3–4-F–Ph	0.1	25	3	3	3	
			12.5	3	3	3	
			6.25	3	3	3	
34c	4-Cl-Ph	0.41	25	3	2	2	
			12.5	0	0	0	
34d	2-F–4-F–Ph	0.1	25	3	4	3	
			12.5	4	4	3	
			6.25	3	4	2	
43	2-F–4-F–6-F–Ph	0.52	25	3	3	0	4
			12.5	3	3	0	3
			6.25	0	2	2	2
			3.13	2	0	2	3

4.1.3. 2-Bromo-1-(4-fluorophenyl)-2-(2-methylsulfanylpyrimidin-4-yl)ethanone (**3**)

Ketone/enol mixture **2** (218 g, 0.833 mol) was slurried in CCl_4 (1.5 L), and charged with tetra-*n*-butylammonium tribromide (402 g, 0.833 mol), then CH_2Cl_2 (3 L). After stirring at room temperature for 2 h, the reaction was diluted with saturated aqueous $NaHCO_3$ solution (3 L), and stirred for an additional 30 min. The aqueous layer was then siphoned off, and the organic layer was dried over Na_2SO_4, and concentrated under reduced pressure, and not purified further. Yield of **3**: 284 g (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 6.19 (s, 1H), 7.09 (t, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 4.8$ Hz, 1H), 7.97–8.05 (m, 2H), 8.47–8.55 (m, 1H). MS (ESI+) 341.0.

4.1.4. [2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl) imidazo[1,2-a]pyridin-7-yl]methanol (**4**)

A suspension of bromide **3** (284 g, 0.833 mol) in ethanol (3 L) was charged with (2-aminopyridin-4-yl)methanol (103 g, 0.833 mol), and 4 Å molecular sieves (300 mL, activated at 175 °C overnight in a vacuum oven), and was then heated 12 h at 60 °C. The reaction was then filtered while hot, and the resulting filtrate was allowed to cool to room temperature. The solid that precipitated out was then collected and dried in a vacuum oven at 40 °C overnight, yielding 92 g of **4** (fraction #1). The resulting filtrate was then concentrated under reduced pressure to an oil that was triturated with EtOH (200 mL). The resulting precipitate was collected by filtration, and was then washed with H_2O (500 mL), and then dried in a vacuum oven at 50 °C for 3 h, yielding 41 g of **4** (fraction #2). Overall yield of **4**: 133 g (43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 3H), 4.60 (s, 2H), 6.85 (d, $J = 5.2$ Hz, 1H), 7.07 (d, $J = 7.2$ Hz, 1H), 7.27 (t, $J = 8.8$ Hz, 2H), 7.58–7.66 (m, 3H), 8.43 (d, $J = 5.2$ Hz, 1H), 9.30 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 367.2.

4.1.5. Methanesulfonic acid 2-(4-fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-ylmethyl ester (5)

A solution of imidazopyridine **4** (161 g, 0.439 mol) in THF (500 mL) and Et_3N (66.7 g, 0.659 mol) was cooled to 5 °C in an ice water bath, then charged with the dropwise addition of methanesulfonyl chloride (55.4 g, 0.484 mol), and the reaction was warmed to room temperature and stirred for 1 h. The reaction was then diluted with H_2O (500 mL) and then extracted with EtOAc (2 × 500 mL). The aqueous layer was then diluted with saturated aqueous NaCl solution (500 mL) and extracted with additional EtOAc (500 mL). All organic fractions were pooled, dried over Na_2SO_4, and concentrated under reduced pressure to yield a solid that was triturated with pentane (500 mL), and the dried in a vacuum oven overnight at 40 °C. Yield of **5**: 165 g (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 3H), 3.07 (s, 3H), 5.32 (s, 2H), 6.82 (d, $J = 5.2$ Hz, 1H), 7.03 (dd, $J = 7.2$, 1.6 Hz, 1H), 7.14 (t, $J = 8.4$ Hz, 2H), 7.57–7.65 (m, 2H), 7.73 (bs, 1H), 8.32 (d, $J = 5.2$ Hz, 1H), 9.59 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 445.2.

4.1.6. [2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl) imidazo[1,2-a]pyridin-7-ylmethyl]dimethylamine (6)

A solution of mesylate **5** (172 g, 0.389 mol) in CH_3CN (1.5 L) was charged with diisopropylethylamine (65.3 g, 0.505 mol) and dimethylamine (253 mL of a 2.0 M solution in THF, 0.505 mol). After stirring for 15 min, the reaction slurry was diluted with CH_2Cl_2 (2 L) and H_2O (2 L), and then stirred for 10 min. The organic layer was separated, then dried over Na_2SO_4, filtered, concentrated under reduced pressure, and dried in a vacuum oven for 5 h at 40 °C. Yield of **6**: 145 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 6H), 2.63 (s, 3H), 3.54 (s, 2H), 6.79 (d, $J = 5.6$ Hz, 1H), 7.08 (d, $J = 7.2$ Hz, 1H), 7.13 (t, $J = 8.8$ Hz, 2H), 7.57 (bs, 1H), 7.56–7.64 (m, 2H), 8.27 (d, $J = 5.6$ Hz, 1H), 9.52 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 394.3.

4.1.7. [2-(4-Fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-ylmethyl]dimethylamine (7)

A solution of sulfide **6** (40.0 g, 102 mmol) in MeOH (1.0 L) was charged with AcOH (30.6 g, 510 mmol), H_2O_2 (46.0 g of a 30% w/w aqueous solution, 41.2 mL, 407 mmol), then sodium tungstate dihydrate (10.1 g, 30.6 mmol). The reaction was allowed to stir at room temperature overnight, and was then chilled to <-70 °C in a CO_2/IPA bath, after which 56.3 g of SO_2 was bubbled in over 15 min to reduce the N-oxide back to the tertiary amine. The reaction was then allowed to warm to room temperature while stirring for 5 h, after which it was diluted slowly with a saturated aqueous $NaHCO_3$ solution (500 mL), and stirred for 10 min. The resulting mixture was then extracted with CH_2Cl_2 (1 × 1 L, then 3 × 500 mL). The organic extracts were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield of **7**: 38.7 g (89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 6H), 3.41 (s, 3H), 3.60 (s, 2H), 7.13–7.30 (m, 2H), 7.21 (t, $J = 8.8$ Hz, 2H), 7.56–7.66 (m, 2H), 7.67 (bs, 1H), 8.49 (d, $J = 5.6$ Hz, 1H), 9.79 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 426.3.

4.2. General procedure for the synthesis of 2-NHR-pyrimidines 8a–ee

Sulfone **7** was charged with 40 equivalents of appropriate amine, and the reaction was heated neat at 60 °C for 2 h. The reaction was then diluted to 10 mL with MeOH, and then purified by HPLC using a MeOH/H_2O gradient, where the aqueous phase was 98.9:1.0:0.1 H_2O:CH_3CN:Et_3N. Any modifications to this procedure are noted when applicable.

4.2.1. {4-[7-Dimethylaminomethyl-2-(4-fluorophenyl) imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}ethylamine (8a)

Amine **8a** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and ethylamine (2.35 mL of a 2.0 M solution in THF, 4.70 mmol). Yield of **8a**: 29.0 mg (63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, $J = 7.2$ Hz, 3H), 2.30 (s, 6H), 3.51 (s, 2H), 3.56 (dt, $J = 12.4$, 7.2 Hz, 2H), 5.18 (bs, 1H), 6.43 (d, $J = 5.2$ Hz, 1H), 7.01 (dd, $J = 7.2$, 1.4 Hz, 1H), 7.13 (t, $J = 8.8$ Hz, 2H), 7.55 (bs, 1H), 7.65–7.69 (m, 2H), 8.11 (d, $J = 5.2$ Hz, 1H), 9.45–9.55 (m, 1H). MS (ESI+) 390.7.

4.2.2. 2-{4-[7-Dimethylaminomethyl-2-(4-fluorophenyl) imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamino}ethanol (8b)

Amine **8b** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 2-aminoethanol (287 mg, 284 μL, 4.70 mmol). Yield of **8b**: 29.8 mg (62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 6H), 3.51 (s, 2H), 3.70 (dt, $J = 5.6$, 4.8 Hz, 2H), 3.90 (t, $J = 4.8$ Hz, 2H), 5.66 (bs, 1H), 6.46 (d, $J = 5.3$ Hz, 1H), 7.01 (dd, $J = 7.2$, 1.4 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.56 (bs, 1H), 7.61–7.67 (m, 2H), 8.09 (d, $J = 5.3$ Hz, 1H), 9.42 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 407.2.

4.2.3. Cyclopropyl{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (8c)

Amine **8c** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and cyclopropylamine (268 mg, 326 μL, 4.70 mmol). Yield of **8c**: 25.1 mg (53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65–0.70 (m, 2H), 0.88–0.94 (m, 2H), 2.30 (s, 6H), 2.83–2.90 (m, 1H), 3.52 (s, 2H), 5.48 (bs, 1H), 6.50 (d, $J = 5.2$ Hz, 1H), 7.01 (dd, $J = 7.2$, 1.4 Hz, 1H), 7.14 (t, $J = 8.7$ Hz, 2H), 7.56 (bs, 1H), 7.63–7.70 (m, 2H), 8.12 (d, $J = 5.2$ Hz, 1H), 9.82 (bs, 1H). MS (ESI+) 402.7.

4.2.4. {4-[7-Dimethylaminomethyl-2-(4-fluorophenyl) imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}propylamine (8d)

Amine **8d** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and *n*-propylamine (278 mg, 386 μL, 4.70 mmol). Yield of **8d**: 30.7 mg (64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, $J = 7.4$ Hz, 3H), 1.67–1.78 (m, 2H), 2.30 (s, 6H), 3.43–3.51 (m, 2H), 3.51 (s, 2H), 5.25 (bs, 1H), 6.42 (d, $J = 5.2$ Hz, 1H), 7.00 (dd, $J = 7.2$, 1.4 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.55 (bs, 1H), 7.63–7.69 (m, 2H), 8.10 (d, $J = 5.2$ Hz, 1H), 9.45–9.55 (m, 1H). MS (ESI+) 404.7.

*4.2.5. {4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}-(2-methoxyethyl)amine (**8e**)*

Amine **8e** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 2-methoxyethylamine (353 mg, 409 μL, 4.70 mmol). Yield of **8e**: 27.3 mg (53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 6H), 3.44 (s, 3H), 3.51 (s, 2H), 3.65 (t, $J = 5.2$ Hz, 2H), 3.72 (q, $J = 5.2$ Hz, 2H), 5.55 (bs, 1H), 6.44 (d, $J = 5.3$ Hz, 1H), 7.00 (dd, $J = 7.1$, 1.5 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.55 (bs, 1H), 7.62–7.68 (m, 2H), 8.11 (d, $J = 5.3$ Hz, 1H), 9.46 (d, J–7.1 Hz, H). MS (ESI+) 420.7.

*4.2.6. 3-{4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamino}propan-1-ol (**8f**)*

Amine **8f** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 3-aminopropan-1-ol (353 mg, 359 μL, 4.70 mmol). Yield of **8f**: 24.9 mg (51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82–1.90 (m, 2H), 2.30 (s, 6H), 3.51 (s, 2H), 3.69 (q, $J = 6.4$ Hz, 2H), 3.74 (t, $J = 5.5$ Hz, 2H), 5.44 (bs, 1H), 6.44 (d, $J = 5.4$ Hz, 1H), 7.01 (dd, $J = 7.2$, 1.5 Hz, 1H), 7.13 (t, $J = 8.7$ Hz, 2H), 7.56 (bs, 1H), 7.61–7.68 (m, 2H), 8.09 (d, $J = 5.4$ Hz, 1H), 9.44 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 421.3.

*4.2.7. Cyclopropylmethyl{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (**8g**)*

Amine **8g** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and cyclopropylmethylamine (334 mg, 408 μL, 4.70 mmol). Yield of **8g**: 25.8 mg (53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.32 (q, $J = 4.8$ Hz, 2H), 0.57–0.63 (m, 2H), 1.11–1.21 (m, 1H), 2.30 (s, 6H), 3.38 (dd, $J = 6.6$, 5.7 Hz, 2H), 3.51 (s, 2H), 5.34 (bs, 1H), 6.43 (d, $J = 5.3$ Hz, 1H), 7.01 (dd, $J = 7.1$, 1.4 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.55 (bs, 1H), 7.62–7.69 (m, 2H), 8.11 (d, $J = 5.3$ Hz, 1H), 9.49 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 416.7.

*4.2.8. Cyclobutyl{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (**8h**)*

Amine **8h** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and cyclobutylamine (334 mg, 401 μL, 4.70 mmol). Yield of **8h**: 24.1 mg (49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73–1.90 (m, 2H), 1.94–2.06 (m, 2H), 2.31 (s, 6H), 2.45–2.55 (m, 2H), 3.52 (s, 2H), 4.49–4.57 (m, 1H), 5.40 (d, $J = 7.4$ Hz, 1H), 6.43 (d, $J = 5.3$ Hz, 1H), 7.02 (bd, $J = 6.8$ Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.55 (bs, 1H), 7.62–7.69 (m, 2H), 8.09 (d, $J = 5.3$ Hz, 1H), 9.49 (d, $J = 6.8$ Hz, 1H). MS (ESI+) 416.8.

*4.2.9. Butyl{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (**8i**)*

Amine **8i** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and *n*-butylamine (344 mg, 465 μL, 4.70 mmol). Yield of **8i**: 23.5 mg (48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, $J = 7.3$ Hz, 3H), 1.49 (tq, $J = 7.3$, 7.3 Hz, 2H), 1.69 (tt, $J = 7.3$, 7.3 Hz, 2H), 2.30 (s, 6H), 3.51 (s, 2H), 3.52 (t, $J = 7.3$ Hz, 2H), 5.21 (bs, 1H), 6.42 (d, $J = 5.2$ Hz, 1H), 7.00 (dd, $J = 7.2$, 1.4 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.55 (bs, 1H), 7.62–7.69 (m, 2H), 8.10 (d, $J = 5.2$ Hz, 1H), 9.49 (bs, 1H). MS (ESI+) 418.7.

*4.2.10. {4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}-(3-methoxypropyl)amine (**8j**)*

Amine **8j** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 3-methoxypropylamine (419 mg, 481 μL, 4.70 mmol). Yield of **8j**: 25.6 mg (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93–2.01 (m, 2H), 2.30 (s, 6H), 3.39 (s, 3H), 3.51 (s, 2H), 3.57 (t, $J = 5.9$ Hz, 2H), 3.63 (q, $J = 6.2$ Hz, 2H), 5.55 (bs, 1H), 6.42 (d, $J = 5.3$ Hz, 1H), 7.00 (dd, $J = 7.2$, 1.5 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.55 (bs, 1H), 7.62–7.69 (m, 2H), 8.10 (d, $J = 5.3$ Hz, 1H), 9.49 (bs, 1H). MS (ESI+) 435.7.

*4.2.11. Cyclopentyl{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (**8k**)*

Amine **8k** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and cyclopentylamine (400 mg, 464 μL, 4.70 mmol). Yield of **8k**: 28.6 mg (56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54–1.65 (m, 2H), 1.65–1.75 (m, 2H), 1.75–1.86 (m, 2H), 2.06–2.18 (m, 2H), 2.30 (s, 6H), 3.51 (s, 2H), 4.30–4.44 (m, 1H), 5.21 (d, $J = 7.1$ Hz, 1H), 6.42 (d, $J = 5.2$ Hz, 1H), 7.01 (dd, $J = 7.2$, 1.5 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.55 (bs, 1H), 7.62–7.71 (m, 2H), 8.09 (d, $J = 5.2$ Hz, 1H), 9.53 (bs, 1H). MS (ESI+) 431.4.

*4.2.12. {4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}pentylamine (**8l**)*

Amine **8l** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and *n*-pentylamine (410 mg, 535 μL, 4.70 mmol). Yield of **8l**: 27.2 mg (53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, $J = 7.0$ Hz, 3H), 1.35–1.50 (m, 4H), 1.71 (quintet, $J = 7.2$ Hz, 2H), 2.30 (s, 6H), 3.47–3.54 (m, 2H), 3.52 (s, 2H), 5.21 (bs, 1H), 6.42 (d, $J = 5.2$ Hz, 1H), 7.00 (dd, $J = 7.2$, 1.5 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.55 (bs, 1H), 7.60–7.71 (m, 2H), 8.10 (d, $J = 5.2$ Hz, 1H), 9.49 (bs, 1H). MS (ESI+) 432.8.

*4.2.13. Cyclohexyl-{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (**8m**)*

Amine **8m** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and cyclohexylamine (466 mg, 538 μL, 4.70 mmol). Yield of **8m**: 33.9 (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–1.39 (m, 2H), 1.39–1.54 (m, 2H), 1.61–1.75 (m, 2H), 1.79–1.89 (m, 2H), 2.08–2.18 (m, 2H), 2.30 (s, 6H), 3.52 (s, 2H), 3.84–3.98 (m, 1H), 5.13 (d, $J = 8.0$ Hz, 1H), 6.41 (d, $J = 5.2$ Hz, 1H), 7.00 (dd, $J = 7.2$, 1.5 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.55 (s, 1H), 7.62–7.70

(m, 2H), 8.09 (d, $J = 5.2$ Hz, 1H), 9.52 (s, 1H). MS (ESI+) 445.3.

*4.2.14. {4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}hexylamine (**8n**)*

Amine **8n** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and *n*-hexylamine (577 mg, 754 μL, 4.70 mmol). Yield of **8n**: 31.5 mg (61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, $J = 7.2$ Hz, 3H), 1.32–1.40 (m, 4H), 1.41–1.51 (m, 2H), 1.69 (quintet, $J = 7.2$ Hz, 2H), 2.30 (s, 6H), 3.46–3.55 (m, 2H), 3.51 (s, 2H), 5.21 (bt, $J = 5.2$ Hz, 1H), 6.42 (d, $J = 5.2$ Hz, 1H), 7.00 (dd, $J = 7.2$, 1.5 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.55 (bs, 1H), 7.63–7.69 (m, 2H), 8.10 (d, $J = 5.2$ Hz, 1H), 9.48 (bs, 1H). MS (ESI+) 446.7.

*4.2.15. {4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}-(2-fluorobenzyl)amine (**8o**)*

Amine **8o** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 2-fluorobenzylamine (588 mg, 537 μL, 4.70 mmol). Yield of **8o**: 32.9 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 6H), 3.49 (s, 2H), 4.80 (d, $J = 6.2$ Hz, 2H), 5.64 (bs, 1H), 6.47 (d, $J = 5.2$ Hz, 1H), 6.84 (bs, 1H), 7.06–7.18 (m, 4H), 7.28–7.35 (m, 1H), 7.45 (t, $J = 7.2$ Hz, 1H), 7.54 (bs, 1H), 7.60–7.69 (m, 2H), 8.13 (d, $J = 5.2$ Hz, 1H), 9.23 (bs, 1H). MS (ESI+) 471.3.

*4.2.16. (2,3-Difluorobenzyl)-{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (**8p**)*

Amine **8p** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 2,3-difluorobenzylamine (673 mg, 550 μL, 4.70 mmol). Yield of **8p**: 32.1 mg (56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.50 (s, 2H), 4.82 (d, $J = 6.2$ Hz, 2H), 5.66 (bs, 1H), 6.49 (d, $J = 5.3$ Hz, 1H), 6.86 (bs, 1H), 7.04–7.17 (m, 2H), 7.12 (t, $J = 8.6$ Hz, 2H), 7.22 (t, $J = 6.8$ Hz, 1H), 7.55 (bs, 1H), 7.60–7.68 (m, 2H), 8.13 (d, $J = 5.3$ Hz, 1H), 9.21 (bs, 1H). MS (ESI+) 489.3.

*4.2.17. (2,4-Difluorobenzyl)-{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (**8q**)*

Amine **8q** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 2,4-difluorobenzylamine (673 mg, 559 μL, 4.70 mmol). Yield of **8q**: 25.2 mg (44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.50 (s, 2H), 4.75 (d, $J = 6.1$ Hz, 2H), 5.57 (bs, 1H), 6.49 (d, $J = 5.3$ Hz, 1H), 6.84–6.92 (m, 1H), 6.88 (t, $J = 7.9$ Hz, 2H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.37–7.48 (m, 1H), 7.55 (bs, 1H), 7.61–7.67 (m, 2H), 8.13 (d, $J = 5.3$ Hz, 1H), 9.27 (bs, 1H). MS (ESI+) 489.3.

*4.2.18. (2,5-Difluorobenzyl)-{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (**8r**)*

Amine **8r** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 2,5-difluorobenzylamine (673 mg, 551 μL, 4.70 mmol). Yield of **8r**: 32.9 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.50 (s, 2H), 4.77 (d, $J = 6.3$ Hz, 2H), 5.65 (bs, 1H), 6.50 (d, $J = 5.3$ Hz, 1H), 6.85 (bs, 1H), 6.93–7.02 (m, 1H), 7.03–7.09 (dd, $J = 8.8$, 4.4 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.15–7.21 (m, 1H), 7.54 (bs, 1H), 7.61–7.69 (m, 2H), 8.13 (d, $J = 5.3$ Hz, 1H), 9.22 (bs, 1H). MS (ESI+) 488.7.

*4.2.19. (2,6-Difluorobenzyl)-{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (**8s**)*

Amine **8s** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 2,6-difluorobenzylamine (673 mg, 562 μL, 4.70 mmol). Yield of **8s**: 29.2 mg (51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 6H), 3.52 (s, 2H), 4.87 (d, $J = 6.0$ Hz, 2H), 5.51 (bs, 1H), 6.47 (d, $J = 5.2$ Hz, 1H), 6.95 (t, $J = 7.8$ Hz, 2H), 7.01 (dd, $J = 7.1$, 1.1 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.25–7.34 (m, 1H), 7.56 (bs, 1H), 7.62–7.69 (m, 2H), 8.12 (d, $J = 5.2$ Hz, 1H), 9.49 (bs, 1H). MS (ESI+) 489.3.

*4.2.20. (2-Chlorobenzyl)-{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (**8t**)*

Amine **8t** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 2-chlorobenzylamine (666 mg, 567 μL, 4.70 mmol). Yield of **8t**: 30.0 mg (53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.49 (s, 2H), 4.83 (d, $J = 6.2$ Hz, 2H), 5.73 (bs, 1H), 6.47 (d, $J = 5.2$ Hz, 1H), 6.79 (bs, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.24–7.31 (m, 1H), 7.42–7.51 (m, 3H), 7.53 (bs, 1H), 7.58–7.69 (m, 2H), 8.13 (d, $J = 5.2$ Hz, 1H), 9.16 (s, 1H). MS (ESI+) 487.3.

*4.2.21. {4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}-(2-methylbenzyl)amine (**8u**)*

Amine **8u** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 2-methylbenzylamine (570 mg, 583 μL, 4.70 mmol). Yield of **8u**: 33.0 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 6H), 2.42 (s, 3H), 3.48 (s, 2H), 4.69 (d, $J = 5.7$ Hz, 2H), 5.51 (bs, 1H), 6.47 (d, $J = 5.3$ Hz, 1H), 6.77 (bs, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.19–7.29 (m, 3H), 7.39 (d, $J = 6.9$ Hz, 1H), 7.53 (bs, 1H), 7.61–7.70 (m, 2H), 8.13 (d, $J = 5.3$ Hz, 1H), 9.15 (bs, 1H). MS (ESI+) 466.7.

*4.2.22. {4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}-(3-fluorobenzyl)amine (**8v**)*

Amine **8v** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 3-fluorobenzylamine (588 mg, 536 μL, 4.70 mmol). Yield of **8v**: 30.0 mg (55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.48 (s, 2H), 4.74 (d, $J = 6.1$ Hz, 2H), 5.68 (bs, 1H), 6.49 (d, $J = 5.3$ Hz, 1H), 6.78 (bs, 1H), 6.98–7.06 (m, 1H), 7.11–7.17 (m, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.21 (d, $J = 7.6$ Hz, 1H), 7.33–7.41 (m,

1H), 7.53 (bs, 1H), 7.64 (dd, $J = 8.6$, 5.5 Hz, 2H), 8.13 (d, $J = 5.3$ Hz, 1H), 9.09 (bs, 1H). MS (ESI+) 471.2.

*4.2.23. (3,4-Difluorobenzyl)-{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (**8w**)*

Amine **8w** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 3,4-difluorobenzylamine (673 mg, 556 μL, 4.70 mmol). Yield of **8w**: 28.8 mg (51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.49 (s, 2H), 4.70 (d, $J = 6.1$ Hz, 2H), 5.64 (bs, 1H), 6.50 (d, $J = 5.3$ Hz, 1H), 6.83 (bs, 1H), 7.12 (t, $J = 8.8$ Hz, 2H), 7.14–7.20 (m, 2H), 7.21–7.28 (m, 1H), 7.54 (bs, 1H), 7.61–7.68 (m, 2H), 8.13 (d, $J = 5.3$ Hz, 1H), 9.15 (s, 1H). MS (ESI+) 488.7.

*4.2.24. (3,5-Difluorobenzyl)-{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (**8x**)*

Amine **8x** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 3,5-difluorobenzylamine (673 mg, 556 μL, 4.70 mmol). Yield of **8x**: 21.8 mg (38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.49 (s, 2H), 4.72 (d, $J = 6.2$ Hz, 2H), 5.72 (bs, 1H), 6.51 (d, $J = 5.3$ Hz, 1H), 6.67–6.84 (m, 1H), 6.80 (bs, 1H), 6.96 (bd, $J = 6.1$ Hz, 2H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.54 (bs, 1H), 7.59–7.68 (m, 2H), 8.14 (d, $J = 5.3$ Hz, 1H), 9.08 (bs, 1H). MS (ESI+) 489.3.

*4.2.25. (3-Chlorobenzyl)-{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (**8y**)*

Amine **8y** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 3-chlorobenzylamine (666 mg, 574 μL, 4.70 mmol). Yield of **8y**: 32.8 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.49 (s, 2H), 4.72 (d, $J = 6.1$ Hz, 2H), 5.68 (bs, 1H), 6.49 (d, $J = 5.3$ Hz, 1H), 6.80 (bs, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.29–7.38 (m, 3H), 7.42 (bs, 1H), 7.53 (bs, 1H), 7.61–7.68 (m, 2H), 8.13 (d, $J = 5.3$ Hz, 1H), 9.08 (bs, 1H). MS (ESI+) 487.3.

*4.2.26. {4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}-(3-methylbenzyl)amine (**8z**)*

Amine **8z** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 3-methylbenzylamine (570 mg, 590 μL, 4.70 mmol). Yield of **8z**: 27.6 mg (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 6H), 2.39 (s, 3H), 3.48 (s, 2H), 4.70 (d, $J = 5.9$ Hz, 2H), 5.63 (bs, 1H), 6.46 (d, $J = 5.3$ Hz, 1H), 6.78 (bs, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.13–7.17 (m, 2H), 7.20–7.25 (m, 1H), 7.28–7.32 (m, 1H), 7.52 (bs, 1H), 7.61–7.71 (m, 2H), 8.13 (d, $J = 5.3$ Hz, 1H), 9.14 (bs, 1H). MS (ESI+) 467.3.

*4.2.27. {4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}-(4-fluorobenzyl)amine (**8aa**)*

Amine **8aa** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 4-fluorobenzylamine (588 mg, 537 μL, 4.70 mmol). Yield of **8aa**: 27.6 mg (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.49 (s, 2H), 4.71 (d, $J = 5.9$ Hz, 2H), 5.60 (bs, 1H), 6.48 (d, $J = 5.3$ Hz, 1H), 6.82 (s, 1H), 7.08 (t, $J = 8.0$ Hz, 2H), 7.12 (t, $J = 8.0$ Hz, 2H), 7.37–7.43 (m, 2H), 7.54 (bs, 1H), 7.62–7.68 (m, 2H), 8.13 (d, $J = 5.3$ Hz, 1H), 9.18 (bs, 1H). MS (ESI+) 471.3.

*4.2.28. (4-Chlorobenzyl)-{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amine (**8bb**)*

Amine **8bb** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 4-chlorobenzylamine (666 mg, 572 μL, 4.70 mmol). Yield of **8bb**: 20.1 mg (35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 6H), 3.58 (s, 2H), 4.71 (d, $J = 6.0$ Hz, 2H), 5.67 (bs, 1H), 6.48 (d, $J = 5.3$ Hz, 1H), 6.89 (bs, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.29–7.44 (m, 4H), 7.54 (bs, 1H), 7.64 (dd, $J = 8.7$, 5.4 Hz, 2H), 8.13 (d, $J = 5.3$ Hz, 1H), 9.12 (bs, 1H). MS (ESI+) 487.3.

*4.2.29. {4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}-(4-methylbenzyl)amine (**8cc**)*

Amine **8cc** was prepared from sulfone **7** (50.0 mg, 0.118 mmol) and 4-methylbenzylamine (570 mg, 598 μL, 4.70 mmol). Yield of **8cc**: 30.6 mg (56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 2.39 (s, 3H), 3.49 (s, 2H), 4.69 (d, $J = 5.8$ Hz, 2H), 5.58 (bs, 1H), 6.46 (d, $J = 5.3$ Hz, 1H), 6.80 (bs, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.21 (d, $J = 7.9$ Hz, 2H), 7.32 (d, $J = 7.9$ Hz, 2H), 7.52 (bs, 1H), 7.61–7.69 (m, 2H), 8.13 (d, $J = 5.3$ Hz, 1H), 9.18 (bs, 1H). MS (ESI+) 467.4.

*4.2.30. {4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}pyridin-2-ylamine (**8dd**)*

Compound **8dd** was prepared from sulfone **7** (72.0 mg, 0.169 mmol) and 2-aminopyridine (637 mg, 6.77 mmol) in diglyme (1.0 mL) by heating at 150 °C for 3 h. Yield of **8dd**: 17.9 mg (24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 6H), 3.53 (s, 2H), 6.70 (d, $J = 5.4$ Hz, 1H), 6.96–7.03 (m, 2H), 7.15 (t, $J = 8.7$ Hz, 2H), 7.60 (bs, 1H), 7.63–7.74 (m, 3H), 8.10 (bs, 1H), 8.31 (d, $J = 5.4$ Hz, 1H), 8.33–8.39 (m, 2H), 9.48 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 440.3.

*4.2.31. 4-[7-Dimethylaminomethyl-2-(4-fluorophenyl) imidazo[1,2,-a]pyridin-3-yl]pyrimidin-2-ylamine (**8ee**)*

A solution of sulfone **7** (21.6 g, 50.8 mmol) in THF (200 mL) in a pressure reactor was chilled to <-70 °C in a CO_2/IPA bath. Ammonia (27.9 g, 1.64 mol) was then bubbled in over 15 min, after which the pressure reactor was sealed, and the reaction was allowed to warm to room temperature and stir 12 h, during which the reaction pressure reached 55 psi. The pressure was then released, and the reaction was concentrated under reduced pressure, then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of

8ee: 9.6 g (52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 6H), 3.51 (s, 2H), 5.39 (bs, 2H), 6.49 (d, $J = 5.3$ Hz, 1H), 7.00 (dd, $J = 7.1$, 1.6 Hz, 1H), 7.11 (t, $J = 8.8$ Hz, 2H), 7.55 (bs, 1H), 7.59–7.67 (m, 2H), 8.08 (d, $J = 5.3$ Hz, 1H), 9.40 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 363.3.

4.3. General procedure for the synthesis of amides **9a–f** and sulfonamides **9g–i**

A solution of 2-aminopyrimidine **8ee** in pyridine was charged with appropriate acid chloride or sulfonyl chloride, and allowed to stir at room temperature for 24 h. Additional portions of appropriate acid chloride or sulfonyl chloride were added as needed at 24 h intervals until the reaction appeared complete by LCMS. The reaction was then diluted to 10 mL with MeOH, and then purified by HPLC using a MeOH/H_2O gradient, where the aqueous phase was 98.9:1.0:0.1 H_2O:CH_3CN:Et_3N. Any modifications to this procedure are noted when applicable.

4.3.1. N-{4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}propionamide (**9a**)

Amide **9a** was prepared from 2-aminopyrimidine **8ee** (50.0 mg, 0.138 mmol) and propionyl chloride (14 mg, 13 μL, 0.15 mmol) in pyridine (0.5 mL). Additional propionyl chloride (7.0 mg, 6.5 μL, 0.075 mmol) was added after 24 h. Yield of **9a**: 37.7 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, $J = 7.5$ Hz, 3H), 2.32 (s, 6H), 2.64 (q, $J = 7.5$ Hz, 2H), 3.57 (s, 2H), 6.85 (d, $J = 5.5$ Hz, 1H), 7.16 (t, $J = 8.6$ Hz, 2H), 7.21 (d, $J = 7.0$ Hz, 1H), 7.60 (bs, 1H), 7.59–7.67 (m, 2H), 8.12 (s, 1H), 8.26 (d, $J = 5.5$ Hz, 1H), 10.18 (d, $J = 7.0$ Hz, 1H). MS (ESI+) 419.3.

4.3.2. Cyclopropanecarboxylic acid {4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amide (**9b**)

Amide **9b** was prepared from 2-aminopyrimidine **8ee** (50.0 mg, 0.138 mmol) and cyclopropanecarbonyl chloride (16 mg, 14 μL, 0.15 mmol) in pyridine (0.5 mL). Additional cyclopropanecarbonyl chloride (8.0 mg, 7.0 μL, 0.075 mmol) was added after 24 h. Yield of **9b**: 43.8 mg (74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92–0.99 (m, 2H), 1.20–1.26 (m, 2H), 1.90–2.05 (m, 1H), 2.29 (s, 6H), 3.53 (s, 2H), 6.84 (d, $J = 5.5$ Hz, 1H), 7.12–7.19 (m, 3H), 7.58 (bs, 1H), 7.59–7.67 (m, 2H), 8.27 (d, $J = 5.5$ Hz, 1H), 8.52 (bs, 1H), 10.17 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 431.3.

4.3.3. N-{4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}butyramide (**9c**)

Amide **9c** was prepared from 2-aminopyrimidine **8ee** (50.0 mg, 0.138 mmol) and butyryl chloride (16 mg, 16 μL, 0.15 mmol) in pyridine (0.5 mL). Additional butyryl chloride (8.0 mg, 8.0 μL, 0.075 mmol) was added after 24 h. Yield of **9c**: 41.1 mg (69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, $J = 7.4$ Hz, 3H), 1.77–1.88 (m, 2H), 2.30 (s, 6H), 2.58 (t, $J = 7.4$ Hz, 2H), 3.53 (s, 2H), 6.84 (d, $J = 5.5$ Hz, 2H), 7.13–7.21 (m, 3H), 7.59 (bs, 1H), 7.59–7.67 (m, 2H), 8.26 (d, $J = 5.5$ Hz, 1H), 10.19 (d, $J = 6.8$ Hz, 1H). MS (ESI+) 433.4.

4.3.4. Cyclobutanecarboxylic acid {4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amide (**9d**)

Amide **9d** was prepared from 2-aminopyrimidine **8ee** (50.0 mg, 0.138 mmol) and cyclobutanecarbonyl chloride (18 mg, 17 μL, 0.15 mmol) in pyridine (0.5 mL). Additional cyclobutanecarbonyl chloride (9.0 mg, 8.5 μL, 0.075 mmol) was added after 24 h. Yield of **9d**: 46.5 mg (76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87–2.13 (m, 2H), 2.20–2.35 (m, 2H), 2.30 (s, 6H), 2.41–2.56 (m, 2H), 3.39–3.45 (m, 1H), 3.54 (s, 2H), 6.84 (d, $J = 5.5$ Hz, 1H), 7.16 (t, $J = 8.5$ Hz, 2H), 7.22 (d, $J = 7.0$ Hz, 1H), 7.59 (bs, 1H), 7.58–7.66 (m, 2H), 8.02 (bs, 1H), 8.24 (d, $J = 5.5$ Hz, 1H), 10.28 (d, $J = 7.0$ Hz, 1H). MS (ESI+) 445.4.

4.3.5. Pentanoic acid {4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amide (**9e**)

Amide **9e** was prepared from 2-aminopyrimidine **8ee** (50.0 mg, 0.138 mmol) and pentanoyl chloride (18 mg, 18 μL, 0.15 mmol) in pyridine (0.5 mL). Additional pentanonyl chloride (9.0 mg, 9.0 μL, 0.075 mmol) was added after 24 h. Yield of **9e**: 41.6 mg (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, $J = 7.2$ Hz, 3H), 1.40–1.52 (m, 2H), 1.67–1.84 (m, 2H), 2.30 (s, 6H), 2.60 (t, $J = 7.2$ Hz, 2H), 3.53 (s, 2H), 6.84 (d, $J = 5.6$ Hz, 1H), 7.12–7.21 (m, 3H), 7.28 (s, 1H), 7.59 (bs, 1H), 7.60–7.66 (m, 2H), 8.26 (d, $J = 5.6$ Hz, 1H), 10.15–10.25 (m, 1H). MS (ESI+) 447.4.

4.3.6. Cyclopentanecarboxylic acid {4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}amide (**9f**)

Amide **9f** was prepared from 2-aminopyrimidine **8ee** (50.0 mg, 0.138 mmol) and cyclopentanecarbonyl chloride (20 mg, 18 μL, 0.15 mmol) in pyridine (0.5 mL). Additional cyclopentanecarbonyl chloride (10 mg, 9.0 μL, 0.075 mmol) was added after 24 h. Yield of **9f**: 47.4 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63–1.73 (m, 2H), 1.78–1.89 (m, 2H), 1.96–2.05 (m, 4H), 2.30 (s, 6H), 2.85–3.00 (m, 1H), 3.54 (s, 2H), 6.84 (d, $J = 5.5$ Hz, 1H), 7.16 (t, $J = 8.5$ Hz, 2H), 7.22 (d, $J = 7.2$ Hz, 1H), 7.58 (s, 1H), 7.59–7.67 (m, 2H), 8.04 (s, 1H), 8.25 (d, $J = 5.5$ Hz, 1H), 10.32 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 459.3.

4.3.7. N-{4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}methansulfonamide (**9g**)

Sulfonamide **9g** was prepared from 2-aminopyrimidine **8ee** (50.0 mg, 0.138 mmol) and methanesulfonyl chloride (17 mg, 12 μL, 0.15 mmol) in pyridine (1.5 mL). Additional portions of methanesulfonyl chloride (8.5 mg, 6.0 μL, 0.075 mmol) were added after 24 h, 48 h, and 72 h. Yield of **9g**: 23.9 mg (39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 6H), 3.44 (s,

3H), 3.54 (s, 2H), 6.83 (d, $J = 5.7$ Hz, 1H), 7.13–7.17 (m, 1H), 7.18 (t, $J = 8.8$ Hz, 2H), 7.62 (s, 1H), 7.61–7.69 (m, 2H), 8.32 (d, $J = 5.7$ Hz, 1H), 9.85 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 441.1.

4.3.8. N-{4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}-C-phenylmethansulfonamide (**9h**)

Sulfonamide **9h** was prepared from 2-aminopyrimidine **8ee** (50.0 mg, 0.138 mmol) and phenylmethanesulfonyl chloride (29 mg, 0.15 mmol) in pyridine (1.5 mL). Additional portions of phenylmethanesulfonyl chloride (15 mg, 0.075 mmol) were added after 24 h, 48 h, and 72 h. Yield of **9h**: 24.2 mg (34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 6H), 3.57 (s, 2H), 4.81 (s, 2H), 6.83 (d, $J = 5.6$ Hz, 1H), 7.10–7.20 (m, 1H), 7.20 (t, $J = 8.7$ Hz, 2H), 7.25–7.40 (m, 5H), 7.64 (bs, 1H), 7.62–7.70 (m, 2H), 8.21 (d, $J = 5.6$ Hz, 1H), 9.90 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 517.2.

4.3.9. N-{4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}benzenesulfonamide (**9i**)

Sulfonamide **9i** was prepared from 2-aminopyrimidine **8ee** (50.0 mg, 0.138 mmol) and benzenesulfonyl chloride (27 mg, 19 μL, 0.15 mmol) in pyridine (1.5 mL). Additional portions of benzenesulfonyl chloride (14 mg, 9.5 μL, 0.075 mmol) were added after 24 h, 48 h, and 72 h. Yield of **9i**: 38.9 mg (56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 6H), 3.57 (s, 2H), 6.75 (d, $J = 5.7$ Hz, 1H), 7.13 (t, $J = 8.7$ Hz, 2H), 7.18 (dd, $J = 7.2$, 1.6 Hz, 1H), 7.40–7.48 (m, 2H), 7.50–7.60 (m, 3H), 7.61 (s, 1H), 8.08 (d, $J = 7.4$ Hz, 2H), 8.26 (d, $J = 5.7$ Hz, 1H), 9.90 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 503.2.

4.3.10. N-{4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl} formamide (**9j**)

A solution of formic acid (10.2 g, 8.40 mL, 222 mmol), was chilled to 0 °C in an ice water bath, and then charged with 2-aminopyrimidine **8ee** (700 mg, 1.93 mmol) in small portions. After 20 min of stirring, acetic anhydride (2.80 mL, 3.03 g, 29.7 mmol) was added dropwise. The resulting yellow solution was stirred at 0 °C for 30 min, and then allowed to warm to room temperature and stir for 3 days. The reaction was then concentrated under reduced pressure, then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **9j**: 240 mg (32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 6H), 3.55 (s, 2H), 6.89 (d, $J = 5.5$ Hz, 1H), 7.09 (dd, $J = 7.0$, 1.5 Hz, 1H), 7.16 (t, $J = 8.7$ Hz, 2H), 7.58–7.67 (m, 3H), 8.28 (d, $J = 5.5$ Hz, 1H), 8.41 (d, $J = 9.8$ Hz, 1H), 9.42 (d, $J = 7.0$ Hz, 1H), 9.59 (d, $J = 9.8$ Hz, 1H). MS (ESI+) 391.3.

4.3.11. 1-tert-Butyl-3-{4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl}urea (**9k**)

A solution of 2-aminopyrimidine **8ee** (100 mg, 0.276 mmol) in DMF (2.0 mL) was charged with NaH (7.0 mg of a 60% w/w suspension in mineral oil, 0.29 mmol), then *tert*-butyl isocyanate (36 mg, 42 μL, 0.36 mmol). After stirring for 48 h at room temperature, the reaction was diluted to 10 mL with MeOH, and then purified by HPLC using a MeOH/H_2O gradient, where the aqueous phase was 98.9:1.0:0.1 H_2O:CH_3CN:Et_3N. Yield of **9k**: 69.6 mg (55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.30 (s, 6H), 3.54 (s, 2H), 6.71 (d, $J = 5.5$ Hz, 1H), 7.07 (d, $J = 7.1$ Hz, 1H), 7.14 (t, $J = 8.7$ Hz, 2H), 7.33 (s, 1H), 7.60 (bs, 1H), 7.61–7.67 (m, 2H), 8.20 (d, $J = 5.5$ Hz, 1H), 8.95 (bs, 1H), 9.36 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 462.4.

4.3.12. {4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-yl} carbamic acid methyl ester (**9l**)

A solution of 2-aminopyrimidine **8ee** (100 mg, 0.276 mmol) in CH_2Cl_2 (3.0 mL) was charged with Et_3N (84.0 mg, 115 μL, 0.828 mmol) then methyl chloroformate (52 mg, 42 μL, 0.55 mmol), and the reaction was allowed to stir at room temperature for 24 h. Additional portions of Et_3N (84.0 mg, 115 μL, 0.828 mmol) and methyl chloroformate (52 mg, 42 μL, 0.55 mmol) were then added, and the reaction stirred at room temperature for another 24 h, was then diluted to 10 mL with MeOH, and then purified by HPLC using a MeOH/H_2O gradient, where the aqueous phase was 98.9:1.0:0.1 H_2O:CH_3CN:Et_3N. Yield of **9l**: 49.9 mg (43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 6H), 3.54 (s, 2H), 3.89 (s, 3H), 6.84 (d, $J = 5.6$ Hz, 1H), 7.13–7.22 (m, 3H), 7.59 (bs, 1H), 7.59–7.67 (m, 2H), 8.26 (d, $J = 5.6$ Hz, 1H), 8.46 (bs, 1H), 10.35 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 421.3.

4.3.13. 2-Bromo-3-(4-fluorophenyl)-3-oxopropionic acid methyl ester (**10**)

A solution of 3-(4-fluorophenyl)-3-oxopropionic acid methyl ester (19.1 g, 97.3 mmol) in CH_2Cl_2 (250 mL) was charged with tetra-*n*-butylammonium tribromide (46.9 g, 97.3 mmol). The reaction stirred at room temperature for 7.5 h, and was then concentrated under reduced pressure, and chromatographed on SiO_2 using a gradient that started with heptane and ended with 30:70 EtOAc:heptane. Yield of **10**: 25.4 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 5.64 (s, 1H), 7.18 (t, $J = 8.7$ Hz, 2H), 8.00–8.08 (m, 2H). MS (ESI+) 274.8.

4.3.14. 2-(4-Fluorophenyl)-7-hydroxymethylimidazo[1,2-a]pyridine-3-carboxylic acid methyl ester (**11**)

A solution of bromide **10** (11.3 g, 41.1 mmol) in ethanol (250 mL) was charged with (2-aminopyridin-4-yl)methanol (5.10 g, 41.1 mmol) and $NaHCO_3$ (3.45 g, 41.1 mmol), and the reaction was heated at 60 °C for 12 h, then concentrated under reduced pressure and chromatographed on SiO_2 first with 30:70 EtOAc:heptane, then with a gradient that started with 10:90 MeOH:CH_2Cl_2 and ended with 20:80 MeOH:CH_2Cl_2. Yield of **11**: 4.1 g (33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 4.82 (s, 2H), 7.05 (dd, $J = 7.1$, 1.5 Hz, 1H), 7.15 (t, $J = 8.8$ Hz, 2H), 7.74 (bs, 1H), 7.72–7.80 (m, 2H), 9.34 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 300.9.

*4.3.15. 2-(4-Fluorophenyl)-7-methanesulfonyloxymethylimidazo[1,2-a]pyridine-3-carboxylic acid methyl ester (**12**)*

A solution of alcohol **11** (500 mg, 1.67 mmol) in THF (100 mL) was charged with methanesulfonyl chloride (285 mg, 193 μL, 2.49 mmol) and Et_3N (337 mg, 464 μL, 3.33 mmol), and the reaction was allowed to stir at room temperature overnight. The reaction was then concentrated under reduced pressure, suspended with a saturated aqueous $NaHCO_3$ solution (50 mL), and extracted into CH_2Cl_2 (2 × 200 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and the product was not purified further. Yield of **12**: 630 mg (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 (s, 3H), 3.90 (s, 3H), 4.69 (s, 2H), 7.25 (t, $J = 8.8$ Hz, 2H), 7.52 (dd, $J = 7.2$, 1.0 Hz, 1H), 7.80–7.88 (m, 2H), 8.47 (bs, 1H), 9.55 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 378.8.

*4.3.16. 7-Dimethylaminomethyl-2-(4-fluorophenyl) imidazo[1,2-a]pyridine-3-carboxylic acid methyl ester (**13**)*

A solution of mesylate **12** (620 mg, 1.64 mmol) in CH_3CN (100 mL) was charged with diisopropylethylamine (265 mg, 357 mL, 2.04 mmol), then dimethylamine (1.07 mL of a 2.0 M solution in THF, 2.13 mmol), and allowed to stir at room temperature for 6 h. The reaction was then concentrated under reduced pressure and chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **13**: 340 mg (63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 6H), 3.54 (s, 2H), 3.83 (s, 3H), 7.09–7.17 (m, 3H), 7.60 (s, 1H), 7.72–7.80 (m, 2H), 9.31 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 328.0.

*4.3.17. 7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxylic acid methoxymethylamide (**14**)*

A solution of ester **13** (8.90 g, 27.2 mmol) in THF (500 mL) was charged with *N*,*O*-dimethylhydroxylamine hydrochloride (7.96 g, 81.6 mmol), and was then chilled to 0 °C in an ice water bath. Isopropylmagnesium chloride (122 mL of a 2.0 M solution in THF, 245 mmol) was then added dropwise. After 30 min, the reaction was quenched with the slow addition of a saturated aqueous NH_4Cl solution (250 mL), and extracted into EtOAc (3 × 250 mL). The organic extracts were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield of **14**: 8.00 g (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 6H), 3.19 (s, 3H), 3.49 (s, 3H), 3.52 (s, 2H), 7.02 (d, $J = 7.1$ Hz, 1H), 7.14 (t, $J = 8.7$ Hz, 2H), 7.54 (bs, 1H), 7.74–7.82 (m, 2H), 8.49 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 357.0.

*4.3.18. 1-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]propane-1-one (**15**)*

A solution of Weinreb amide **14** (892 mg, 2.50 mmol) in THF (100 mL), was charged with the dropwise addition of ethylmagnesium bromide (2.50 mL of a 1.0 M solution in THF, 2.50 mmol), and allowed to stir at room temperature for 21 h. Additional portions of ethylmagnesium bromide (5.00 mL of a 1.0 M solution in THF, 5.00 mmol) were then added at $t = 21$ h, 22 h, and 23 h since the start of the reaction, after which starting material was consumed. The reaction was then quenched with the dropwise addition of H_2O (50 mL), then concentrated under reduced pressure, then diluted with a saturated aqueous $NaHCO_3$ solution (100 mL), which was then extracted into CH_2Cl_2 (3 × 200 mL), with filtering of emulsions when necessary. The organic fractions were pooled, dried over Na_2SO_4, filtered and concentrated under reduced pressure, then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **15**: 320 mg (39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, $J = 7.3$ Hz, 3H), 2.28 (s, 6H), 2.45 (q, $J = 7.3$ Hz, 2H), 3.52 (s, 2H), 7.12–7.15 (m, 1H), 7.17 (t, $J = 8.6$ Hz, 2H), 7.50–7.58 (m, 2H), 7.58 (bs, 1H), 9.66 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 326.0.

*4.3.19. 3-Dimethylamino-1-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]-2-methylpropenone (**16**)*

A solution of ketone **15** (360 mg, 1.11 mmol) in DMFDMA (263 mg, 294 μL, 2.21 mmol) was heated to 100 °C for 7 h to give enone **16**, which was not isolated, but instead was carried onto the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.34 (s, 6H), 2.76 (s, 6H), 3.52 (s, 2H), 6.89 (s, 1H), 7.00 (d, $J = 7.1$ Hz, 1H), 7.09 (t, $J = 8.7$ Hz, 2H), 7.52 (bs, 1H), 7.63–7.71 (m, 2H), 8.66 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 381.0.

*4.3.20. 4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]-5-methylpyrimidin-2-ylamine (**17**)*

Crude reaction mixture of enone **16** (theoretically 422 mg, 1.11 mmol) in DMFDMA (263 mg, 294 μL, 2.21 mmol) was charged with 1-propanol (4.0 mL), guanidine hydrochloride (157 mg, 1.65 mmol), and sodium methoxide (89.0 mg of a solution 25% w/v in MeOH, 379 μL, 1.65 mmol), and was heated to 80 °C for 9 h. The reaction was then concentrated under reduced pressure, then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **17**: 117 mg (28% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 3H), 2.29 (s, 6H), 3.49 (s, 2H), 5.11–5.19 (m, 2H), 6.91 (dd, $J = 7.1$, 1.1 Hz, 1H), 7.04 (t, $J = 8.7$ Hz, 2H), 7.54 (bs, 1H), 7.56–7.64 (m, 2H), 8.16–8.30 (m, 2H). MS (ESI+) 377.0.

*4.3.21. 1-[7-Dimethylaminomethyl-2-(4-fluorophenyl) imidazo[1,2-a]pyridin-3-yl]ethanone (**18**)*

A solution of Weinreb amide **14** (1.66 g, 4.66 mmol) in THF (100 mL) was chilled to 0 °C in an ice water bath, then charged with the dropwise addition of methylmagnesium bromide (16.7 mL of a 1.4 M solution in 3:1 toluene:THF, 23.3 mmol), and the reaction was allowed to stir at room

temperature overnight, after which it was quenched with the slow addition of a saturated aqueous NH_4Cl solution (100 mL), and extracted into EtOAc (3 × 250 mL). The organic extracts were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and the residue was chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **18**: 965 mg (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.30 (s, 6H), 3.55 (s, 2H), 7.17 (dd, $J = 7.1$, 1,2 Hz, 1H), 7.20 (t, $J = 8.6$ Hz, 2H), 7.54–7.62 (m, 2H), 7.61 (bs, 1H), 9.68 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 311.9.

*4.3.22. 2-Bromo-1-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]ethanone (**19**)*

A solution of ketone **18** (1.80 g, 5.78 mmol) in AcOH (300 mL) was charged with the dropwise addition of a solution of bromine (0.462 g, 148 μL, 2.89 mmol) in AcOH (30 mL), and the reaction was heated to 90 °C for 12 h. An additional portion of bromine (0.231 g, 74.0 μL, 1.45 mmol) in AcOH (20 mL) was then added, and heating at 90 °C continued for 5 h, followed by a third portion of bromine (0.13 g, 37 μL, 0.72 mmol) in AcOH (10 mL) with heating for another 2 h, then by a fourth portion of bromine (0.063 g, 19 μL, 0.36 mmol) in AcOH (10 mL) with heating for another 1 h, after which the reaction was concentrated and stored under vacuum for 12 h before proceeding to the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 6H), 3.63 (s, 2H), 3.98 (s, 2H), 7.20–7.30 (m, 3H), 7.61–7.69 (m, 2H), 7.68 (bs, 1H), 9.67 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 391.8.

*4.3.23. 3-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]-3-oxopropionitrile (**20**)*

A solution of crude α-bromoketone **19** (theoretically 2.90 g, 5.78 mmol) in ethanol (450 mL) was chilled to 5 °C in an ice water bath, then charged with the dropwise addition of sodium cyanide (3.60 g, 74.3 mmol) dissolved in H_2O (70 mL). The reaction was allowed to warm to room temperature and stir for 4 h, and was then concentrated under reduced pressure, then extracted into EtOAc (3 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield of **20**: 1.70 g (71% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 6H), 3.53 (s, 2H), 3.63 (s, 2H), 7.27 (t, $J = 8.5$ Hz, 2H), 7.33 (d, $J = 7.0$ Hz, 1H), 7.54–7.62 (m, 2H), 7.70 (bs, 1H), 9.63 (d, $J = 7.0$ Hz, 1H). MS (ESI+) 336.9.

*4.3.24. 3-Dimethylamino-2-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridine-3-carbonyl]acrylonitrile (**21**)*

A solution of α-cyanoketone **20** (196 mg, 0.583 mmol) in DMFDMA (139 mg, 154 μL, 1.17 mmol) was heated to 80 °C for 6 h to give enone **21**, which was not isolated, but instead was carried onto the next step.

*4.3.25. 2-Amino-4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidine-5-carbonitrile (**22**)*

The crude reaction mixture of enone **21** (theoretically 231 mg, 0.583 mmol) in DMFDMA (139 mg, 154 μL, 1.17 mmol) was charged with 1-propanol (3.0 mL), guanidine hydrochloride (83 mg, 0.87 mmol), and sodium methoxide (47 mg of a 25% w/v solution in MeOH, 200 μL, 0.87 mmol), and was heated to 80 °C for 12 h. The reaction was then concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH, and then purified by HPLC using a MeOH/H_2O gradient, where the aqueous phase was 98.9:1.0:0.1 H_2O:CH_3CN:Et_3N. Yield of **22**: 130 mg (58% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (s, 6H), 3.76 (s, 2H), 7.10 (t, $J = 8.6$ Hz, 2H), 7.15–7.30 (m, 1H), 7.47–7.55 (m, 2H), 7.58 (bs, 1H), 8.43 (s, 1H), 8.78 (d, $J = 6.8$ Hz, 1H). MS (ESI+) 388.0.

*4.3.26. 3-Dimethylamino-1-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]propenone (**23**)*

A solution of ketone **18** (8.06 g, 25.9 mmol) in DMFDMA (9.25 g, 10.3 mL, 77.6 mmol) was heated to 90 °C for 12 h. The reaction was then concentrated under reduced pressure, and chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **23**: 6.89 g (73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 2.47 (bs, 3H), 3.04 (bs, 3H), 3.50 (s, 2H), 5.10 (d, $J = 12.4$ Hz, 1H), 7.02 (dd, $J = 7.2$, 1.1 Hz, 1H), 7.13 (t, $J = 8.6$ Hz, 2H), 7.52 (bs, 1H), 7.62 (d, $J = 12.4$ Hz, 1H), 7.66–7.74 (m, 2H), 9.56 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 367.0.

*4.3.27. 3-Dimethylamino-1-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]-2-fluoropropenone (**24**)*

A solution of enone **23** (0.610 g, 1.67 mmol) in CH_2Cl_2 (15 mL) was cooled to −15 °C, then charged with a solution of *N*-fluorobenzensulfonimide (0.63 g) in CH_3CN (20 mL), and the reaction was allowed to warm to room temperature while stirring for 12 h. The reaction was then concentrated under reduced pressure, then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **24**: 0.35 g (55%). The sample was carried directly onto the next step.

*4.3.28. 4-[7-Dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]-5-fluoropyrimidin-2-ylamine (**25**)*

A solution of enone **24** (170 mg, 0.442 mmol) in 1-propanol (5 mL) was charged with guanidine hydrochloride (63 mg, 0.66 mmol), then sodium methoxide (25% w/v in MeOH, 143 mg, 151 μL, 0.662 mmol), and the reaction was heated to 80 °C for 2 h. The reaction was then concentrated under reduced pressure, then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. The product mixture

isolated was then purified by HPLC using a MeOH/H_2O gradient, where the aqueous phase was 98.9:1.0:0.1 H_2O:CH_3CN:Et_3N. Yield of **25**: 21.7 mg (13%). ^{1}H NMR (400 MHz, CD_3OD) δ 2.32 (s, 6H), 3.60 (s, 2H), 7.08 (dd, $J = 7.3$, 1.7 Hz, 1H), 7.14 (t, $J = 8.8$ Hz, 2H), 7.58–7.60 (m, 1H), 7.57–7.65 (m, 2H), 8.19 (d, $J = 2.5$ Hz, 1H), 8.90 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 381.3.

*4.3.29. 5-Bromo-4-[7-dimethylaminomethyl-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**26**)*

A solution of 2-aminopyrimidine **8ee** (50 mg, 0.14 mmol) in ethanol (5.0 mL) was charged with *N*-bromosuccinimide (25 mg, 0.14 mmol), and the reaction was stirred at room temperature for 12 h. The reaction was then concentrated under reduced pressure, then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **26**: 24 mg (40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 6H), 3.53 (s, 2H), 5.37 (bs, 2H), 6.99 (dd, $J = 7.1$, 1.2 Hz, 1H), 7.06 (t, $J = 8.7$ Hz, 2H), 7.57 (bs, 1H), 7.57–7.65 (m, 2H), 8.15 (d, $J = 7.1$ Hz, 1H), 8.47 (s, 1H). MS (ESI+) 442.8.

*4.4. General procedure for the synthesis of methyl esters **27a–b***

A solution of appropriate benzoic acid in MeOH was charged with concentrated H_2SO_4 and heated at 80 °C for the time specified. The reaction was then concentrated under reduced pressure, suspended in a saturated aqueous $NaHCO_3$ solution, and extracted into EtOAc. The organic extracts were then pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

*4.4.1. 3-Bromo-4-fluorobenzoic acid methyl ester (**27a**)*

Methyl ester **27a** was prepared from 3-bromo-4-fluorobenzoic acid (24.0 g, 110 mmol) and concentrated H_2SO_4 (1.0 mL) in MeOH (400 mL), with heating at 80 °C for 36 h. Yield of **27a**: 23.7 g (92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 7.18 (t, $J = 8.3$ Hz, 1H), 7.91–8.10 (m, 1H), 8.28 (dd, $J = 6.6$, 2.1 Hz, 1H).

*4.4.2. 4-Fluoro-3-methylbenzoic acid methyl ester (**27b**)*

Methyl ester **27b** was prepared from 4-fluoro-3-methylbenzoic acid (15.0 g, 97.3 mmol) and concentrated H_2SO_4 (1.0 mL) in MeOH (200 mL), with heating to 80 °C for 18 h. Yield of **27b**: 13.4 g (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.91 (s, 3H), 7.05 (t, $J = 8.9$ Hz, 1H), 7.82–7.89 (m, 1H), 7.91 (d, $J = 7.4$ Hz, 1H).

*4.5. General procedure for the synthesis of ketones **28a–d***

A solution of 4-methylpyrimidine **1** in THF was cooled to −78 °C in a CO_2/IPA bath, then charged with the dropwise addition of lithium diisopropylamide (2.0 M in heptane/THF/ethylbenzene), and allowed to stir at −78 °C for 1 h. A solution of appropriate ester dissolved in THF was then added, and the reaction was allowed to warm to room temperature while stirring for 12 h. The reaction was then concentrated under reduced pressure, suspended in EtOAc and washed with a saturated aqueous NH_4Cl solution. The organic solution was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The solid obtained was washed with heptane, from which additional batches of product could be obtained by crystallization upon freezing. Any modifications to this procedure are noted below.

*4.5.1. 1-(3-Bromo-4-fluorophenyl)-2-(2-methylsulfanylpyrimidin-4-yl)ethanone and 1-(3-bromo-4-fluorophenyl)-2-(2-methylsulfanylpyrimidin-4-yl)ethenol (**28a**)*

Ketone/enol mixture **28a** was prepared from 4-methylpyrimidine **1** (7.05 g, 50.3 mmol), ester **27a** (12.9 g, 55.3 mmol), and lithium diisopropylamide (27.7 mL of a 2.0 M solution in THF, 55.3 mmol) in THF (20 mL). Yield of **28a**: 6.78 g (36%) as a 2.6:1.0 mixture of enol:ketone tautomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ enol tautomer: 2.64 (s, 3H), 5.93 (s, 1H), 6.68 (d, $J = 5.4$ Hz, 1H), 7.19 (t, $J = 8.4$ Hz, 1H), 7.70–7.83 (m, 1H), 8.06 (dd, $J = 6.5$, 1.9 Hz, 1H), 8.34 (d, $J = 5.4$ Hz, 1H); ketone tautomer: 2.54 (s, 3H), 4.34 (s, 2H), 6.99 (d, $J = 4.9$ Hz, 1H), 7.21–7.25 (m, 1H), 7.70–7.83 (m, 1H), 7.99–8.05 (m, 1H), 8.48 (d, $J = 4.9$ Hz, 1H). MS (ESI+) 342.5.

*4.5.2. 1-(4-Fluoro-3-methylphenyl)-2-(2-methylsulfanylpyrimidin-4-yl)ethanone and 1-(4-fluoro-3-methylphenyl)-2-(2-methylsulfanylpyrimidin-4-yl)ethenol (**28b**)*

Ketone/enol mixture **28b** was prepared from 4-methylpyrimidine **1** (10.0 g, 71.3 mmol), ester **27b** (13.2 g, 78.5 mmol), and lithium diisopropylamide (46.0 mL of a 2.0 M solution in heptane/THF/ethylbenzene, 92.7 mmol) in THF (250 mL). Yield of **28b**: 7.22 g (37%) as a 1.3:1.0 mixture of enol:ketone tautomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ enol tautomer: 2.34 (s, 3H), 2.62 (s, 3H), 5.91 (s, 1H), 6.63 (d, $J = 5.4$ Hz, 1H), 7.05 (t, $J = 8.8$ Hz, 1H), 7.61–7.67 (m, 1H), 7.68 (d, $J = 7.3$ Hz, 1H), 8.30 (d, $J = 5.4$ Hz, 1H); ketone tautomer: 2.34 (s, 3H), 2.54 (s, 3H), 4.34 (s, 2H), 6.98 (d, $J = 5.1$ Hz, 1H), 7.09 (t, $J = 8.8$ Hz, 1H), 7.84–7.91 (m, 1H), 7.92 (d, $J = 7.3$ Hz, 1H), 8.45 (d, $J = 5.1$ Hz, 1H). MS (ESI+) 276.9.

*4.5.3. 1-(4-Chlorophenyl)-2-(2-methylsulfanylpyrimidin-4-yl) ethanone and 1-(4-chlorophenyl)-2-(2-methylsulfanylpyrimidin-4-yl)ethenol (**28c**)*

Ketone/enol mixture **28c** was prepared from 4-methylpyrimidine **1** (10.1 g, 71.9 mmol), 4-chlorobenzoic acid methyl ester (13.5 g, 79.1 mmol), and lithium diisopropylamide (46.8 mL of 2.0 M solution in heptane/THF/ethylbenzene, 93.5 mmol) in THF (250 mL). Yield of **28c**: 7.38 g (37%) as a 2.7:1.0 mixture of enol:ketone tautomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ enol tautomer: 2.62 (s, 3H), 5.96 (s, 1H), 6.66 (d, $J = 5.4$ Hz, 1H), 7.41 (d, $J = 8.6$ Hz, 2H), 7.99

(d, $J = 8.6$ Hz, 2H), 8.33 (d, $J = 5.4$ Hz, 1H); ketone tautomer: 2.52 (s, 3H), 4.35 (s, 2H), 6.98 (d, $J = 5.1$ Hz, 1H), 7.46 (d, $J = 8.6$ Hz, 2H), 7.99 (d, $J = 8.6$ Hz, 2H), 8.47 (d, $J = 5.1$ Hz, 1H). MS (ESI+) 278.8.

*4.5.4. 1-(2,4-Difluorophenyl)-2-(2-methylsulfanylpyrimidin-4-yl)ethanone and 1-(2,4-difluorophenyl)-2-(2-methylsulfanylpyrimidin-4-yl)ethenol (**28d**)*

Ketone/enol mixture **28d** was prepared from 4-methylpyrimidine **1** (10.0 g, 71.3 mmol), 2,4-difluorobenzoic acid methyl ester (14.6 g, 78.4 mmol), and lithium diisopropylamide (46.3 mL of a 2.0 M solution in heptane/THF/ethylbenzene, 92.7 mmol) in THF (250 mL). Yield of **28d**: 9.90 g (50%) as a 3.5:1.0 mixture of enol:ketone tautomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ enol tautomer: 2.62 (s, 3H), 6.14 (s, 1H), 6.68 (d, $J = 5.4$ Hz, 1H), 6.86–7.03 (m, 2H), 7.89–7.97 (m, 1H), 8.35 (d, $J = 5.4$ Hz, 1H); ketone tautomer: 2.49 (s, 3H), 4.37 (d, $J = 2.9$ Hz, 2H), 6.86–7.03 (m, 3H), 7.95–8.04 (m, 1H), 8.48 (d, $J = 5.0$ Hz, 1H). MS (ESI+) 280.9.

*4.6. General procedure for the synthesis of bromides **29a–d** and imidazopyridines **30a–d***

A solution of appropriate ketone **28a–d** (1.0 equivalent) in CH_2Cl_2 was charged with tetra-*n*-butylammonium tribromide (1.0 equivalent). The reaction was stirred at room temperature for 3 h, and was then concentrated under reduced pressure, and chromatographed on SiO_2 using a gradient that started with heptane and ended with 25:75 EtOAc:heptane. A solution of appropriate bromide **29a–d** (1.0 equivalent) in ethanol was then charged with (2-aminopyridin-4-yl)methanol (1.0 equivalent), and the reaction was heated to 60 °C for 12 h. The reaction was then concentrated under reduced pressure, then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Any modifications to this procedure are noted below.

*4.6.1. 2-Bromo-1-(3-bromo-4-fluorophenyl)-2-(2-methylsulfanylpyrimidin-4-yl)ethanone (**29a**)*

Bromide **29a** was prepared from ketone/enol mixture **28a** (6.51 g, 19.1 mmol) and tetra-*n*-butylammonium tribromide (9.20 g, 19.1 mmol) in CH_2Cl_2 (200 mL). Yield of **29a**: 3.68 g (46%).

*4.6.2. [2-(3-Bromo-4-fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]methanol (**30a**)*

Imidazopyridine **30a** was prepared from bromide **29a** (3.68 g, 8.76 mmol) and (2-aminopyridin-4-yl)methanol (1.08 g, 8.76 mmol) in ethanol (200 mL). Yield of **30a**: 1.72 g (44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 4.84 (s, 2H), 6.84 (d, $J = 5.4$ Hz, 1H), 7.02 (d, $J = 7.0$ Hz, 1H), 7.19 (t, $J = 8.4$ Hz, 1H), 7.52–7.59 (m, 1H), 7.73 (bs, 1H), 7.92 (dd, $J = 6.5$, 1.7 Hz, 1H), 8.36 (d, $J = 5.4$ Hz, 1H), 9.50 (d, $J = 7.0$ Hz, 1H). MS (ESI+) 446.6.

*4.6.3. 2-Bromo-1-(4-fluoro-3-methylphenyl)-2-(2-methylsulfanylpyrimidin-4-yl)ethanone (**29b**)*

Bromide **29b** was prepared from ketone/enol mixture **28b** (7.20 g, 26.1 mmol) and tetra-*n*-butylammonium tribromide (12.6 g, 26.1 mmol) in CH_2Cl_2 (200 mL). Yield of **29b**: 4.60 g (50%).

*4.6.4. [2-(4-Fluoro-3-methylphenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]methanol (**30b**)*

Imidazopyridine **30b** was prepared from bromide **29b** (4.50 g, 12.7 mmol), (2-aminopyridin-4-yl)methanol (1.58 g, 12.7 mmol), and Na_2CO_3 (2.13 g, 25.3 mmol) in ethanol (100 mL). Yield of **30b**: 2.10 g (44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.66 (s, 3H), 4.83 (s, 2H), 6.85 (d, $J = 5.4$ Hz, 1H), 6.99 (dd, $J = 7.2$, 1.4 Hz, 1H), 7.06 (t, $J = 8.9$ Hz, 1H), 7.33–7.43 (m, 1H), 7.52 (d, 1H), 7.69 (bs, 1H), 8.29 (d, $J = 5.4$ Hz, 1H), 9.57 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 380.9.

*4.6.5. 2-Bromo-1-(4-chlorophenyl)-2-(2-methylsulfanylpyrimidin-4-yl)ethanone (**29c**)*

Bromide **29c** was prepared from ketone/enol mixture **28c** (7.38 g, 26.5 mmol) and tetra-*n*-butylammonium tribromide (12.8 g, 26.5 mmol) in CH_2Cl_2 (250 mL). Yield of **29c**: 4.65 g (49%).

*4.6.6. [2-(4-Chlorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]methanol (**30c**)*

Imidazopyridine **30c** was prepared from bromide **29c** (4.65 g, 13.0 mmol), (2-aminopyridin-4-yl)methanol (1.61 g, 13.0 mmol), and in this case $NaHCO_3$ (2.18 g, 26.0 mmol) in ethanol (100 mL). Yield of **30c**: 2.13 g (43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (s, 3H), 4.82 (s, 2H), 6.83 (d, $J = 5.4$ Hz, 1H), 6.98 (dd, $J = 7.3$, 1.6 Hz, 1H), 7.43 (d, $J = 8.5$ Hz, 2H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.71 (bs, 1H), 8.32 (d, $J = 5.4$ Hz, 1H), 9.52 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 382.8.

*4.6.7. 2-Bromo-1-(2,4-difluorophenyl)-2-(2-methylsulfanylpyrimidin-4-yl)ethanone (**29d**)*

Bromide **29d** was prepared from ketone/enol mixture **28d** (9.90 g, 35.3 mmol) and tetra-*n*-butylammonium tribromide (17.0 g, 35.3 mmol) in CH_2Cl_2 (250 mL). Yield of **29d**: 8.60 g (68%).

*4.6.8. [2-(2,4-Difluorophenyl)-3-(2-methylsulfanyl)pyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]methanol (**30d**)*

Imidazopyridine **30d** was prepared from bromide **29d** (8.60 g, 23.9 mmol), (2-aminopyridin-4-yl)methanol (2.97 g, 23.9 mmol), and in this case $NaHCO_3$ (2.00 g, 23.9 mmol) in ethanol (100 mL). Yield of **30d**: 3.50 g (38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 3H), 4.82 (s, 2H), 6.72 (dd, $J = 5.4$, 0.5 Hz, 1H), 6.90–6.96 (m, 1H), 7.01 (dd, $J = 7.3$, 1.6 Hz, 1H), 7.05 (dt, $J = 8.4$, 2.4 Hz, 1H), 7.65 (dd,

$J = 14.8$, 8.4 Hz, 1H), 7.71 (bs, 1H), 8.32 (d, $J = 5.4$ Hz, 1H), 9.66 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 384.9.

4.7. General procedure for the synthesis of sulfones **31a–d**

A solution of appropriate sulfide (**30a–d**) in MeOH/acetone was charged with an aqueous solution of OXONE® and the reaction was stirred at room temperature for 12 h. The reaction was then concentrated under reduced pressure to remove as much organic solvent as possible, then diluted with additional H_2O, and filtered. The filter cake was then dried in a vacuum oven at 60 °C for 4 h. The filtrate was back extracted with CH_2Cl_2, which was then dried with Na_2SO_4, filtered, and concentrated under reduced pressure to yield additional product. Any modifications to this procedure are noted below.

4.7.1. [2-(3-Bromo-4-fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]methanol (**31a**)

Sulfone **31a** was prepared from sulfide **30a** (1.72 g, 3.86 mmol) in MeOH (80 mL)/acetone (80 mL) that was charged with OXONE® (7.12 g, 11.6 mmol) dissolved in H_2O (80 mL). Yield of **31a**: 1.59 g (86%). MS (ESI+) 478.7.

4.7.2. [2-(4-Fluoro-3-methylphenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]methanol (**31b**)

Sulfone **31b** was prepared from sulfide **30b** (2.10 g, 5.52 mmol) in MeOH (125 mL)/acetone (100 mL) that was charged with OXONE® (10.2 g, 16.6 mmol) dissolved in H_2O (90 mL). Yield of **31b**: 2.03 g (89%). MS (ESI+) 412.9.

4.7.3. [2-(4-Chlorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]methanol (**31c**)

Sulfone **31c** was prepared from sulfide **30c** (2.13 g, 5.56 mmol) in MeOH (100 mL)/acetone (75 mL) that was charged with OXONE® (10.3 g, 16.7 mmol) dissolved in H_2O (90 mL). Yield of **31c**: 1.65 g (71%). MS (ESI+) 414.8.

4.7.4. [2-(2,4-Difluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]methanol (**31d**)

Sulfone **31d** was prepared from sulfide **30d** (3.50 g, 9.11 mmol) in MeOH (220 mL)/acetone (160 mL) that was charged with OXONE® (16.8 g, 27.3 mmol) dissolved in H_2O (150 mL). Yield of **31d**: 2.88 g (76%). MS (ESI+) 416.8.

4.8. General procedure for the synthesis of 2-aminopyrimidines **32a–d**

A mixture of appropriate sulfone (**31a–d**) in THF in a pressure bottle was cooled to −78 °C in a CO_2/IPA bath, and charged with excess ammonia gas that was bubbled in over 10–15 min. The reaction vessel was then sealed, and the reaction was allowed to warm to room temperature with stirring for 12 h, while reaching 40–50 psi. Pressure was then released, and the reaction mixture was concentrated under reduced pressure, then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Any modifications to this procedure are noted below.

4.8.1. [3-(2-Aminopyrimidin-4-yl)-2-(3-bromo-4-fluorophenyl)imidazo[1,2-a]pyridin-7-yl]methanol (**32a**)

2-Aminopyrimdine **32a** was prepared from sulfone **31a** (1.59 g, 3.33 mmol) and ammonia (42.4 g, 2.49 mol) in THF (100 mL). Yield of **32a**: 920 mg (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (s, 2H), 5.48 (bs, 2H), 6.56 (d, $J = 5.5$ Hz, 1H), 6.98–7.04 (m, 1H), 7.19 (t, $J = 8.4$ Hz, 1H), 7.54–7.60 (m, 1H), 7.72 (bs, 1H), 7.94 (dd, $J = 6.5$, 1.9 Hz, 1H), 8.13 (d, $J = 5.5$ Hz, 1H), 9.47 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 413.7.

4.8.2. [3-(2-Aminopyrimidin-4-yl)-2-(4-fluoro-3-methylphenyl)imidazo[1,2-a]pyridin-7-yl]methanol (**32b**)

2-Aminopyrimdine **32b** was prepared from sulfone **31b** (2.03 g, 4.92 mmol) and ammonia (18.2 g, 1.07 mol) in THF (200 mL). Yield of **32b**: 1.10 g (64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 4.82 (s, 2H), 5.57 (bs, 2H), 6.55 (d, $J = 5.5$ Hz, 1H), 7.00 (d, $J = 7.4$ Hz, 1H), 7.05 (t, $J = 8.9$ Hz, 1H), 7.35–7.41 (m, 1H), 7.52 (dd, $J = 7.4$, 1.0 Hz, 1H), 7.73 (s, 1H), 8.05 (d, $J = 5.5$ Hz, 1H), 9.52 (d, $J = 7.4$ Hz, 1H). MS (ESI+) 349.9.

4.8.3. [3-(2-Aminopyrimidin-4-yl)-2-(4-chlorophenyl)imidazo[1,2-a]pyridin-7-yl]methanol (**32c**)

2-Aminopyrimdine **32c** was prepared from sulfone **31c** (1.65 g, 3.98 mmol) and ammonia (15.0 g, 881 mmol) in THF (200 mL). Yield of **32c**: 0.75 g (54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (s, 2H), 5.32 (bs, 2H), 6.50 (d, $J = 5.4$ Hz, 1H), 6.86 (dd, $J = 7.2$, 1.3 Hz, 1H), 7.38 (d, $J = 8.5$ Hz, 2H), 7.57 (d, $J = 8.5$ Hz, 2H), 7.62 (bs, 1H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.31 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 351.9.

4.8.4. [3-(2-Aminopyrimidin-4-yl)-2-(2,4-difluorophenyl)imidazo[1,2-a]pyridin-7-yl]methanol (**32d**)

2-Aminopyrimdine **32d** was prepared from sulfone **31d** (2.88 g, 6.92 mmol) and ammonia (11.5 g, 675 mmol) in THF (100 mL). Yield of **32d**: 1.29 g (53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (s, 2H), 5.38 (bs, 2H), 6.43 (d, $J = 5.4$ Hz, 1H), 6.92 (t, $J = 9.2$ Hz, 1H), 7.00 (d, $J = 7.0$ Hz, 1H), 7.01–7.08 (m, 1H), 7.61–7.69 (m, 1H), 7.71 (bs, 1H), 8.10 (d, $J = 5.4$ Hz, 1H), 9.61 (d, $J = 7.0$ Hz, 1H). MS (ESI+) 353.9.

4.9. General procedure for the synthesis of aldehydes **33a–d**

A solution of appropriate alcohol **32a–d** in CH_2Cl_2 was charged with excess manganese(IV) oxide, and the reaction was allowed to stir for 12 h at room temperature. The reaction was then filtered through celite, and the celite filter cake was

then rinsed with additional CH_2Cl_2 and/or EtOAc. The combined filtrates were concentrated under reduced pressure to yield aldehydes **33a–d**, which were not purified further. Any modifications to this procedure are noted below.

*4.9.1. 3-(2-Aminopyrimidin-4-yl)-2-(3-bromo-4-fluorophenyl)imidazo[1,2-a]pyridine-7-carbaldehyde (**33a**)*

Aldehyde **33a** was prepared from alcohol **32a** (910 mg, 2.20 mmol) and manganese(IV) oxide (4.77 g, 54.9 mmol). Yield of **33a**: 530 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (bs, 2H), 6.60 (d, $J = 5.3$ Hz, 1H), 7.20 (t, $J = 8.4$ Hz, 1H), 7.45 (dd, $J = 7.3$, 1.5 Hz, 1H), 7.50–7.64 (m, 1H), 7.97 (dd, $J = 6.6$, 2.1 Hz, 1H), 8.17 (bs, 1H), 8.25 (d, $J = 5.3$ Hz, 1H), 9.43 (d, $J = 7.3$ Hz, 1H), 10.07 (s, 1H). MS (ESI+) 411.7.

*4.9.2. 3-(2-Aminopyrimidin-4-yl)-2-(4-fluoro-3-methylphenyl)imidazo[1,2-a]pyridine-7-carbaldehyde (**33b**)*

Aldehyde **33b** was prepared from alcohol **32b** (730 mg, 2.09 mmol) and manganese(IV) oxide (4.54 g, 52.2 mmol). Yield of **33b**: 540 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 5.26 (bs, 2H), 6.60 (d, $J = 5.3$ Hz, 1H), 7.07 (t, $J = 8.9$ Hz, 1H), 7.38–7.46 (m, 2H), 7.57 (dd, $J = 7.2$, 1.3 Hz, 1H), 8.17 (bs, 1H), 8.20 (d, $J = 5.3$ Hz, 1H), 9.50 (d, $J = 7.2$ Hz, 1H), 10.06 (s, 1H). MS (ESI+) 347.9.

*4.9.3. 3-(2-Aminopyrimidin-4-yl)-2-(4-chlorophenyl)imidazo[1,2-a]pyridine-7-carbaldehyde (**33c**)*

Aldehyde **33c** was prepared from alcohol **32c** (620 mg, 1.76 mmol) and manganese(IV) oxide (3.83 g, 44.1 mmol). Yield of **33c**: 290 mg (47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (bs, 2H), 6.62 (d, $J = 5.5$ Hz, 1H), 7.43–7.50 (m, 3H), 7.63 (d, $J = 8.4$ Hz, 2H), 8.16 (d, $J = 5.5$ Hz, 1H), 8.20 (bs, 1H), 9.52 (d, $J = 7.3$ Hz, 1H), 10.08 (s, 1H). MS (ESI+) 349.8.

*4.9.4. 3-(2-Aminopyrimidin-4-yl)-2-(2,4-difluorophenyl)imidazo[1,2-a]pyridine-7-carbaldehyde (**33d**)*

Aldehyde **33d** was prepared from alcohol **32d** (970 mg, 2.75 mmol) and manganese(IV) oxide (5.98 g, 68.8 mmol). Yield of **33d**: 670 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (bs, 2H), 6.48 (d, $J = 5.3$ Hz, 1H), 6.90–6.99 (m, 1H), 7.07 (td, $J = 8.3$, 1.6 Hz, 1H), 7.47 (dd, $J = 7.3$, 1.6 Hz, 1H), 7.69 (td, $J = 8.3$, 6.5 Hz, 1H), 8.17–8.23 (m, 2H), 9.63 (d, $J = 7.3$ Hz, 1H), 10.08 (s, 1H). MS (ESI+) 351.9.

*4.10. General procedure for the synthesis of tertiary amines **34a–d***

A solution of appropriate aldehyde **33a–d** in THF was charged with dimethylamine (2.0 M in THF) and sodium triacetoxyborohydride. After stirring at room temperature for 12 h, the reaction was concentrated under reduced pressure, then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Any modifications to this procedure are noted below.

*4.10.1. 4-[2-(3-Bromo-4-fluorophenyl)-7-dimethylaminomethylimidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**34a**)*

Amine **34a** was prepared from aldehyde **33a** (520 mg, 1.26 mmol), dimethylamine (945 μL of a 2.0 M solution in THF, 1.89 mmol), and sodium triacetoxyborohydride (401 mg, 1.89 mmol) in THF (100 mL). Yield of **34a**: 250 mg (45%). The product was then purified further by HPLC using a MeOH/H_2O gradient, where the aqueous phase was 98.9:1.0:0.1 H_2O:CH_3CN:Et_3N. Final yield of **34a**: 161 mg (29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 6H), 3.52 (s, 2H), 5.25 (bs, 2H), 6.53 (d, $J = 5.3$ Hz, 1H), 7.02 (dd, $J = 7.2$, 1.4 Hz, 1H), 7.15 (t, $J = 8.4$ Hz, 1H), 7.48–7.61 (m, 2H), 7.94 (dd, $J = 6.6$, 2.1 Hz, 1H), 8.16 (d, $J = 5.3$ Hz, 1H), 9.35 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 440.7.

*4.10.2. 4-[7-Dimethylaminomethyl-2-(4-fluoro-3-methylphenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**34b**)*

Amine **34b** was prepared from aldehyde **33b** (540 mg, 1.55 mmol), dimethylamine (1.17 mL of a 2.0 M solution in THF, 2.33 mmol), and sodium triacetoxyborohydride (493 mg, 2.33 mmol) in THF (100 mL). Yield of **34b**: 389 mg (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 6H), 2.31 (s, 3H), 3.51 (s, 2H), 5.25 (bs, 2H), 6.54 (d, $J = 5.3$ Hz, 1H), 6.97–7.06 (m, 2H), 7.35–7.42 (m, 1H), 7.51–7.56 (m, 2H), 8.11 (d, $J = 5.3$ Hz, 1H), 9.42 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 377.0.

*4.10.3. 4-[2-(4-Chlorophenyl)-7-dimethylaminomethylimidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**34c**)*

Amine **34c** was prepared from aldehyde **33c** (290 mg, 0.829 mmol), dimethylamine (620 μL of a 2.0 M solution in THF, 1.24 mmol), and sodium triacetoxyborohydride (352 mg, 1.66 mmol) in THF (100 mL). Yield of **34c**: 185 mg (59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 6H), 3.53 (s, 2H), 5.22 (bs, 2H), 6.53 (d, $J = 5.3$ Hz, 1H), 7.02 (d, $J = 7.1$ Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.56 (bs, 1H), 7.61 (d, $J = 8.4$ Hz, 2H), 8.14 (d, $J = 5.3$ Hz, 1H), 9.37 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 379.0.

*4.10.4. 4-[2-(2,4-Difluorophenyl)-7-dimethylaminomethylimidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**34d**)*

Amine **34d** was prepared from aldehyde **33d** (670 mg, 1.91 mmol), dimethylamine (1.43 mL of a 2.0 M solution in THF, 2.87 mmol), and sodium triacetoxyborohydride (810 mg, 3.82 mmol) in THF (250 mL). Yield of **34d**: 340 mg (47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 6H), 3.60 (s, 2H), 5.16 (bs, 2H), 6.41 (d, $J = 5.3$ Hz, 1H), 6.88–6.95 (m, 1H), 7.00–7.06 (m, 1H), 7.12 (d, $J = 7.1$ Hz, 1H), 7.58 (bs, 1H), 7.60–7.69 (m, 1H), 8.13 (d, $J = 5.3$ Hz, 1H), 9.57 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 380.9.

*4.10.5. 3-Oxo-3-(2,4,6-trifluorophenyl)propionic acid ethyl ester (**35**)*

A solution of monoethyl malonate (1.19 g, 9.00 mmol) in THF (200 mL) was cooled to −78 °C in a CO_2/IPA bath, and charged with the dropwise addition of *n*-butyllithium (11.2 mL of a 1.6 M solution in hexanes, 18.0 mmol). After the addition, the reaction was allowed to warm to room temperature for 40 min, and then cooled back to −78 °C. A solution of 2,4,6-triflurobenzoyl chloride (1.00 g, 5.14 mmol) in THF (50 mL) was then added dropwise. The reaction then warmed to room temperature and stirred for 1.5 h, after which it was concentrated under reduced pressure, suspended in 5:1 CH_2Cl_2:MeOH (600 mL), and washed with a saturated aqueous $NaHCO_3$ solution (100 mL). The organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was then chromatographed on SiO_2 using a gradient that started with heptane and ended with 30:70 EtOAc:heptane. Yield of **35**: 730 mg (57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ketone tautomer: 1.25 (t, $J = 7.2$ Hz, 3H), 3.89 (s, 2H), 4.20 (q, $J = 7.2$ Hz, 2H), 6.63–6.90 (m, 2H); enol tautomer: 1.34 (t, $J = 7.2$ Hz, 3H), 4.28 (q, $J = 7.2$ Hz, 2H), 5.39 (s, 1H), 6.63–6.90 (m, 2H), 12.38 (s, 1H). MS (ESI+) 246.8.

*4.10.6. 2-Bromo-3-oxo-3-(2,4,6-trifluorophenyl)propionic acid ethyl ester (**36**)*

A solution of ketone/enol mixture **35** (730 mg, 2.97 mmol) in CH_2Cl_2 (50 mL) was charged with tetra-*n*-butylammonium tribromide (1.43 g, 2.97 mmol). The reaction was stirred at room temperature for 30 min, and was then chromatographed on SiO_2 using a gradient that started with heptane and ended with 30:70 EtOAc:heptane. Yield of **36**: 811 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, $J = 7.1$ Hz, 3H), 4.31 (q, $J = 7.1$ Hz, 2H), 5.48 (s, 1H), 6.79 (t, $J = 8.4$ Hz, 2H). MS (ESI+) 324.2.

*4.10.7. 7-Hydroxymethyl-2-(2,4,6-trifluorophenyl)imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (**37**)*

A solution of bromide **36** (12.8 g, 39.4 mmol) in ethanol (100 mL) was charged with (2-aminopyridin-4-yl)methanol (4.89 g, 39.4 mmol), and heated at 60 °C for 36 h. The reaction was then concentrated under reduced pressure and chromatographed on SiO_2 first with a gradient that started with heptane and ended with 30:70 EtOAc:heptane, and then with a gradient that started with CH_2Cl_2 and ended with 40:60 MeOH:CH_2Cl_2. Yield of **37**: 5.20 g (38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, $J = 7.1$ Hz, 3H), 4.25 (q, $J = 7.1$ Hz, 2H), 4.81 (s, 2H), 6.77 (t, $J = 8.0$ Hz, 2H), 7.06 (dd, $J = 7.1$, 0.9 Hz, 1H), 7.75 (bs, 1H), 9.31 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 350.5.

*4.10.8. 7-Methanesulfonyloxymethyl-2-(2,4,6-trifluorophenyl)imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (**38**)*

A solution of alcohol **37** (5.20 g, 14.8 mmol) in THF (200 mL) was charged with Et_3N (3.00 g, 4.13 mL, 29.7 mmol), then methanesulfonyl chloride (2.55 g, 1.73 mL, 22.3 mmol), and the reaction stirred at room temperature for 2 h, and was then concentrated under reduced pressure and carried on to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, $J = 7.2$ Hz, 3H), 3.10 (s, 3H), 4.38 (q, $J = 7.2$ Hz, 2H), 5.36 (s, 2H), 6.80 (dd, $J = 8.4$, 7.2 Hz, 2H), 7.17 (dd, $J = 7.2$, 1.5 Hz, 1H), 7.85 (bs, 1H), 9.45 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 428.8.

*4.10.9. 7-Dimethylaminomethyl-2-(2,4,6-trifluorophenyl) imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (**39**)*

A solution of crude mesylate **38** (theoretically 6.34 g, 14.8 mmol) in THF (250 mL) was charged with diisopropylethylamine (2.49 g, 3.36 mL, 19.3 mmol) and dimethylamine (9.65 mL of a 2.0 M solution in THF, 19.3 mmol), and the reaction was allowed to stir at room temperature for 12 h. The reaction was then concentrated under reduced pressure, then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **39**: 3.50 g (63% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, $J = 7.1$ Hz, 3H), 2.35 (s, 6H), 3.59 (s, 2H), 4.26 (q, $J = 7.1$ Hz, 2H), 6.78 (dd, $J = 8.5$, 7.6 Hz, 2H), 7.15–7.30 (m, 1H), 7.65 (bs, 1H), 9.34 (d, $J = 7.0$ Hz, 1H). MS (ESI+) 377.9.

*4.10.10. 7-Dimethylaminomethyl-2-(2,4,6-trifluorophenyl)imidazo[1,2-a]pyridine-3-carboxylic acid methoxymethylamide (**40**)*

A solution of ethyl ester **39** (3.50 g, 9.27 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (2.71 g, 27.8 mmol) in THF (250 mL) was cooled to 0 °C in an ice water bath, then charged with the dropwise addition of isopropylmagnesium chloride (27.8 mL of a 2.0 M solution in THF, 55.6 mmol), and the reaction was stirred at 0 °C. After 1 h, additional portions of both *N*,*O*-dimethylhydroxylamine (2.71 g, 27.8 mmol) and isopropylmagnesium chloride (27.8 mL of a 2.0 M solution in THF, 55.6 mmol) were added, and stirring at 0 °C continued for another 0.5 h. The reaction was then quenched with the slow addition of a saturated aqueous NH_4Cl solution (200 mL). The layers were separated, and the organic layer was washed again with a saturated aqueous NH_4Cl solution (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and carried onto the next step without further purification. Yield of **40**: 3.50 g (96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 6H), 3.26 (s, 3H), 3.43 (s, 3H), 3.56 (s, 2H), 6.78 (t, $J = 8.2$ Hz, 2H), 7.02–7.18 (m, 1H), 7.59 (bs, 1H), 8.72 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 392.9.

*4.10.11. 1-[7-Dimethylaminomethyl-2-(2,4,6-trifluorophenyl)imidazo[1,2-a]pyridin-3-yl]ethanone (**41**)*

A solution of crude Weinreb amide **40** (3.50 g, theoretically 8.92 mmol) in THF (250 mL) was cooled to 0 °C in an ice water bath, then charged with dropwise addition of methylmagnesium bromide (32.0 mL of a 1.4 M solution in 3:1 toluene:THF, 44.6 mmol). The reaction was then allowed to

warm to room temperature and stirred for 12 h. The reaction was then washed with a saturated aqueous NH_4Cl solution (2×150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **41**: 1.37 g (44% over two steps). ^1H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.30 (s, 6H), 3.54 (s, 2H), 6.86 (dd, $J = 8.4$, 7.2 Hz, 2H), 7.21 (dd, $J = 7.3$, 1.5 Hz, 1H), 7.65 (bs, 1H), 9.70 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 347.5.

*4.10.12. 3-Dimethylamino-1-[7-dimethylaminomethyl-2-(2,4,6-trifluorophenyl)imidazo[1,2-a]pyridin-3-yl]propenone (**42**)*

A solution of ketone **41** (0.981 g, 2.82 mmol) in DMFDMA (1.83 g, 1.88 mL, 14.1 mmol) was heated to 80 °C for 12 h, then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **42**: 750 mg (66%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 6H), 2.46 (bs, 3H), 3.07 (bs, 3H), 3.54 (s, 2H), 5.01 (d, $J = 12.3$ Hz, 1H), 6.82 (dd, $J = 8.6$, 7.2 Hz, 2H), 7.09 (d, $J = 7.1$ Hz, 1H), 7.56 (bs, 1H), 7.68 (d, $J = 12.3$ Hz, 1H), 9.67 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 402.9.

*4.10.13. 4-[7-Dimethylaminomethyl-2-(2,4,6-trifluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**43**)*

A solution of enone **42** (750 mg, 1.86 mmol) in 1-propanol (10 mL) was charged with guanidine hydrochloride (267 mg, 2.80 mmol) and sodium methoxide (25% w/v in MeOH, 151 mg, 640 μL, 2.80 mmol), and was heated to 80 °C for 12 h. The reaction was then concentrated under reduced pressure, and chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:-concentrated NH_4OH. Yield of **43**: 580 mg (78%), which was then purified further by HPLC using a MeOH/H_2O gradient, where the aqueous phase was 98.9:1.0:0.1 H_2O:CH_3CN:Et_3N. Final yield of **43**: 210 mg (28%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 6H), 3.52 (s, 2H), 5.14 (bs, 2H), 6.39 (d, $J = 5.4$ Hz, 1H), 6.81 (dd, $J = 8.6$, 7.4 Hz, 2H), 7.06 (dd, $J = 7.3$, 1.5 Hz, 1H), 7.59 (bs, 1H), 8.14 (d, $J = 5.4$ Hz, 1H), 9.61 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 399.4.

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