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Structure-Based Design of a Novel Series of Potent, Selective Inhibitors of the Class I Phosphatidylinositol 3-Kinases

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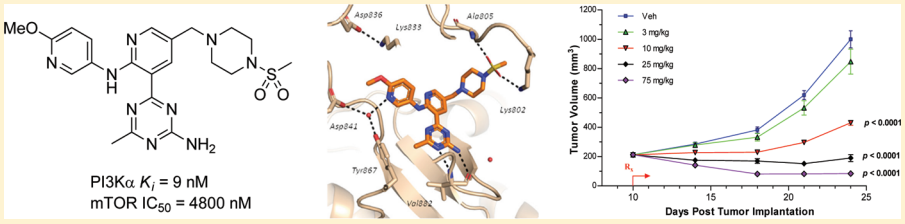
Supporting Information



ABSTRACT: A highly selective series of inhibitors of the class I phosphatidylinositol 3-kinases (PI3Ks) has been designed and synthesized. Starting from the dual PI3K/mTOR inhibitor **5**, a structure-based approach was used to improve potency and selectivity, resulting in the identification of **54** as a potent inhibitor of the class I PI3Ks with excellent selectivity over mTOR, related phosphatidylinositol kinases, and a broad panel of protein kinases. Compound **54** demonstrated a robust PD−PK relationship inhibiting the PI3K/Akt pathway in vivo in a mouse model, and it potently inhibited tumor growth in a U-87 MG xenograft model with an activated PI3K/Akt pathway.

INTRODUCTION

The phosphatidylinositol 3-kinases (PI 3-kinases or PI3Ks) are a family of lipid kinases involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival, and intracellular trafficking. The PI3Ks are activated by receptor tyrosine kinases and Ras and Rho family GTPases, and subsequently, they phosphorylate the 3′-hydroxyl group of phosphatidylinositol (PtdIns) and phosphoinositides, leading to the activation of many intracellular signaling pathways. The PI3K family is divided into three different classes—class I, class II, and class III—on the basis of primary structure, regulation, and in vitro lipid substrate specificity. The class I PI3Ks have a strong preference for phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2). They are heterodimeric molecules composed of a regulatory and a catalytic subunit and are further divided between IA and IB subsets on the basis of sequence similarity. The class IA PI3Ks (PI3Kα, PI3Kβ, and PI3Kδ) are composed of heterodimers between a p110 catalytic subunit (p110α, p110β, and p110δ, respectively) and a p85 regulatory subunit. The sole class IB subtype (PI3Kγ) is comprised of a catalytic p110γ and a regulatory p101 subunit.[1−3]

Many of the functions of the class I PI3Ks relate to their ability to activate protein kinase B (PKB, Akt) through phosphatidylinositol-3,4,5-trisphosphate (PI(3,4,5)P3), with downstream signaling stimulating cellular proliferation, differentiation, and survival.[2] PI3K signaling is constitutively activated in many cancers by a variety of genetic alterations that result in increased flux through the PI3K pathway. Mutations in PIK3CA, the gene encoding p110α, are particularly prominent in many cancers, including approximately 30% of breast, cervix, and endometrium tumors.[4,5] In addition, loss of function of the PI(3,4,5)P3 phosphatase PTEN, a critical negative regulator of PI3K signaling, is also a frequent event in many tumor types.[6] PI3K signaling leads to the phosphorylation of multiple substrates involved in survival signaling by Akt. The mammalian target of rapamycin (mTOR), a downstream target of Akt, is a critical regulator of PI3K/Akt signaling through positive and negative feedback loops, and there is preclinical evidence that certain tumors with

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deregulated PI3K/Akt signaling are particularly sensitive to mTOR inhibition.[7−9] Hence, it is clear that dysregulation of the PI3K/Akt pathway contributes significantly to cellular transformation and the development of cancer.

Upregulation of the PI3K/Akt pathway in many cancers and its impact on tumor growth and survival has led to considerable interest in several members of this pathway as possible anticancer targets.[10−13] Close structural homology between the p110 and mTOR kinase domains has permitted the design of selective dual inhibitors of PI3K and mTOR,[12−21] offering the possibility of targeting cancers by inhibiting two critical nodes in this pathway. In an attempt to balance efficacy with clinical tolerability, recent efforts have also focused upon deriving inhibitors with selectivity for either PI3K[22,23] or mTOR.[8,9,24−26] Several compounds have recently entered clinical development, including dual PI3K/mTOR inhibitors[15,17,20] and a more selective inhibitor of the class I PI3K family[23] (Figure 1). We report herein the structure-based

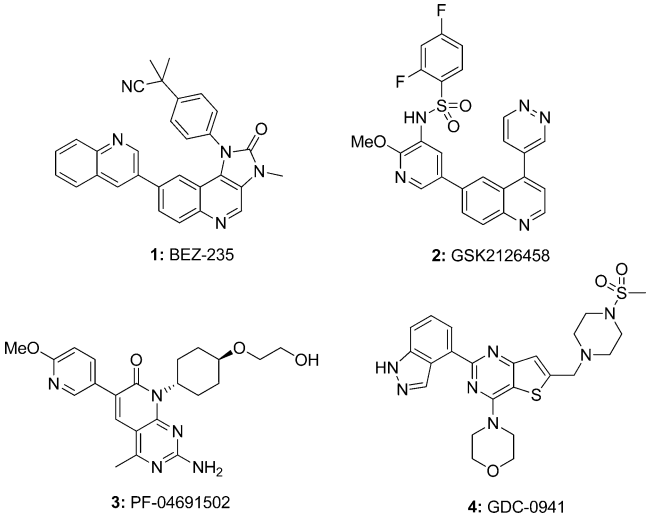

Figure 1. PI3K/mTOR dual inhibitors (**1**−**3**) and the class I selective PI3K inhibitor **4**.

design of a new series of selective inhibitors of the class I PI3Ks and its optimization to give a compound with potent antitumor activity in a preclinical cancer model in vivo. A complementary approach to a novel series of mTOR inhibitors from a similar starting point has been described previously.[24]

RESULTS AND DISCUSSION

PI3K Inhibitor Design. The identification of the benzimidazole triazine **5** (Figure 2) as a dual PI3K/mTOR inhibitor has been described previously.[24] As was noted in this previous disclosure, the dual activity of **5** against the PI3Ks and mTOR was a consequence of the high homology between the PI3Ks and mTOR within the ATP binding site. Compound **5** was originally prepared during the course of an earlier program targeting B-Raf, and it demonstrates potent inhibition of B-Raf in addition to its PI3K/mTOR activities (^{V600E}B-Raf IC_{50} = 3 nM; PI3Kα K_i = 350 nM; mTOR IC_{50} = 93 nM: see Supporting Information for kinase selectivity data). Cocrystal structures of PI3Kα with inhibitors had proven to be difficult to obtain at the outset of this work,[27,28] but a cocrystal structure of inhibitor **5** with PI3Kγ (for which there is close sequence homology with PI3Kα in the kinase domain)[1] was readily obtained (Figure 2). In this cocrystal structure, the aminotriazine of compound **5** forms a bidentate hydrogen bond interaction with Val882 in the hinge region of the kinase domain of PI3Kγ, and the phenolic −OH forms a bridging hydrogen bond between Asp841 and Tyr867 in a region of the protein commonly referred to as either the affinity or selectivity pocket. A similar phenolic substituent was reported for the lead that ultimately gave rise to **4** (GDC-0941).[23] The benzimidazole group itself serves as a central scaffold, with an intramolecular hydrogen bond from the aminobenzimidazole N−H to the adjacent triazine nitrogen atom locking the conformation in a manner favorable for binding. The benzene ring of the benzimidazole is orientated toward the ribose pocket of the protein but does not substantially penetrate it.

The main liabilities of **5** as a starting point for a medicinal chemistry program were the poor pharmacokinetic properties associated with this scaffold.[24] Not only was the phenolic substituent susceptible to glucuronidation in vivo,[23] but the benzimidazole triazine scaffold itself was problematic due to extensive metabolism of the benzimidazole.[24] In contrast, previous work from this group had demonstrated that it was possible to obtain good in vivo properties with related pyridylpyrimidine and pyridylpurine scaffolds.[29] This prompted us to explore the general scaffold **6** (Figure 3), which contains either a monocyclic or bicyclic hinge binder motif linked to a central 2-aminopyridine core. We postulated that the central 6-membered ring core would serve as a suitable template to project the appropriate pharmacophoric moieties into each of

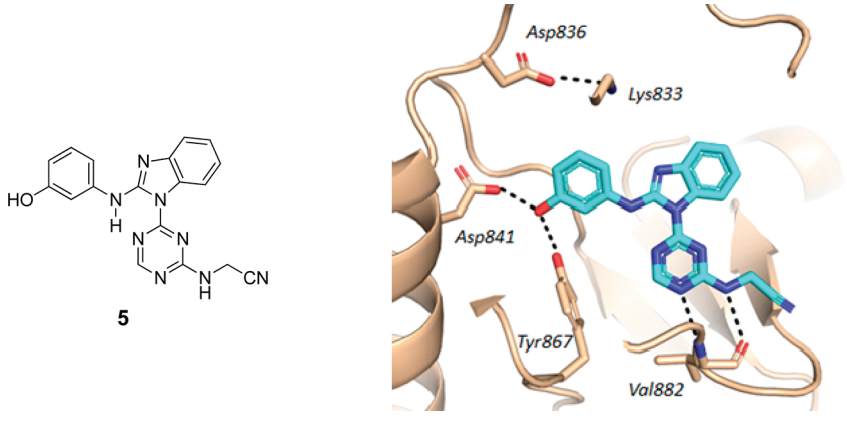

Figure 2. High throughput screening hit **5** and the cocrystal structure of **5** bound to the ATP binding site of PI3Kγ determined at 2.9 Å resolution.

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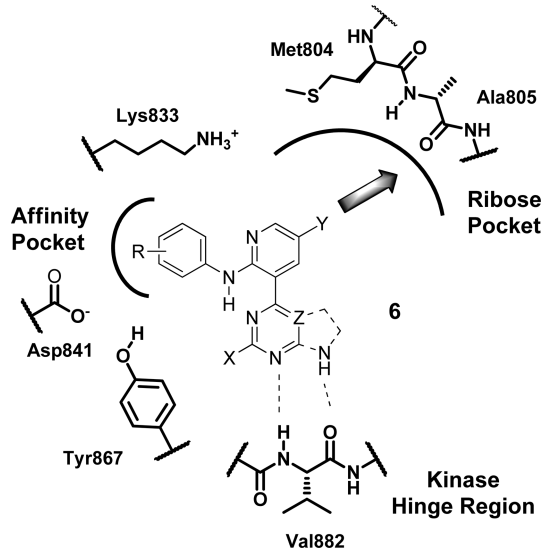

Figure 3. Generic structure **6** showing potential interactions with PI3Kγ.

the three key regions of the enzyme: the hinge region, the affinity pocket, and the ribose pocket.

As illustrated in Figure 3, the monocyclic or bicyclic heterocycle appended to the 3 position of the pyridine core would provide the critical hydrogen bonding interactions with the hinge region of the enzyme (Val882). In addition, the cocrystal structure of compound **5** with PI3Kγ suggested that a small lipophilic substituent X on the hinge-binding group of **6**, such as a methyl group, would favorably fill a small hydrophobic pocket found in the PI3Ks (near Tyr867) which is not generally present in protein kinases (excluding mTOR) due to the presence of an additional amino acid in the hinge region of the PI3Ks. This added substitution would give the opportunity for significant selectivity over a broad range of protein kinases, as was observed with the related series of mTOR inhibitors.[24]

The aminopyridine N−H of **6** would form an intramolecular hydrogen bond with the adjacent hinge-binder nitrogen, providing conformational rigidity to this bis-aryl combination in a similar manner to that observed in **5** and in a conformation that should favorably project the N-aryl substituent into the affinity pocket. It was previously noted that the amino phenol of **5** was likely to be subject to glucuronidation in vivo. However, the methoxypyridine and indazole substituents of **3** (PF-04691502)[17] and **4** overlaid well with the phenol, suggesting that it may be possible to replace the phenol substituent in the affinity pocket.

Finally, molecular modeling suggested that substituents projecting from the 5-position of the pyridine core into the ribose pocket should be able to access similar interactions that the respective alkoxycyclohexane and piperazine sulfonamide substituents of **3** and **4** make in this region of the protein (the Y substituent of generic structure **6** projecting toward Met804 and Ala805 of PI3Kγ). Some subtle residue differences exist between the different PI3K isoforms and mTOR in the ribose pocket region of these proteins, and we postulated that substitution at the pyridine 5-position would offer the potential to improve the potency, selectivity (over mTOR and between PI3K isoforms), and pharmacokinetic properties of this new series, as has been reported for these two clinical candidates.[17,23]

Chemistry. The compounds highlighted in this report are shown in Figure 4. Compounds **5**, **7**, and **8** have been

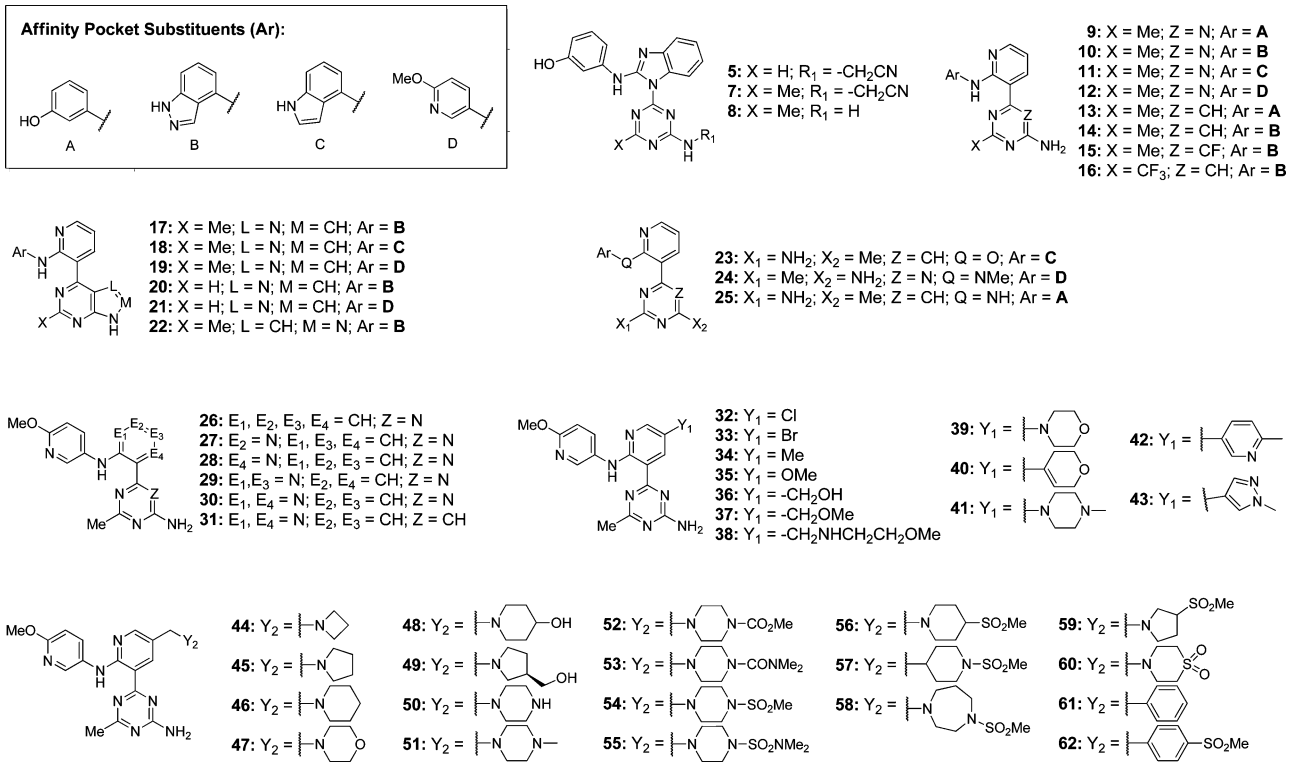

Figure 4. Structures of the scaffold **6** analogues described below.

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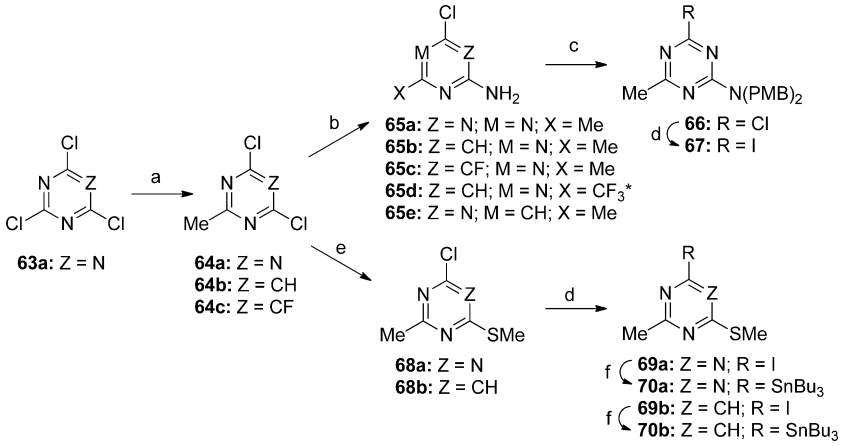
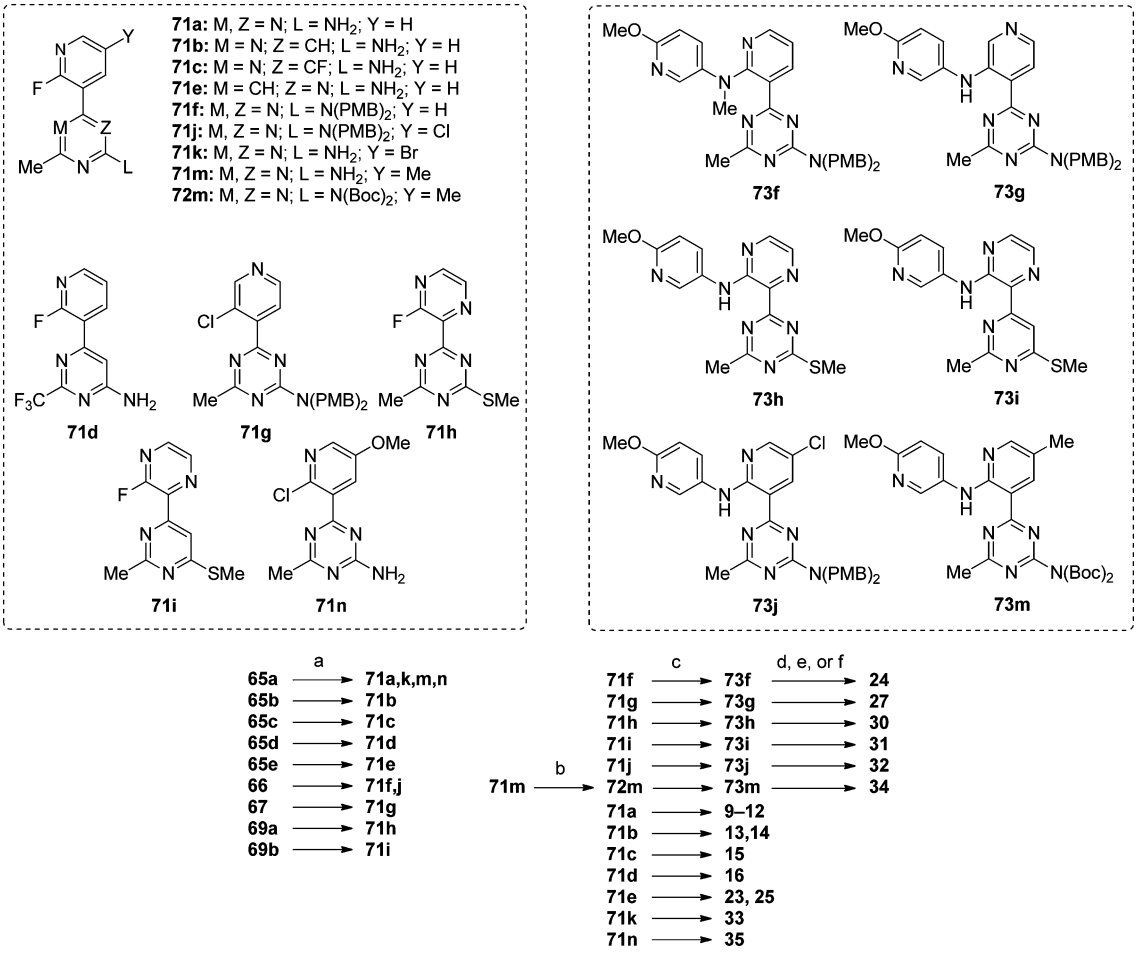
Scheme 1. Synthesis of Monocyclic Hinge-Binder Intermediates[a]



[a]Reagents and conditions: (a) MeMgBr, Et_2O; (b) NH_3, MeOH; (c) 4-methoxybenzyl chloride, NaH, DMF; (d) HI, CH_2Cl_2, H_2O; (e) NaSMe, PhH; (f) *i*-PrMgCl, *n*-Bu_3SnCl, THF, −78 °C. *Intermediate **65d** is commercially available.

Scheme 2. Main Routes for Coupling the Central Core with the Hinge-Binder and Affinity Pocket Substituents[a]



[a]Reagents and conditions: (a) Arylboronic acid + base, *or* arylstannane, Pd cat., Δ; (b) NaH, Boc_2O, DMF; (c) Method A: Ar-QH, base; Method B: Ar-NH_2, HCl, 1,4-dioxane, H_2O, Δ; (d) L = $N(PMB)_2$: TFA, TfOH, Δ; (e) L = SMe: NH_3, 1,4-dioxane, H_2O, Δ; (f) L = $N(Boc)_2$: TFA, CH_2Cl_2.

previously described.[24] The synthetic routes used to prepare compounds **9**–**62** are described below.

Scheme 1 summarizes the syntheses of key intermediates used for the introduction of the monocyclic hinge-binder fragments onto the inhibitor scaffold from commercially available **63a**, **64b**, **64c**, **65d**, and **65e**. The chemistry is exemplified by the versatility of 2,4,6-trichloro-1,3,5-triazine (**63a**), where the differential reactivities of the three chlorine atoms to successive substitution made it possible to selectively replace the first chlorine atom with a methyl group (**64a**) and

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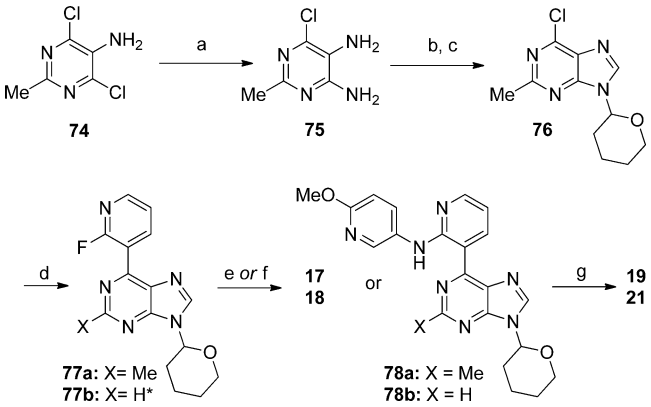
the second with either an amino group (**65a**) or a thiomethyl ether (**68a**). One of the more versatile intermediates was the bis(4-methoxybenzyl)amino-protected derivative **66**, which incorporated two PMB protecting groups for the amino substituent that facilitated subsequent chemistry steps. The corresponding thiomethyl ether **68a** provided an alternative route for late-stage introduction of an amino substituent. The third chloro substituent (e.g., on **66** or **68a**) served as a suitable coupling partner in palladium-catalyzed coupling reactions to the central core in most cases, although the corresponding iodides (e.g., **67**) or stannanes (e.g., **70a,b**; for reversed coupling reactivity) were sometimes employed. The synthetic routes involving the corresponding pyrimidine intermediates (e.g., **65b** or **68b**) were very similar to those employed for the triazines.

Scheme 2 summarizes the main strategies for coupling the central core with the hinge-binder and affinity pocket substituents. The syntheses of compounds **9**–**12** illustrate the basic strategy used throughout this work, with a Pd-mediated coupling between the chlorotriazine **65a** and 2-fluoro-3-pyridylboronic acid (to give **71a**) being followed by introduction of the affinity pocket substituent either through a base-mediated S_NAr displacement or an acid-catalyzed displacement on the 2-fluoropyridine to give compounds **9**–**12**. Bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)-dichloropalladium(II) [$Pd(Amphos)_2Cl_2$] was the preferred Pd catalyst with potassium acetate as base in either 1,4-dioxane/water or ethanol/water as solvent for the Pd-mediated Suzuki–Miyaura coupling reactions.[30] The use of potassium acetate as base helped minimize hydrolysis of the 2-fluoropyridine under the reaction conditions compared with stronger bases such as potassium or sodium carbonate. A Suzuki–Miyaura cross-coupling reaction was used in most cases throughout this work, although the pyrazines **71h,i** were more conveniently prepared from 2-fluoro-3-(tributylstannyl)-pyrazine using a Stille coupling.[31] The S_NAr reaction of amines on 2-fluoropyridines using lithium bis(trimethylsilyl)amide (LiHMDS) as base in tetrahydrofuran (THF) was the most convenient method for introducing many of the amino substituents explored in the affinity pocket. The ether linkage of **23** was introduced by phenolic displacement of the 2-fluoropyridine using potassium carbonate in *N*,*N*-dimethylformamide (DMF). Some of the early compounds in this series, such as **9**–**12**, utilized an alternative acid-catalyzed coupling using dilute hydrochloric acid in 1,4-dioxane at reflux to facilitate introduction of the affinity pocket substituents onto the 2-halopyridine central core.

A problem encountered in the syntheses of earlier compounds such as **9**–**16** was the low isolated yields of the desired products, partly due to their poor solubility and competing deprotonation of the amino group when base-mediated introduction of affinity pocket substituents was attempted. The most successful strategy for overcoming this was by masking the amino substituent with bis(4-methoxybenzyl) protecting groups (e.g., **66** → **71f** → **73f** → **24**). This significantly improved the solubility of intermediates and resulted in much higher isolated yields. The PMB protecting groups were readily removed at the end of the synthetic sequence by heating in trifluoroacetic acid (TFA) containing a small amount of trifluoromethanesulfonic acid (TfOH). Bis-protection of the amino group with benzyloxycarbonyl (Boc) groups (**71m** → **72m** → **73m** → **34**) or masking as a thiomethyl ether followed by displacement with ammonia at the end (**69a** → **71h** → **73h** → **30**) was also used, although these strategies were generally less efficient than bis-PMB protection of the amino group. The 5-chloro substituent on the central core of **73j** provided a convenient synthetic handle for additional functionalization at this position to access the ribose pocket, making **73j** a versatile synthetic intermediate.

The synthesis of bicyclic pyridylpurine hinge-binder analogues is outlined in Scheme 3. An efficient synthesis of

Scheme 3. Synthesis of Pyridylpurine Analogues[a]



[a]Reagents and conditions: (a) NH_3, H_2O, Δ; (b) $(EtO)_3CH$, Δ; (c) 3,4-dihydro-2*H*-pyran, TsOH, CH_2Cl_2; (d) 2-fluoropyridin-3-ylboronic acid, $Pd(Amphos)_2Cl_2$, KOAc, EtOH, H_2O, Δ; (e) Ar-NH_2, HCl, EtOH, H_2O, Δ; (f) 3-amino-6-methoxypyridine, LiHMDS, THF, 0 °C; (g) HCl, H_2O, Δ. *Synthesis of **77b** described in ref 29.

the intermediate **77a** is shown starting from commercially available 5-amino-4,6-dichloro-2-methylpyrimidine (**74**). Selective monoamination gave the diaminopyrimidine **75**, which furnished 6-chloro-2-methyl-9*H*-purine upon treatment with triethyl orthoformate. Subsequent protection with a tetrahydro-2*H*-pyran-2-yl (THP) protecting group gave purine **76**, which underwent a Suzuki–Miyaura coupling with 2-fluoro-3-pyridylboronic acid, giving **77a**. Intermediates **77a** and **77b**[29] were converted to **17**–**19** and **21** by coupling with the relevant amines to install the affinity pocket substituents followed by removal of the THP protecting group under acidic conditions.

The 4-amino-1*H*-indazole affinity pocket substituent used for compounds **10** and **14**–**17** was found to be chemically sensitive and underwent extensive decomposition during the course of the reactions used to prepare them, particularly under basic conditions. It is likely that deprotonation at the 3-position of the 1*H*-indazole under basic conditions gave rise to cleavage and decomposition of the 1*H*-indazole.[32] This problem could be circumvented by THP-protection of 4-nitro-1*H*-indazole (**79**) to give a readily separable mixture of 1*H*-indazole and 2*H*-indazole products (**80a,b**) in approximately equal proportions, which were reduced to the corresponding amines **81a,b** (Scheme 4). While the 1*H*-indazole derivative **81a** was still relatively sensitive to base, the 4-amino-2*H*-indazole **81b** was able to be coupled to the central core in moderate yield, as illustrated in Scheme 5 with the pyridylpurine **77b** and the related 1*H*-pyrazolo[3,4-*d*]pyrimidine **84** (Scheme 6). The overall yields for coupling and subsequent deprotection to prepare **20** and **22** (27–37%) were noticeably improved relative to the coupling yields for **10** and **14**–**17** (5–22%), where the unprotected indazole was used.

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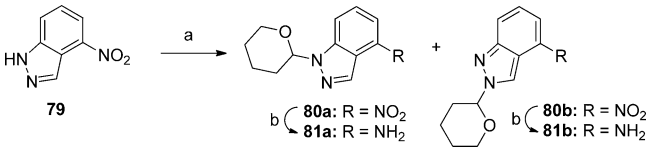
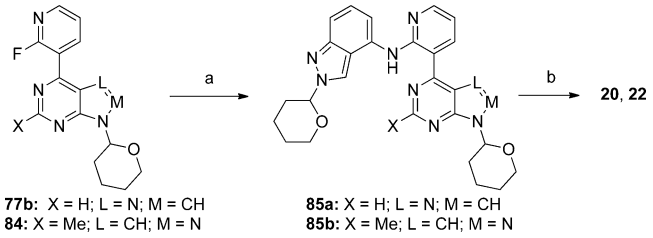
Scheme 4. Synthesis of Protected Indazole Intermediates[a]



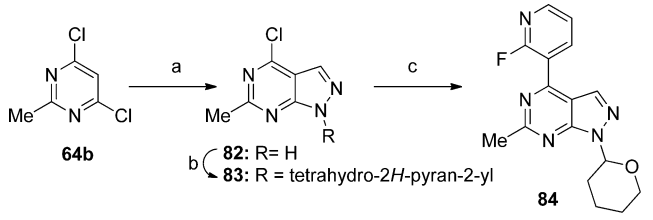
[a]Reagents and conditions: (a) 3,4-dihydro-2*H*-pyran, MP-TsOH, EtOAc, Δ; (b) H_2, 10% Pd/C, EtOAc.

Scheme 5. Improved Synthesis of 1*H*-Indazole Analogues[a]



[a]Reagents and conditions: (a) **81b**, LiHMDS, THF, 0 °C; (b) CSA, CH_2Cl_2, MeOH, Δ.

Scheme 6. Synthesis of 1*H*-Pyrazolo[3,4-*d*]pyrimidine Intermediate[a]

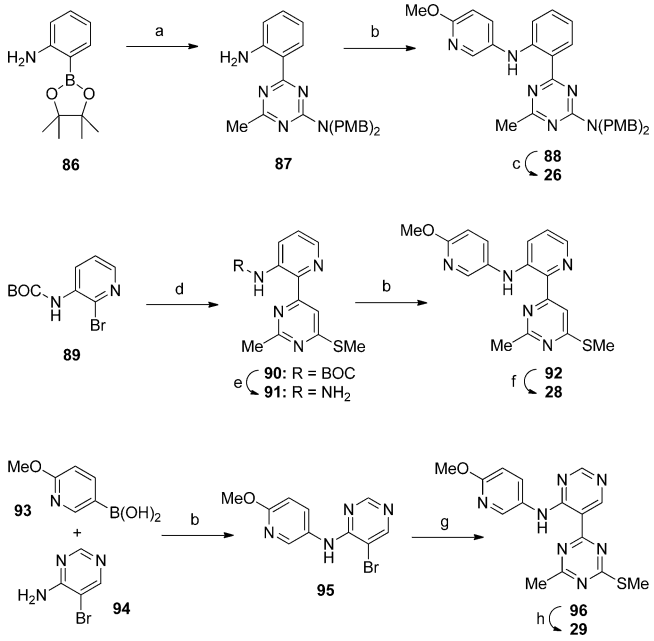


[a]Reagents and conditions: (a) LDA, *N*-methyl-*N*-(2-pyridyl)-formamide, THF, −78 °C; then NH_2NH_2; (b) 3,4-dihydro-2*H*-pyran, MP-TsOH, EtOAc, Δ; (c) 2-fluoropyridin-3-ylboronic acid, $Pd(Amphos)_2Cl_2$, KOAc, EtOH, H_2O, Δ.

Scheme 7 illustrates the syntheses of some of the analogues containing alternative central cores. The syntheses of **26**, **28**, and **29** deviated from the previously described methodologies by the use of a copper-mediated coupling[33] of the boronic acid **93** with an amino-substituted central core to introduce the affinity pocket substituent. Stille reactions[31] were used for joining the central cores and hinge-binders in the syntheses of **28** and **29**, reversing the polarity of the coupling relative to the analogous couplings described so far. Additionally, the order of attaching the affinity pocket and hinge-binding substituents to the central core was switched during the synthesis of **29**.

Scheme 8 outlines the synthesis of the key intermediates **103a** and **105**, which provided useful aldehyde and methanesulfonate functional handles for exploring the ribose pocket. The thiomethyl ether derivative **103b** was also used to a lesser extent. Commercially available 6-fluoronicotinaldehyde (**97**) underwent regioselective ortho-lithiation adjacent to the fluoro-substituent after first protecting the aldehyde as an acetal, allowing efficient formation of boronic acid **99**. The corresponding boronate ester **100** underwent Suzuki−Miyaura coupling with triazines **66** and **68a**, and the resulting products (**101a,b**) underwent a base-mediated S_NAr displacement reaction with 3-amino-6-methoxypyridine to give **102a,b**. Once the affinity pocket substituent was installed, the acetal group became exceptionally sensitive to acid hydrolysis. This

Scheme 7. Alternative Synthetic Routes Used To Access Central-Core Analogues[a]



[a]Reagents and conditions: (a) **66**, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, Δ; (b) **93**, $Cu(OAc)_2$, *i*-Pr_2NEt, CH_2Cl_2; (c) TFA, TfOH, Δ; (d) **70b**, $Pd(PPh_3)_4$, toluene, Δ; (e) HCl, 1,4-dioxane, MeOH, Δ; (f) *m*-CPBA, CH_2Cl_2 *then* NH_3, 1,4-dioxane, Δ; (g) **70a**, $Pd(PPh_3)_4$, CuI, CsF, THF, Δ; (h) NH_3, 1,4-dioxane, Δ.

enhanced sensitivity was presumably due to the amino substituent on the central core participating in the opening of the acetal group under acidic catalysis. The aldehydes **103a,b** were therefore readily obtained. Reduction and deprotection of **103a** then provided **36**.

The main methods used for late-stage introduction of a wide range of ribose pocket substituents are illustrated in Scheme 9. The chloropyridine **73j** was an effective partner in a variety of palladium-mediated coupling reactions. Alkyl substituents were readily incorporated at the 5-pyridyl position using trifluoroborate salts,[34] amine substituents were introduced using Buchwald−Hartwig aminations,[35] and aryl substituents were introduced using Suzuki−Miyaura couplings.[30] The aldehydes **103a,b** were versatile intermediates for introduction of aminomethyl substituents into the 5-pyridyl position via reductive amination, with amine displacement on the methanesulfonate **105** being an alternative route to these aminomethyl analogues, as illustrated by the syntheses of compounds **48** and **60**.

During the later stages of this work, more efficient routes for the synthesis of 5-(piperazin-1-ylmethyl)pyridine derivatives were explored, particularly for the larger-scale synthesis of compounds such as **54**. The route shown in Scheme 10 was found to be both versatile and efficient. Starting from commercially available 2-fluoro-5-methylpyridine (**109**), benzylic bromination followed by nucleophilic displacement with *tert*-butyl piperazine-1-carboxylate gave **111**. Selective ortho-lithiation/boronic acid formation was possible to give **112**, and subsequent Suzuki−Miyaura cross-coupling reactions with **66** or **68a** (**113a,b**) followed by S_NAr displacement with 3-amino-6-methoxypyridine gave intermediates **114a,b**. The Boc protecting-group was readily removed with TFA in CH_2Cl_2

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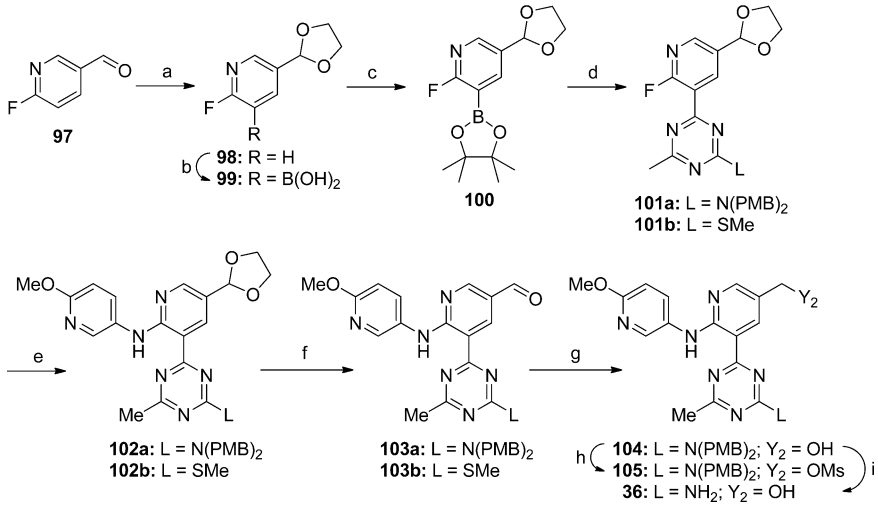
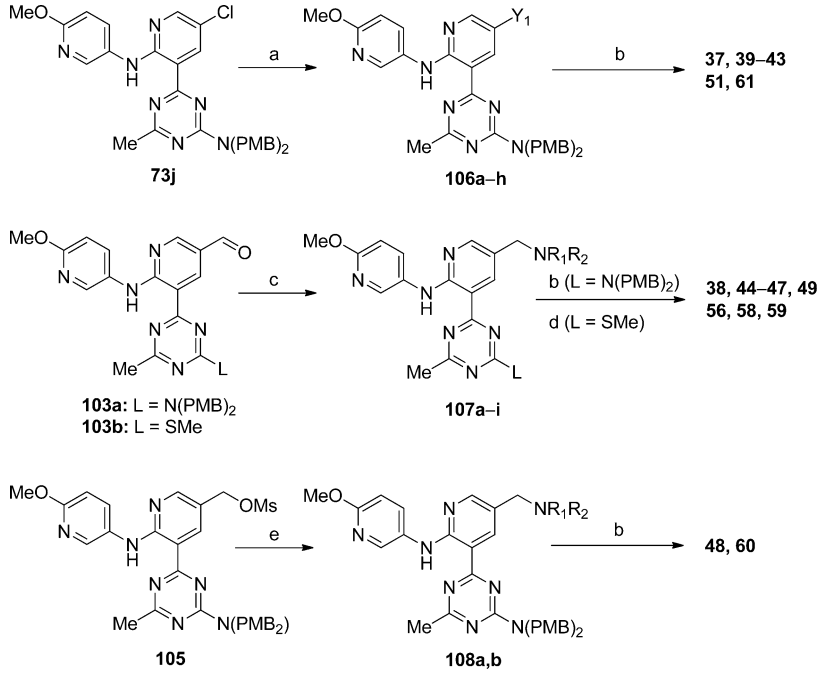
Scheme 8. Synthesis of Key Intermediates for Exploring the Ribose Pocket[a]



[a]Reagents and conditions: (a) $HOCH_2CH_2OH$, TsOH, toluene, Δ; (b) LDA, $(i\text{-PrO})_3B$, THF, −78 °C; (c) pinacol, $MgSO_4$, toluene; (d) **66** or **68a**, Pd cat., base, 1,4-dioxane, H_2O, Δ; (e) 3-amino-6-methoxypyridine, LiHMDS, THF, 0 °C; (f) HCl, H_2O; (g) $NaBH_4$, CH_2Cl_2, MeOH, 0 °C; (h) MsCl, Et_3N, CH_2Cl_2, 0 °C; (i) TFA, TfOH, Δ.

Scheme 9. Alternative Methods for Introducing Ribose Pocket Substituents[a]



[a]Reagents and conditions: (a) R-$BF_3^-K^+$ or R_1R_2NH or R_1-$B(OR)_2$, Pd cat., solvent, Δ; (b) TFA, TfOH, Δ; (c) R_1R_2NH, $NaBH_3(CN)$, CH_2Cl_2/MeOH, or EtOH/AcOH; (d) NH_3, *i*-PrOH, Δ; (e) R_1R_2NH, Et_3N, CH_2Cl_2.

while leaving the PMB-protecting group of **114a** intact, giving **115a,b**. These could both be converted to the aminotriazine **50**, which was then converted to the carbamate **52**. Compound **115a** was the more versatile of the two intermediates **115a** and **115b** and generally gave better overall yields of final products. The versatility of **115a** is illustrated in Scheme 10 by its conversion into **53**−**55** via intermediates **116**−**118**.

Schemes 11 and 12 show the syntheses of compounds **57** and **62**, respectively. The piperidinesulfonamide moiety of **57** was introduced by hydroboration of *tert*-butyl 4-methylenepiperidine-1-carboxylate (**119**), and coupling the resulting borane to the chloride **73j** to give **120**, which was then converted to the methanesulfonamide **122** before final deprotection to **57**. The phenylsulfone **62** was efficiently prepared from **67**. Addition of the Grignard derived from 4-bromothioanisole to the aldehyde of **67** gave the hydroxymethylene intermediate **123**. The thiomethyl ether substituent permitted a facile reduction of the alcohol with triethylsilane in TFA by stabilizing the benzylic cation intermediate in this reaction, resulting in **124**. Ortho-lithiation was used to install a boronic acid group on the pyridine (**125**), a Suzuki−Miyaura coupling with the hinge-binder intermediate **66** gave **126**, and then the thiomethyl ether group was oxidized to the corresponding

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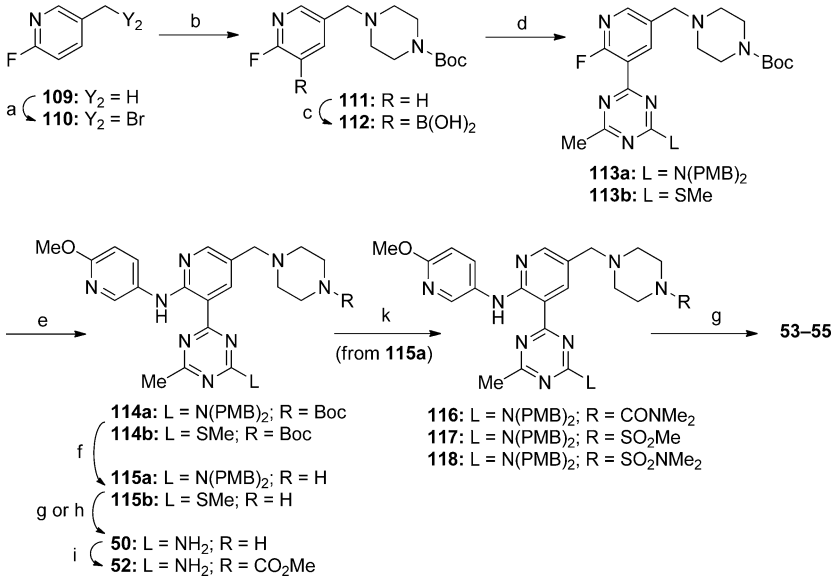
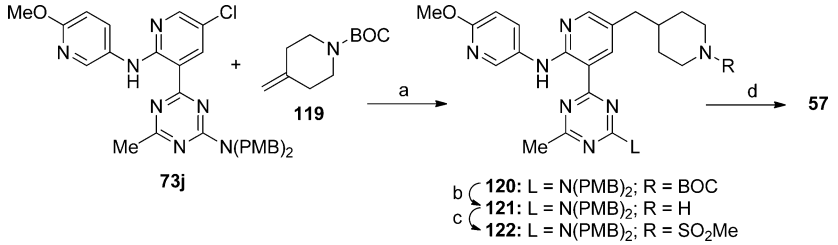
Scheme 10. Synthesis of 1-Piperazinylmethyl Ribose Pocket Analogues[a]



[a]Reagents and conditions: (a) NBS, Bz_2O_2, CCl_4, Δ; (b) *tert*-butyl piperazine-1-carboxylate, DMF; (c) LDA, $(i\text{-PrO})_3B$, THF, −78 °C; (d) **66** or **68a**, Pd cat., base, 1,4-dioxane, H_2O, Δ; (e) 3-amino-6-methoxypyridine, LiHMDS, THF, 0 °C; (f) TFA, CH_2Cl_2; (g) L = $N(PMB)_2$: TFA, TfOH, Δ; (h) L = SMe: NH_3, *i*-PrOH, Δ; (i) MeO(CO)Cl, Et_3N, CH_2Cl_2, 0 °C; (k) R-Cl, Et_3N, CH_2Cl_2.

Scheme 11. Synthesis of the Piperidine Sulfonamide 57[a]

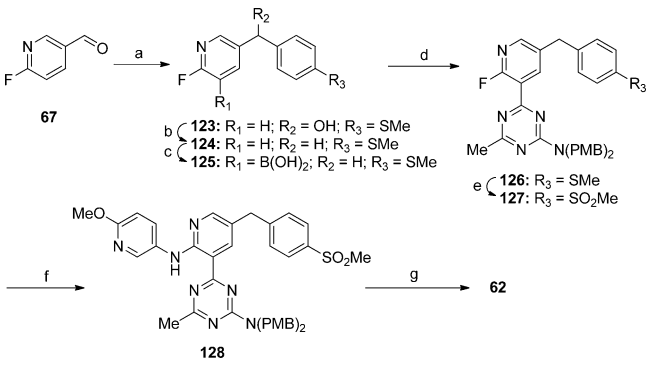


[a]Reagents and conditions: (a) **119**, 9-BBN, THF, Δ *then* **73j**, $Pd_2(dba)_3$, X-Phos, Na_2CO_3, 1,4-dioxane, H_2O, Δ; (b) TFA, CH_2Cl_2; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C; (d) TFA, TfOH, Δ.

sulfone **127**. Installation of the affinity pocket substituent (**128**) followed by deprotection then gave **62**.

Structure–Activity Relationships. In vitro inhibitory activities of compounds against recombinant PI3K*α*, PI3K*β*, PI3K*γ*, and PI3K*δ* were measured in modified AlphaScreen assays, mTOR kinase domain inhibitory activity was measured in a LanthaScreen FRET assay, and cellular activity measuring downstream inhibition of Akt phosphorylation at Ser473 was measured in the U-87 MG human glioblastoma cell line using a SureFire detection kit, all as previously described.[14] The U-87 MG cell line was used, since it harbors a loss-of-function PTEN mutation which results in an activated PI3K/Akt pathway. Data from these assays is presented in Table 1 for compounds **5** and **7**–**31** highlighting basic structure–activity relationships (SARs) around the hinge-binder, central core, and affinity pocket regions of the scaffold **6**. The data demonstrate a good correlation between PI3K enzyme inhibition and cellular activity, with minimal enzyme to cell shift being observed. Additionally, compounds in this series had good cellular permeability and generally little P-gp liability (see the Supporting Information). Structure–activity relationship (SAR) discussions around PI3K enzymatic activity will focus primarily upon PI3K*α*, since mutations in this subtype are a major contributor to many cancers. In vitro rat microsomal stability data is also included in Table 1, providing an estimate of the oxidative metabolism liability for the compounds to guide selection of compounds for progression into rodent in vivo studies.[36]

Scheme 12. Synthesis of the Phenylsulfone 62[a]



[a]Reagents and conditions: (a) *p*-$MeSC_6H_4MgBr$, THF, −78 °C; (b) TFA, Et_3SiH, CH_2Cl_2; (c) LiTMP, $(i\text{-PrO})_3B$, THF, −78 °C; (d) **66**, $Pd(Amphos)_2Cl_2$, KOAc, EtOH, H_2O, Δ; (e) *m*-CPBA, CH_2Cl_2; (f) 3-amino-6-methoxypyridine, LiHMDS, THF, 0 °C; (g) TFA, Δ.

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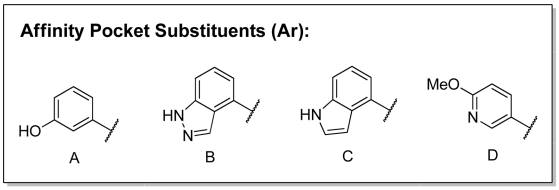
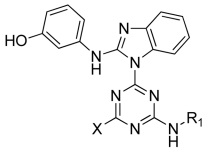
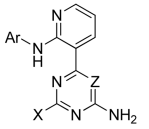
Table 1. Structure–Activity Relationships: Hinge-Binder, Affinity Pocket, and Central Core[a]

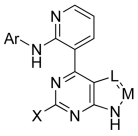




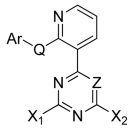
5: X = H; R_1 = -CH_2CN
7: X = Me; R_1 = -CH_2CN
8: X = Me; R_1 = H



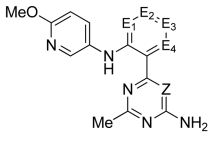
9: X = Me; Z = N; Ar = **A**
10: X = Me; Z = N; Ar = **B**
11: X = Me; Z = N; Ar = **C**
12: X = Me; Z = N; Ar = **D**
13: X = Me; Z = CH; Ar = **A**
14: X = Me; Z = CH; Ar = **B**
15: X = Me; Z = CF; Ar = **B**
16: X = CF_3; Z = CH; Ar = **B**



17: X = Me; L = N; M = CH; Ar = **B**
18: X = Me; L = N; M = CH; Ar = **C**
19: X = Me; L = N; M = CH; Ar = **D**
20: X = H; L = N; M = CH; Ar = **B**
21: X = H; L = N; M = CH; Ar = **D**
22: X = Me; L = CH; M = N; Ar = **B**



23: X_1 = NH_2; X_2 = Me; Z = CH; Q = O; Ar = **C**
24: X_1 = Me; X_2 = NH_2; Z = N; Q = NMe; Ar = **D**
25: X_1 = NH_2; X_2 = Me; Z = CH; Q = NH; Ar = **A**



26: E_1, E_2, E_3, E_4 = CH; Z = N
27: E_2 = N; E_1, E_3, E_4 = CH; Z = N
28: E_4 = N; E_1, E_2, E_3 = CH; Z = N
29: E_1,E_3 = N; E_2, E_4 = CH; Z = N
30: E_1, E_4 = N; E_2, E_3 = CH; Z = N
31: E_1, E_4 = N; E_2, E_3 = CH; Z = CH

	PI3K enzyme K_i (nM)						
cmpd	α	β	γ	δ	mTOR enzyme IC_{50} (nM)	U-87 MG cell pAkt IC_{50} (nM)	rat microsomal CL_{int} (μL/min/mg)
5	350	190	120	52	93	190	291
7	16	43	69	11	8	17	394
8	2	4	4	3	7	9	218
9	12	3	12	9	200	60	80
10	92	51	88	130	>10 000	230	65
11	200	9	45	25	7200	150	110
12	110	23	29	37	7800	360	51
13	28	35	51	56	360	300	62
14	150	110	91	370	>10 000	810	75
15	930	990	330	810	>10 000	>1000	71
16	3200	1300	3600	>10 000	>10 000	>1000	76
17	39	28	12	350	530	340	44
18	190	130	23	360	560	730	90
19	67	45	12	70	290	280	68
20	>10 000	9700	750	>10 000	>10 000	>1000	115
21	8300	>10 000	1100	5700	5100	>1000	109
22	1700	2300	450	5000	>10 000	>1000	56
23	>10 000	>10 000	>10 000	>10 000	>10 000	>1000	218
24	>10 000	>10 000	>10 000	>10 000	>10 000	>1000	41
25	4900	>10 000	2600	6000	>10 000	>1000	118
26	640	580	380	310	>10 000	>1000	190
27	620	320	690	240	>10 000	>1000	133
28	1300	610	480	910	>10 000	>1000	96
29	120	81	59	62	>10 000	>1000	110
30	520	740	90	300	>10 000	>1000	41
31	120	130	58	130	>10 000	590	72

[a]Assays described in ref 14. Data represents an average of at least two determinations.

Starting with the moderately potent PI3K inhibitor **5**, addition of a methyl group to the triazine hinge-binder in order to occupy the previously mentioned small hydrophobic pocket (compound **7**)[24] resulted in a 20-fold improvement in PI3Kα inhibitory activity along with a similar increase in cellular activity. In addition, this methyl substituent resulted in extremely high kinase selectivity, as evidenced by the loss of B-Raf activity[37] (^{V600E}B-Raf IC_{50}: compound **5** = 3 nM; compound **7** = 1200 nM) and broad selectivity over protein kinases in a custom panel of 100 kinases (see Supporting Information). This loss of activity against B-Raf was maintained for all compounds tested with a methyl substituent at this position on the hinge-binder (^{V600E}B-Raf IC_{50} >1000 nM for compounds **7**–**17**, **19**, **22**–**26**, **29**–**31**). Removal of the cyanomethyl substituent from the aminotriazine (compound **8**)[24] gave an additional 10-fold improvement in PI3Kα activity while retaining excellent broad protein kinase selectivity (see Supporting Information). Little or no selectivity was observed

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between the class I PI3K subtypes or over mTOR for **5**, **7**, and **8**. The promising levels of activity secured through these initial changes to the hinge-binding region of the molecule therefore allowed the SAR of the different regions of scaffold **6** to be explored.

As a first step, the aminobenzimidazole central core was replaced with the 2-aminopyridine core of **6** to give the pyridyltriazine **9**. This modification resulted in a modest loss of activity against PI3Kα and in U-87 MG pAkt cellular activity and, unexpectedly, caused a larger loss of activity against mTOR, as noted in Table 1. The pyridyl substituent does not penetrate as far back into the ribose pocket as the benzimidazole, and it was presumed that the reduced hydrophobic interactions in this region were responsible for the observed reduction in activity. It was therefore hoped that it would be possible to regain the modest loss of activity against PI3Kα observed with this central core by suitable substitution from the pyridine into the ribose pocket region (Figure 3: structure **6**, substituent Y). The data for **9** also demonstrated that it was possible to engineer selectivity against mTOR into the scaffold **6**, although the source of the selectivity over mTOR at this stage was not obvious from an examination of an mTOR homology model derived from the PI3Kγ structure.[24] The improvement in rat microsomal stability going from **8** to **9** (Table 1) was noteworthy, reflecting the previously noted superior rat PK of the pyridyltriazine scaffold relative to the benzimidazole trazine scaffold.

The next issue to address was finding a suitable replacement for the phenol substituent with one more likely to have favorable pharmacokinetic properties while maintaining PI3K activity. With this goal in mind, the indazole, indole, and methoxypyridine analogues **10**, **11**, and **12** were prepared. All three compounds displayed similar levels of activity (Table 1), with roughly a 10-fold drop in PI3K enzyme activity relative to that of the phenol **9** being mitigated by a slightly smaller (approximately 4-fold) reduction in cellular activity. All three compounds maintained good selectivity over mTOR, and **10** and **11** lacked activity against the class III PI3K hVPS34 (IC_{50} >9000 nM), giving the first indication of selectivity for this scaffold against nonclass I PI3Ks. Compounds **10**, **11**, and **12** also displayed excellent kinase selectivity in a custom panel of 100 kinases (see Supporting Information). Rat microsomal stabilities for the indazole **10** and especially the methoxypyridine **12** were reasonable, with the indole **11** demonstrating the least favorable stability. While compounds **10**−**12** were significantly less active than the starting point (compound **8**), they had low molecular weights (MW = 318, 317, and 309, respectively) and consequently high ligand efficiencies (LE = 0.29, 0.28, and 0.30 for PI3Kα, respectively).[38] The trade-off in potency for the potential of improved in vivo properties was therefore considered worthwhile. The favorable overall profile of compounds containing the methoxypyridine affinity pocket substituent relative to the corresponding indazole or indole motifs led to the methoxypyridine being adopted during the later stages of the work described herein.

Molecular modeling suggested that the 2-amino-4-methyltriazine hinge-binder formed favorable interactions with a hinge Val residue of the PI3Ks through hydrogen bonds with the 3-aza and 2-amino triazine substituents, while the 4-methyl group formed a favorable hydrophobic interaction in a small pocket flanked by a Tyr side chain, as indicated in the PI3Kγ model with **6** (Figure 3). The triazine 1-aza group appeared to have little interaction with the protein and, as can be seen with the 4-amino-2-methylpyrimidines **13** and **14**, substitution with a carbon atom at this position only had a modest deleterious effect on PI3K enzyme activity, although they were approximately 4-fold weaker than the corresponding triazines **9** and **10** in the U-87 MG cellular assay. Fluoro substitution has often been found to be a viable replacement for an aza substituent, but in this case replacement of the triazine 1-aza group with C−F severely impacted activity (compound **15**; c.f. **14**). Increasing the size of the 4-methyl substituent of the hinge-binder to a trifluoromethyl group (compound **16**) resulted in a large loss of activity relative to that of **14**, indicating little room to push back further into the hydrophobic pocket.

Expanding the size of the triazine hinge-binder to a larger bicyclic group was also explored. The 2-methylpurine analogues **17**−**19** displayed similar levels of activity against the PI3Ks compared with the triazines **10**−**12**, with **19** being equipotent to **12** in the U-87 MG cellular assay. There was, however, a marked reduction in selectivity over mTOR. The importance of the hinge-binder methyl group was confirmed at this stage with the corresponding desmethyl purine analogues **20** and **21**, which both lost greater than 100-fold activity against the PI3Ks compared with **17** and **19**. Other bicyclic hinge-binders were explored. For example, the 6-methyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine **22** was significantly less active compared with **17**.

It was previously noted in the design of scaffold **6** that the aminopyridine N−H should form an intramolecular hydrogen bond with the adjacent hinge-binder aza group and lock the bis-aryl group in a conformation favorable for binding to the PI3Ks. Replacing the N−H with an O linker and a corresponding pyrimidine hinge-binder has been an effective strategy for other kinase projects, particularly in improving physicochemical properties such as solubility.[39−42] An unfavorable lone pair−lone pair repulsion between the O linker and an adjacent pyrimidine N should result in the hinge-binder rotating 180° relative to the cases of **13**−**15** in its preferred binding conformation, making **23** an appropriate test of this strategy. The data for **23** suggested that incorporation of an O linker was a highly disadvantageous strategy for the PI3Ks. Similarly, as expected, methylation of the N−H (compound **24**) severely impacted activity, as did reversing the positions of the amino and methyl substituents on the pyrimidine hinge-binder (compound **25**). The 2-amino-4-methyl-1,3,5-triazine hinge-binding motif was therefore focused upon in subsequent work on this series.

Variations on the central pyridine core were next explored. Replacing the pyridine with a phenyl ring (compound **26**) resulted in a 6-fold loss in PI3Kα activity relative to the case of compound **12**, and moving the pyridine nitrogen around the ring (compounds **27** and **28**) had a similar detrimental effect on enzyme potency. Addition of a nitrogen atom to give a pyrimidine central core (compound **29**) had little effect on PI3Kα enzyme activity but was deleterious to U-87 MG cellular activity. The isomeric 2-pyrazinyltriazine **30** lost a little activity, possibly due to an unfavorable lone pair−lone pair repulsion between the pyrazine and triazine nitrogen atoms, while the corresponding 2-pyrazinylpyrimidine **31** (where no such interaction can exist) regained the lost enzyme activity. In summary, the preliminary SAR efforts involving the hinge-binder and central core variants suggested that the 2-aminopyridine was an appropriate central core to build out from into the ribose pocket in combination with the 2-amino-4-

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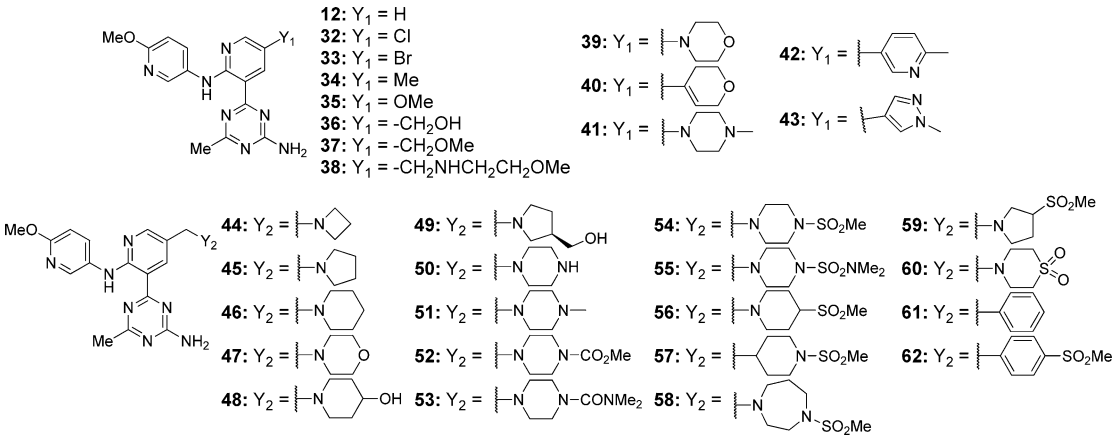
Table 2. Structure–Activity Relationships: Ribose Pocket[a]



	PI3K enzyme K_i (nM)						
cmpd	α	β	γ	δ	mTOR enzyme IC_{50} (nM)	U-87 MG cell (nM)pAkt IC_{50}	rat microsomal CL_{int} (μL/min/mg)
12	110	23	29	37	7800	360	51
32	290	38	40	39	>10 000	390	58
33	250	75	22	92	>10 000	830	111
34	240	86	54	110	>10 000	310	243
35	55	15	9	7	>10 000	42	86
36	63	56	24	20	2500	88	43
37	49	20	9	10	>10 000	150	58
38	280	67	99	30	>10 000	150	31
39	22	9	4	4	>10 000	83	67
40	5	3	2	2	>10 000	47	83
41	39	7	21	16	1400	88	23
42	8	89	8	7	>10 000	29	25
43	8	6	6	6	>10 000	34	24
44	160	22	140	50	>10 000	620	37
45	270	65	210	60	>10 000	220	37
46	150	11	80	19	>10 000	140	51
47	100	7	17	18	>10 000	130	31
48	200	41	110	63	>10 000	350	23
49	280	59	100	51	>10 000	390	20
50	61	17	200	27	>10 000	200	35
51	260	44	130	34	>10 000	230	48
52	94	18	18	6	3700	62	20
53	84	16	8	3	1400	140	17
54	9	5	4	2	4800	16	26
55	17	7	9	6	>10 000	23	73
56	22	5	9	3	>10 000	46	20
57	9	15	8	4	>10 000	54	111
58	33	61	46	21	>10 000	65	242
59	16	5	5	3	3600	38	23
60	73	13	30	13	>10 000	120	21
61	59	48	11	15	>10 000	700	62
62	3	2	7	1	>10 000	11	59

[a]Assays described in ref 14. Data represents an average of at least two determinations.

methyltriazine hinge-binder and methoxypyridine affinity pocket groups.

Table 2 shows the SAR obtained by substitution from the 5-pyridyl position of compound **12**, with the indicated substituents Y_1 and Y_2 extending into the ribose pocket of the PI3Ks. Compounds **32**–**62** all continued to demonstrate good selectivity over mTOR. The introduction of small substituents (Cl, Br, Me: compounds **32**–**34**) into the ribose pocket was well tolerated by the PI3Ks but had minimal effect on enzyme and cellular activity relative to the case of **12**. Metabolite ID studies with this scaffold had suggested that the 5-pyridyl position was a potential metabolic "soft spot", but this was not supported by the lack of improvement observed in microsomal stability by substituting at this position (cf. compounds **12** and **32**). Deeper projection into the ribose pocket with either a methoxy or hydroxymethyl group (compounds **35**, **36**) gave a more sizable increase in enzyme inhibitory activity, which translated into significant improvements in cellular activity. Further extension into the ribose pocket with compounds **37** and **38** resulted in a slight drop in

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cellular activity relative to the case of **35**, indicating that careful exploration of substituents in the ribose pocket would be necessary.

Substitution of the 5-pyridyl position with a range of heterocyclic groups (for example, compounds **39**–**43**) was successful at improving activity, with **40**, **42**, and **43** inhibiting the PI3K enzyme subtypes with K_i values <10 nM and possessing cellular activities <50 nM. Selectivity over mTOR was maintained with these compounds, and the intrinsic clearances observed when incubated with rat liver microsomes were low.

Modeling studies with the PI3Kγ crystal structure indicated that a methylene spacer at the 5-pyridyl position would provide a favorable trajectory for substitutents to access and obtain favorable interactions in the ribose pocket, and considerable effort was therefore put into exploring this substitution mode (compounds **44**–**62**, Table 2). A range of aliphatic heterocycles (Y_2) of varying ring size were well accommodated (compounds **44**–**51**), but they appeared to offer little improvement in inhibiting the PI3Ks relative to the case of **34**. The piperazine groups of compounds **50** and **51** were of particular interest, however, since modeling in PI3Kγ suggested that substitution from the distal piperazine nitrogen atom with hydrogen bond acceptors capable of interacting with the side chain of Lys802 or the backbone N–H of Ala805 may give a boost in affinity by picking up additional hydrogen bonding interactions with the protein. The methyl carbamate **52** and *N*,*N*-dimethyl urea **53** provided only modest improvements in PI3K inhibition. By contrast, the corresponding methyl sulfonamide-substituted piperazine **54** resulted in a significant improvement in PI3K inhibition that translated into a 15-fold improvement in cellular activity relative to the cases of **50** and **51**. In profiling compound **54** more fully, it not only demonstrated extremely high selectivity over a panel of protein kinases (minimal inhibition at 1 μM against 98 protein kinases tested), but it also demonstrated some selectivity against class II PI3Ks (PIK3C2α IC_{50} >10 μM; PIK3C2β IC_{50} = 29 nM), excellent selectivity against the class III PI3K VPS34 (IC_{50} >9 μM), excellent selectivity against the PI4-kinases (PIK4α IC_{50} >10 μM; PIK4β IC_{50} = 5.2 μM), and excellent selectivity against the PI3K-related protein kinase DNA-PK (IC_{50} >10 μM), indicating that **54** was a highly selective inhibitor of the class I PI3Ks.

A cocrystal structure of **54** was obtained with PI3Kγ (Figure 5). Compound **54** bound with two hydrogen bonds from the aminotriazine ring to the hinge, with the triazine methyl substituent oriented toward the Tyr867 side chain, and with the 4-methoxypyridine substituent projected into the affinity pocket. The methoxypyridine nitrogen atom made a hydrogen bond to an ordered water molecule sitting between Tyr867 and Asp841, and the piperazine sulfonamide extended into the ribose pocket with the sulfonamide oxygen atoms making hydrogen bonds to the backbone N–H of Ala805 and the side chain of Lys802. No specific interactions were observed between the central pyridyl nitrogen atom and the protein.

Having identified the piperazine sulfonamide **54** as a potent inhibitor of cellular Akt phosphorylation, modifications were explored that attempted to maintain similar favorable interactions with the protein. The *N*,*N*-dimethylsulfamide **55** was equipotent to **54** but displayed inferior rat microsomal stability. The importance of the piperazine nitrogen atoms was explored through the corresponding piperidines **56** and **57**, with both compounds showing an approximately 3-fold reduction in cellular activity. Expanding or contracting the

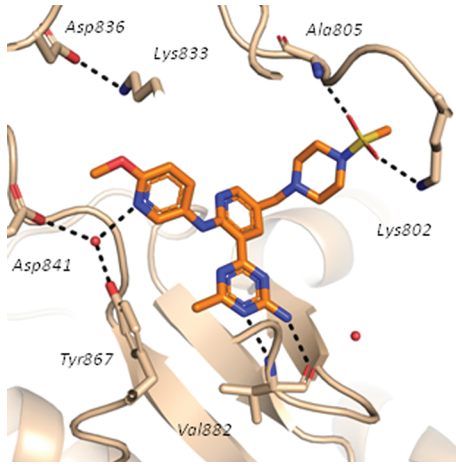

Figure 5. Cocrystal structure of **54** with PI3Kγ determined at 2.95 Å resolution. Dashed lines indicate hydrogen bonds, and red spheres represent ordered water molecules.

piperazine ring size (compounds **58** and **59**) or incorporating the SO_2 group within the ring (the thiomorpholine 1,1-dioxide **60**) appeared to offer no advantage. However, the methyl phenylsulfone **62** was 4-fold more active at inhibiting the PI3Kα enzyme and slightly more active in the cellular assay compared with **54**. The contribution of the methylsulfone moiety to the activity of **62** was illustrated by comparison with the case of analogue **61**, which was 24-fold less active against PI3Kα and 60-fold less active in the cellular assay.

In Vivo Studies. The rat pharmacokinetic (PK) properties of some of the more potent analogues were evaluated in order to select compounds to progress into in vivo pharmacodynamic (PD) and xenograft efficacy studies. The key PK parameters for compounds **54**, **56**, **57**, and **62** are shown in Table 3. Rat iv clearance was only moderate for both **54** and **62**, and high for **56** and **57**, despite the rat in vitro microsomal stabilities of these compounds being generally good. The oral bioavailability and plasma exposure of **54** were significantly better than those obtained with **56**, **57**, or **62**, and it had the lowest iv clearance out of this group. Mouse PK was therefore obtained on **54** (Table 3), confirming that mouse PK parameters were comparable to those in rat and that good oral exposure in mouse could be achieved. In addition, plasma protein binding (PPB) data for **54** indicated that there would be a high

Table 3. Pharmacokinetic Parameters for Compounds 54, 56, 57, and 62

		iv (1 mg/kg)[a]			po	
cmpd	species	MRT (h)	CL (L/(h·kg))	Vss (L/kg)	AUC (μM·h)	F (%)
54	rat	1.6	1.7	2.6	0.68[b]	77[c]
54	mouse	1.6	2.5	4.1	19.1[d]	95[d]
56	rat	1.3	2.5	2.9	0.33[b]	18[b]
57	rat	1.0	2.8	2.7	0.04[b]	3[b]
62	rat	1.2	1.8	2.1	0.04[b]	2[b]

[a]Compound dosed iv as a DMSO solution. [b]Compound dosed at 2 mg/kg po in 1% Pluronic F68/2% HPMC/15% HPBCD/82% H_2O/pH 2.2 with MsOH. [c]Compound dosed at 25 mg/kg po in 1% Pluronic F68/2% HPMC/15% HPBCD/82% H_2O/pH 2.2 with MsOH. [d]Compound dosed at 25 mg/kg po in 1% Tween 80/2% HPMC/97% H_2O/pH 2.2 with MsOH.

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unbound fraction in plasma in vivo (PPB: mouse = 87.5%; rat = 82.6%; human = 82.7%).

The ability of **54** to inhibit HGF-stimulated PI3K signaling was evaluated in a mouse liver PD assay. Compound **54** was dosed at 25 and 75 mg/kg in CD1 nude mice. Human HGF was injected iv at 3, 8, and 24 h postdose to induce PI3K-dependent Akt phosphorylation in the liver, and pAkt(S473) levels in the liver were then measured 5 min after HGF administration. The levels of pAkt(S473) inhibition relative to vehicle control are shown in Table 4, together with measured plasma concentrations. The lower 25 mg/kg dose provided near-complete target coverage for 8 h, but the relatively short mean residence time of the compound resulted in loss of target coverage by 24 h. By contrast, the higher 75 mg/kg dose was able to maintain sufficient plasma concentrations for 24 h to provide at least 64% target coverage over a 24 h period (plasma free fraction concentration = 68 nM at 24 h). The ability of **54** to inhibit tumor growth in CD1 nude mice in an established U-87 MG xenograft model was therefore evaluated (Figure 6).

Table 4. Liver PD Assay Data for Compound 54

	dose[a]			
	25 mg/kg		75 mg/kg	
time	pAkt %Inh[b]	plasma conc (μM)	pAkt %Inh[b]	plasma conc (μM)
3 h	96 ± 4	2.70	98 ± 2	7.36
8 h	93 ± 7	1.22	99 ± 1	2.80
24 h	11 ± 10	0.00	64 ± 32	0.54

[a]Female CD1 nude mice were dosed po with **54** in 1% Pluronic F68/2% HPMC/15% HPBCD/82% H_2O/pH 2.2 with MsOH. [b]Percent inhibition of phosphorylation of Akt at Ser473 in liver determined by comparison of pAkt(S473)/total Akt ratios between drug treated groups and a 3 h vehicle-treated group (n = 3 per group).

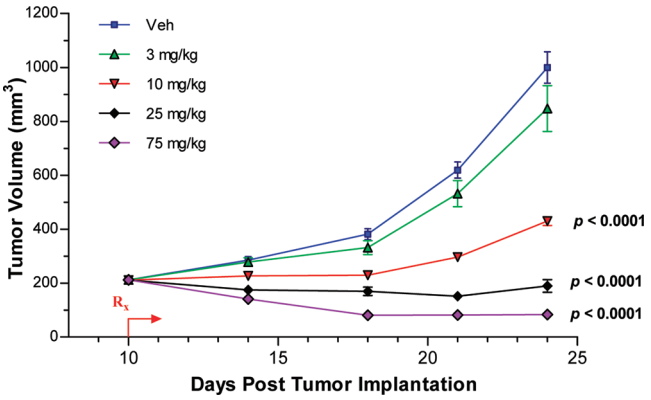

Figure 6. Daily dosing with **54** caused tumor growth inhibition in an established U-87 MG glioblastoma xenograft model in female CD1 nude mice (n = 10 per group).

Dosed orally at 3, 10, 25, and 75 mg/kg QD, compound **54** caused a dose-dependent inhibition of tumor growth with an ED_{50} of 6.0 mg/kg ($AUC_{0-24\ h}$ = 7.6 μM·h), and tumor stasis was achieved at 25 mg/kg QD. No significant reduction in body weight was observed over 14 days dosing up to 25 mg/kg QD, but the highest 75 mg/kg QD dose resulted in 15% body weight loss after dosing for 14 days. Figure 7 shows corresponding U-87 MG tumor PD data from a single dose study at 10 and 75 mg/kg. The data indicated that antitumor efficacy could be achieved in this PTEN-null xenograft model by daily dosing with **54** at doses that achieved >60% inhibition of PI3K for at least 8 h per day over 14 days, but maintaining continuous robust inhibition of PI3K over 14 days may be poorly tolerated.

CONCLUSIONS

A new series of highly selective inhibitors of the class I PI3Ks has been designed and synthesized. The most potent compounds have K_i values <10 nM against PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ; have >1000-fold selectivity against mTOR; and inhibit phosphorylation of Akt with IC_{50} values <50 nM in the U-87 MG glioblastoma cell line containing an upregulated PI3K/Akt pathway. Compound **54** demonstrated excellent selectivity over related phosphatidylinositol kinases as well as a broad panel of protein kinases. Compound **54** had good oral exposure in mice, and this led to significant inhibition of PI3K/Akt pathway signaling and antitumor efficacy in a mouse U-87 MG xenograft model. Further optimization of this series, including substantial improvements in PK properties and in vivo efficacy, will be reported in due course.

EXPERIMENTAL SECTION

Chemistry. All reactions were run under N_2 and stirred using a PTFE-coated magnetic stirbar unless noted otherwise. Reactions run at elevated temperature were performed using a magnetic hot plate stirrer at the temperature indicated utilizing an oil-bath, aluminum heating block, or aluminum beads for heat transfer. Microwave reactions were run either in a Biotage microwave reactor set to normal power at the indicated temperature or in a CEM Discover microwave equipped with a PowerMAX feature, and they were performed in sealed microwave reaction vessels. All solvents and reagents obtained from commercial sources were used without further purification unless noted. Solutions were concentrated using a rotary evaporator, and solids were collected by filtration using either a Büchner funnel or a sintered funnel. Residual solvent was removed from all nonvolatile products and intermediates using a vacuum manifold maintained at approximately 1 Torr. All yields reported are isolated yields after removal of residual solvents.

Analytical TLC was performed with EMD 0.25 mm silica gel 60 plates with a 254 nm fluorescent indicator. Plates were developed in a covered chamber and visualized with ultraviolet light. Silica gel column chromatography refers to column chromatography as described by Still using EMD silica gel 60, 230−400 mesh, as the stationary phase,[43] or by the use of an automated medium pressure Teledyne ISCO purification system using RediSep columns. The eluent solvent systems and gradients are as noted.

^{1}H NMR spectra were obtained on a Bruker BioSpin GmbH magnetic resonance spectrometer. ^{1}H NMR spectra are reported as chemical shifts in parts-per-million (ppm) relative to an internal solvent reference. Peak multiplicity abbreviations are as follows: s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), quin (quintet), and m (multiplet).

Analytical HPLC and mass spectroscopy were conducted using a reversed-phase Agilent 1100 Series HPLC-mass spectrometer. Purities for final compounds were measured using UV detection at 254 and 215 nm and are ≥95.0% unless otherwise noted. A detailed description of the HPLC methods

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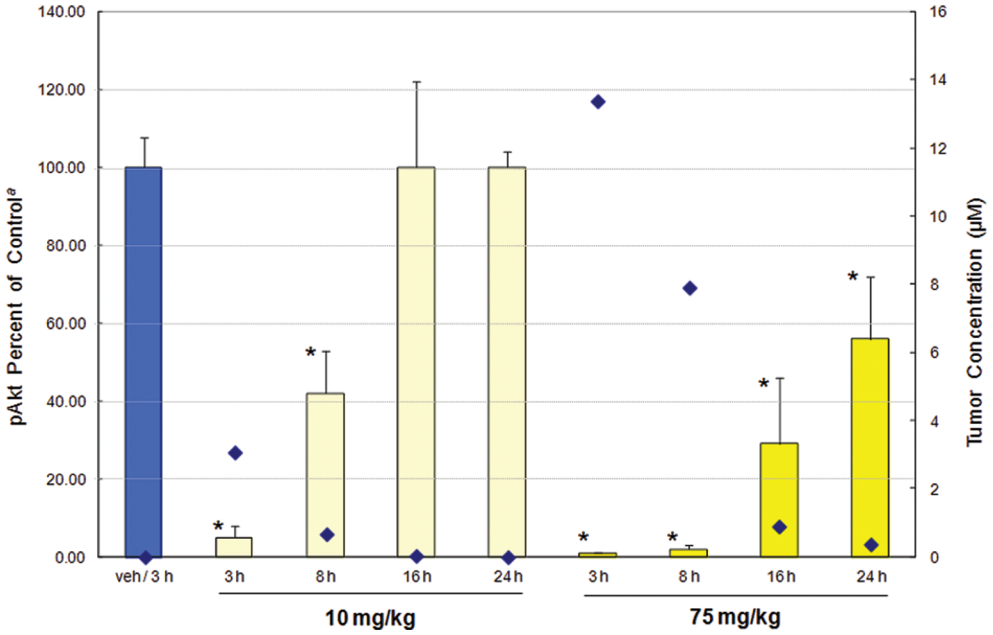

Figure 7. U-87 MG tumor PD assay in female CD1 nude mice following a single dose with compound **54** at 10 mg/kg or 75 mg/kg PO in 1% Pluronic F68/2% HPMC/15% HPBCD/82% H_2O/pH 2.2 with MsOH. [a]Determined by comparison of pAkt(S473)/total Akt ratios between drug treated groups and a 3 h vehicle-treated group (n = 3 per group). *p < 0.0006 (Dunnett's method).

that were used for analyzing final compounds is included in the Supporting Information.

2,4-Dichloro-6-methyl-1,3,5-triazine (64a). A 3.0 M solution of MeMgBr in Et_2O (10.0 mL, 30 mmol) was added slowly to a white suspension of 2,4,6-trichloro-1,3,5-triazine (**63a**) (3.68 g, 20 mmol) in CH_2Cl_2 (25 mL) at 0 °C, and the resulting yellow suspension was allowed to warm to 22 °C and was stirred for 3 h. The reaction was carefully quenched with saturated aqueous NH_4Cl at 0 °C and then diluted with H_2O and CH_2Cl_2 (25 mL). The organic layer was separated, dried, filtered, and concentrated to give **64a** as a yellow solid (2.94 g, 90%), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74 (s, 3H).

4-Chloro-6-methyl-1,3,5-triazin-2-amine (65a). A 2.0 M solution of NH_3 in MeOH (36 mL, 72 mmol) was added dropwise at 22 °C to a stirred suspension of **64a** (2.94 g, 18.0 mmol) in toluene (20 mL) over 1.5 h [note: the reaction was slightly exothermic]. The resulting mixture was stirred for an additional 2.5 h, concentrated, and purified by silica gel column chromatography (gradient: 0% → 10% MeOH/CH_2Cl_2) to give **65a** (1.88 g, 73%) as a yellow solid. ^{1}H NMR (300 MHz, CD_3OD): δ 2.32 (s, 3H).

6-Chloro-2-methylpyrimidin-4-amine (65b). NH_3 (2 M) in MeOH (6 mL, 12 mmol) was added to a stirred suspension of 4,6-dichloro-2-methylpyrimidine (**64b**) (487 mg, 2.99 mmol) in 1,4-dioxane (10 mL) at 22 °C. The reaction vessel was sealed and stirred at 70 °C for 16 h. After cooling, the reaction mixture was concentrated and the residue was purified by silica gel column chromatography (gradient: 0% → 10% MeOH/CH_2Cl_2) to give **65b** (250 mg, 58%) as a white solid. LC−MS m/z: 144 $(M + H)^+$.

6-Chloro-5-fluoro-2-methylpyrimidin-4-amine (65c). A mixture of 4,6-dichloro-5-fluoro-2-methylpyrimidine (**64c**) (1.55 g, 8.60 mmol) in aqueous NH_3 (~28% w/v) (10 mL) and MeOH (1 mL) was heated at 70 °C for 2 h (sealed tube). After cooling, H_2O (10 mL) was added and the mixture was stirred for 30 min. The resulting solid was collected by filtration, washed with H_2O, and dried to give **65c** (924 mg, 67%) as a white solid. LC−MS m/z: 163 $(M + H)^+$.

4-Chloro-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-1,3,5-triazine-2-amine (66). A suspension of **65a** (10.00 g, 69.2 mmol) in DMF (60 mL) at 0 °C was treated with NaH (60% dispersion in mineral oil; 6.9 g, 160 mmol) portionwise. The mixture was stirred for 30 min, and then 4-methoxybenzyl chloride (2.1 mL, 15 mmol) was added dropwise. The mixture was kept at 0 °C for 30 min, then at 22 °C for 3 h, and then cooled to 0 °C, and the reaction was quenched with ice−water (100 mL). The mixture was diluted with EtOAc (100 mL) and separated, and the organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (gradient: 0% → 8% EtOAc/hexanes) to give **66** (13.18 g, 50%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (t, J = 8.12 Hz, 4H), 6.95−6.81 (m, 4H), 4.74 (s, 2H), 4.69 (s, 2H), 3.81 (s, 6H), 2.45 (s, 3H).

4-Iodo-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-1,3,5-triazin-2-amine (67). A mixture of **66** (1.02 g, 2.65 mmol) and 67% aqueous HI (0.50 mL, 6.6 mmol) in CH_2Cl_2 (10 mL) was stirred at 22 °C for 19 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (30 mL) and extracted with EtOAc (2 × 40 mL). The organic extract was washed with saturated brine (20 mL), dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (50% CH_2Cl_2/hexanes) to give crude **67** (826 mg, 65%) as a 3:1 mixture of **67** and **66**. This was used in subsequent reactions without further purification. LC−MS m/z: 476 $(M + H)^+$.

2-Chloro-4-methyl-6-(methylthio)-1,3,5-triazine (68a). MeSNa (490 mg, 7.0 mmol) was added portionwise at 0 °C to a stirred cloudy solution of **64a** (1.04 g, 6.3 mmol) in toluene (10 mL) over 15 min. The pale-yellow mixture was stirred at 0 °C for a further 1 h, and then H_2O (10 mL) was added. The separated aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with saturated brine, dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (gradient: 0% → 70%

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CH_2Cl_2/hexanes) to give **68** (870 mg, 78%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (s, 3H), 2.51 (br s, 3H).

4-Chloro-2-methyl-6-(methylthio)pyrimidine (68b). A suspension of **64b** (11.50 g, 70.6 mmol) and MeSNa (5.93 g, 85 mmol) in toluene (100 mL) was stirred at 22 °C for 24 h. The reaction mixture was concentrated, and the residue was partitioned between EtOAc (100 mL) and saturated brine (100 mL). The organic layer was separated, washed with saturated brine (50 mL), and dried (Na_2SO_4). The crude product was purified by recrystallization from hexanes to give **68b** (5.50 g, 45%) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (s, 1H), 2.64 (s, 3H), 2.56 (s, 3H).

2-Iodo-4-methyl-6-(methylthio)-1,3,5-triazine (69a). A mixture of **68a** (2.11 g, 12.0 mmol) and 67% aqueous HI (2.3 mL, 30 mmol) in CH_2Cl_2 (4 mL) was stirred at 22 °C for 3 h. The solid was collected by filtration and washed with CH_2Cl_2. The solid was treated with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with saturated brine (10 mL), dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (50% CH_2Cl_2/hexanes) to give **69a** (2.10 g, 65%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 3H), 2.50 (s, 3H).

4-Iodo-2-methyl-6-(methylthio)pyrimidine (69b). A solution of **68b** (5.30 g, 30.3 mmol) and 67% aqueous HI (5.7 mL, 76 mmol) in CH_2Cl_2 (20 mL) was stirred at 22 °C for 20 h. The solid was collected by filtration and washed with CH_2Cl_2. The solid was suspended in saturated aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated brine, dried (Na_2SO_4), and concentrated to give **69b** (7.30 g, 90%) as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s, 1H), 2.62 (s, 3H), 2.52 (s, 3H).

2-Methyl-4-(methylthio)-6-(tributylstannyl)-1,3,5-triazine (70a). A solution of **69a** (2.67 g, 10.0 mmol) in THF (10 mL) at −78 °C was treated dropwise with a 2.0 M solution of *i*-PrMgCl in THF (6.0 mL, 12.0 mmol). The reaction mixture was stirred at −78 °C for 30 min, and then Bu_3SnCl (2.7 mL, 10.0 mmol) was added dropwise. The reaction mixture was allowed to warm to 22 °C for 16 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 × 40 mL). The organic extract was washed with saturated brine (10 mL), dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (50% CH_2Cl_2/hexanes) to give **70a** (2.40 g, 56%) as a clear colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51 (s, 3H), 2.47 (s, 3H), 1.70−1.40 (m, 6H), 1.40−1.10 (m, 12H), 0.90 (t, 9H).

2-Methyl-4-(methylthio)-6-(tributylstannyl)pyrimidine (70b). A solution of **69b** (1.63 g, 6.12 mmol) in 30 mL of THF at −78 °C was treated with 2.0 M *i*-PrMgCl in THF (3.67 mL, 7.35 mmol). After 10 min, Bu_3SnCl (1.65 mL, 6.12 mmol) was added and the mixture was stirred at −78 °C for 1 h. The mixture was allowed to warm to 22 °C and stirred for 16 h. The mixture was diluted with EtOAc (100 mL) and saturated aqueous KF (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (gradient: 0% → 5% EtOAc/hexanes) to give **70b** (1.39 g, 53%) as a clear colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07 (s, 1H), 2.62 (s, 3H), 2.51 (s, 3H), 1.70−1.44 (m, 6H), 1.42−1.21 (m, 6H), 1.21−0.98 (m, 6H), 0.91 (t, 9H).

4-(2-Fluoropyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (71a). A mixture of **65a** (423 mg, 2.93 mmol), 2-fluoropyridin-3-ylboronic acid (619 mg, 4.39 mmol), Pd(Amphos)$_2$Cl$_2$ (91 mg, 146 μmol), and KOAc (862 mg, 8.78 mmol) in 1,4-dioxane (6 mL) was heated at 100 °C for 16 h. The mixture was allowed to cool and passed through a short plug of diatomaceous earth, washing with EtOAc (3 × 15 mL). The filtrate was concentrated and purified by silica gel column chromatography (gradient: 0% → 3% MeOH/CH_2Cl_2) to give **71a** (454 mg, 76%) as a pale-brown powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.48 (ddd, J = 9.91, 7.65, 2.01 Hz, 1H), 8.39 (d, J = 5.02 Hz, 1H), 7.65 (br s, 2H), 7.51 (ddd, J = 7.15, 5.14, 1.76 Hz, 1H), 2.37 (s, 3H).

6-(2-Fluoropyridin-3-yl)-2-methylpyrimidin-4-amine (71b). A mixture of **65b** (256 mg, 1.78 mmol), 2-fluoropyridin-3-ylboronic acid (376 mg, 2.67 mmol), Pd(Amphos)$_2$Cl$_2$ (55 mg, 89 μmol), and KOAc (524 mg, 5.34 mmol) in 1,4-dioxane (3 mL) was heated at 120 °C for 30 min in a microwave reactor. The mixture was allowed to cool and passed through a short plug of diatomaceous earth, washing with EtOAc (3 × 10 mL). The filtrate was concentrated and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2) to give **71b** (304 mg, 84%) as a white solid. LC−MS m/z: 205 $(M + H)^+$.

5-Fluoro-6-(2-fluoropyridin-3-yl)-2-methylpyrimidine-4-amine (71c). A mixture of 2-fluoropyridin-3-ylboronic acid (666 mg, 4.73 mmol), **65c** (509 mg, 3.15 mmol), $Na_2CO_3 \cdot H_2O$ (835 mg, 7.89 mmol), and $Pd(PPh_3)_4$ (364 mg, 0.32 mmol) in DME (6 mL) and H_2O (0.6 mL) was heated at 100 °C for 60 min in a microwave reactor. The mixture was diluted with H_2O (100 mL), and the precipitate was collected by filtration, washing with CH_2Cl_2, to give **71c** (418 mg, 60%) as an off-white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (d, J = 4.02 Hz, 1H), 8.18 (t, J = 8.03 Hz, 1H), 7.53 (t, J = 5.27 Hz, 1H), 7.38 (br s, 2H), 2.37 (s, 3H).

6-(2-Fluoropyridin-3-yl)-2-(trifluoromethyl)pyrimidin-4-amine (71d). A mixture of 6-chloro-2-(trifluoromethyl)-pyrimidin-4-amine (**65d**) (400 mg, 2.02 mmol), 2-fluoropyridin-3-ylboronic acid (428 mg, 3.04 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (63 mg, 101 μmol), and KOAc (596 mg, 6.08 mmol) in 1,4-dioxane (3 mL) was heated at 120 °C for 30 min in a microwave reactor. The mixture was passed through a short plug of diatomaceous earth and washed with CH_2Cl_2 (3 × 20 mL). The filtrate was concentrated and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2) to give **71d** as a white solid (180 mg, 34%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.57 (t, J = 8.80 Hz, 1H), 8.38 (d, J = 3.91 Hz, 1H), 7.83 (br s, 2H), 7.63−7.46 (m, 1H), 7.15 (s, 1H).

4-(2-Fluoropyridin-3-yl)-6-methylpyrimidin-2-amine (71e). A mixture of $Pd(PPh_3)_4$ (58 mg, 50 μmol), 2-amino-4-chloro-6-methylpyrimidine (**65e**) (143 mg, 0.10 mmol), 2-fluoropyridin-3-ylboronic acid (211 mg, 1.49 mmol), and CsF (454 mg, 2.99 mmol) in 1,4-dioxane (2 mL) was heated at 150 °C for 30 min in a microwave reactor. The mixture was concentrated and purified by silica gel column chromatography (gradient: 33% → 50% EtOAc/hexanes) to give **71e** (55 mg, 27%) as a white solid. LC−MS m/z: 205.1 $(M + H)^+$.

4-(2-Fluoropyridin-3-yl)-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-1,3,5-triazin-2-amine (71f). A mixture of **66** (1.57 g, 4.08 mmol), 2-fluoropyridin-3-ylboronic acid (632 mg, 4.48 mmol), Pd(Amphos)$_2$Cl$_2$ (144 mg, 0.20 mmol), and KOAc (1.22 g, 12.4 mmol) in EtOH (15 mL) and H_2O (1.5 mL) contained in a 20 mL microwave tube was degassed by

bubbling Ar through it for 5 min. The mixture was heated in a microwave reactor at 100 °C for 20 min. The reaction mixture was partitioned between a 1:1 mixture of H_2O and saturated brine (150 mL) and EtOAc (50 mL). The aqueous phase was extracted with EtOAc (50 mL). The combined organic phases were washed with saturated brine (50 mL). The organic phase was dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (gradient: 10% → 50% EtOAc/hexanes) to give **71f** (1.65 g, 91%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62−8.49 (m, 1H), 7.99−7.86 (m, 1H), 7.36−7.27 (m, 1H), 7.23 (dd, J = 8.31, 4.99 Hz, 4H), 6.87 (t, J = 8.51 Hz, 4H), 3.81 (s, 3H), 4.81 (s, 4H), 3.80 (s, 3H), 2.55 (s, 3H).

4-(3-Chloropyridin-4-yl)-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-1,3,5-triazin-2-amine (71g). A mixture of **67** (306 mg, 0.64 mmol), 3-chloropyridine-4-boronic acid (101 mg, 0.64 mmol), dichloro 1,1′-bis(diphenylphosphino)ferrocene palladium(II) (52 mg, 0.064 mmol), and Cs_2CO_3 (251 mg, 0.77 mmol) in 1,4-dioxane (6 mL) and H_2O (1 mL) was stirred at 90 °C for 1 h. The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with saturated brine (10 mL), dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (50% EtOAc/hexanes) to give **71g** (129 mg, 44%) as a glass. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69 (s, 1H), 8.58 (d, J = 4.97 Hz, 1H), 7.71 (d, J = 4.82 Hz, 1H), 7.26−7.10 (m, 4H), 6.86 (t, J = 8.77 Hz, 4H), 4.80 (s, 4H), 3.81 (s, 3H), 3.80 (s, 3H), 2.56 (s, 3H).

2-(3-Fluoropyrazin-2-yl)-4-methyl-6-(methylthio)-1,3,5-triazine (71h). A 1.6 M solution of *n*-BuLi in hexanes (0.92 mL, 11 mmol) was added to 2,2,6,6-tetramethylpiperidine (2.0 mL, 12 mmol) in THF (50 mL) at −50 °C. Following the addition, the mixture was stirred at 0 °C for 20 min and then cooled to −100 °C. 2-Fluoropyrazine (980 mg, 10 mmol) in THF (5 mL) was then added dropwise. After 5 min, Bu_3SnCl (3.3 mL, 12 mmol) in THF (5 mL) was added dropwise and stirring was continued for 1 h. The reaction was quenched with a solution of 35% aqueous HCl, EtOH, THF (1:4:5) and allowed to warm to 22 °C. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (30 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with saturated brine (30 mL), dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (50% CH_2Cl_2/hexanes) to give 2-fluoro-3-(tributylstannyl)-pyrazine (2.98 g, 77%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.02 (s, H), 1.68−1.46 (m, 6H), 1.42−1.12 (m, 12H), 0.88 (t, J = 7.23 Hz, 9H).

A mixture of **69a** (100 mg, 0.37 mmol), 2-fluoro-3-(tributylstannyl)pyrazine (145 mg, 0.37 mmol), and $Pd(PPh_3)_4$ (43 mg, 0.037 mmol) in toluene (2 mL) was stirred at 110 °C for 18 h. The mixture was allowed to cool, concentrated, and purified by silica gel column chromatography (40% EtOAc/hexanes) to give **71h** (42 mg, 47%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.42 (s, 1H), 2.73 (s, 3H), 2.65 (s, 3H).

4-(3-Fluoropyrazin-2-yl)-2-methyl-6-(methylthio)-pyrimidine (71i). A mixture of **69b** (266 mg, 1.00 mmol), 2-fluoro-3-(tributylstannyl)pyrazine (see: **71h**) (387 mg, 1.00 mmol), and $Pd(PPh_3)_4$ (116 mg, 0.10 mmol) in toluene (3 mL) was heated in a microwave reactor at 140 °C for 40 min. The mixture was concentrated and purified by silica gel column chromatography (40% EtOAc/hexanes) to give **71i** (28 mg, 12%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.32 (s, 1H), 7.67 (s, 1H), 2.79 (s, 3H), 2.63 (s, 3H).

4-(5-Chloro-2-fluoropyridin-3-yl)-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-1,3,5-triazin-2-amine (71j). A mixture of 5-chloro-2-fluoropyridin-3-ylboronic acid (1.22 g, 6.96 mmol), **66** (2.30 g, 5.98 mmol), KOAc (1.20 g, 12.2 mmol), and $Pd(Amphos)_2Cl_2$ (150 mg, 0.21 mmol) in 1,4-dioxane (10 mL) and H_2O (2 mL) under Ar was heated at 95 °C. After 2 h, more 5-chloro-2-fluoropyridin-3-ylboronic acid (600 mg) was added and the mixture was heated for another 1 h. The mixture was allowed to cool to 22 °C, saturated aqueous NH_4Cl (5 mL) was added, and the mixture was partitioned between H_2O (5 mL) and EtOAc (30 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (gradient: 10% → 50% EtOAc/hexanes) to give **71j** (2.30 g, 80%) as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (dd, J = 8.02, 2.74 Hz, 1H), 8.25 (d, J = 1.37 Hz, 1H), 7.21 (d, J = 8.41 Hz, 4H), 6.86 (t, J = 8.22 Hz, 4H), 4.81 (d, J = 7.24 Hz, 4H), 3.80 (2s, 6H), 2.54 (s, 3H).

4-(5-Bromo-2-fluoropyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (71k). A glass microwave reaction vessel was charged with 5-bromo-2-fluoropyridin-3-ylboronic acid (760 mg, 3.46 mmol), **65a** (500 mg, 3.46 mmol), $Pd(PPh_3)_4$ (200 mg, 0.17 mmol), $Na_2CO_3{\cdot}H_2O$ (1.29 g, 10.4 mmol), 1,2-dimethoxyethane (16 mL), and H_2O (62 μL, 3.4 mmol) under N_2. The reaction mixture was heated in a microwave reactor at 100 °C for 60 min. The mixture was filtered through diatomaceous earth, washing with EtOAc (100 mL). The filtrate was concentrated and purified by silica gel column chromatography (gradient: 5% → 10% 2 M NH_3 in MeOH/CH_2Cl_2) to give **71k** (345 mg, 35%) as a brown solid. LC−MS m/z: 284.1/286.2 $(M + H)^+$.

4-(2-Fluoro-5-methylpyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (71m). A 2.5 M solution of *n*-BuLi in hexanes (9.6 mL, 24 mmol) was added to a mixture of *i*-Pr_2NH (3.4 mL, 24 mmol) in THF (5 mL) at 0 °C, and the resulting pale-yellow solution was stirred for 30 min and then cooled to −78 °C. A suspension of 2-fluoro-5-methylpyridine (2.22 g, 20 mmol) in THF (5 mL) was slowly added. The resulting bright-yellow solution was stirred at −78 °C for 1 h, treated with a solution of $(i\text{-PrO})_3B$ (6.9 mL, 30 mmol) in THF (10 mL), and then allowed to warm to 22 °C. The yellow suspension was quenched with 1 M aqueous NaOH until basic (pH ∼10), and the organic layer was separated. The aqueous layer was carefully acidified with 6 M aqueous HCl until slightly acidic and then was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resulting white solid was washed with Et_2O to give 2-fluoro-5-methylpyridin-3-ylboronic acid (2.92 g, 94%) as a white solid. LC−MS m/z: 156 $(M + H)^+$.

1,4-Dioxane (3 mL) was added to a mixture of $Pd(Amphos)_2Cl_2$ (270 mg, 0.43 mmol), 2-fluoro-5-methylpyridin-3-ylboronic acid (1.60 g, 10 mmol), **65a** (1.24 g, 8.5 mmol), and KOAc (2.50 g, 26 mmol) in 1,4-dioxane (3 mL) that was heated at 120 °C for 30 min in a microwave reactor. The mixture was passed through a short plug of diatomaceous earth, washing with CH_2Cl_2 (3 × 20 mL). The filtrate was concentrated and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2) to give **71m** (760 mg, 41%) as a white solid. LC−MS m/z: 220 $(M + H)^+$.

4-(2-Chloro-5-methoxypyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (71n). K_2CO_3 (500 mg, 3.6 mmol) followed by MeI (0.20 mL, 2.9 mmol) were added to a stirred mixture of

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5-bromo-6-chloropyridin-3-ol (500 mg, 2.4 mmol) in DMF (3 mL). The mixture was heated at 45 °C for 4 h and then allowed to stand at 22 °C for 16 h. The mixture was diluted with H_2O (100 mL), and the precipitate was collected by filtration and dried to give 3-bromo-2-chloro-5-methoxypyridine as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.49 (d, J = 1.37 Hz, 1H), 3.86 (s, 3H).

A 2.5 M solution of *n*-BuLi in hexanes (3.7 mL, 9.3 mmol) was added slowly to a stirred premixed solution of 3-bromo-2-chloro-5-methoxypyridine (1.73 g, 7.8 mmol) and $(i\text{-PrO})_3B$ (2.1 mL, 9.3 mmol) in THF (10 mL) at −78 °C. The resulting dark mixture was stirred for 1 h and then allowed to warm up to 22 °C over 1 h. The reaction was quenched with 1 M aqueous NaOH (50 mL), and then EtOAc (50 mL) was added. The separated aqueous layer was acidified with 5 M HCl to pH ∼ 5 and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with saturated brine, dried (Na_2SO_4), and concentrated to give 2-chloro-5-methoxypyridin-3-ylboronic acid (1.03 g, 71%) as a brown solid. LC−MS m/z: 188/190 $(M + H)^+$.

A stirred mixture of 2-chloro-5-methoxypyridin-3-ylboronic acid (1.03 g, 5.48 mmol), **65a** (720 mg, 4.98 mmol), $Na_2CO_3 \cdot H_2O$ (1.32 g, 12.5 mmol), and $Pd(PPh_3)_4$ (576 mg, 0.1 equiv) in 1,4-dioxane (10 mL) and H_2O (2.5 mL) under N_2 was heated at 90 °C for 16 h. The mixture was concentrated and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2) to give **71n** (644 mg, 51%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (d, J = 1.17 Hz, 1H), 7.68 (br s, 2H), 7.65 (d, J = 1.17 Hz, 1H), 3.87 (s, 3H), 2.36 (s, 3H).

3-(3-(4-Amino-6-methyl-1,3,5-triazin-2-yl)pyridin-2-ylamino)phenol (9). A solution of **71a** (133 mg, 0.65 mmol) and 3-aminophenol (85 mg, 0.78 mmol) in 1,4-dioxane (1 mL) was treated with 2 M aqueous HCl (0.33 mL, 0.66 mmol), and the mixture was heated at 100 °C for 16 h. After cooling, the reaction mixture was concentrated and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2) to give **9** (66 mg, 34%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.97 (s, 1H), 9.27 (s, 1H), 8.76 (dd, J = 7.78, 1.76 Hz, 1H), 8.35 (dd, J = 4.77, 1.76 Hz, 1H), 7.92−7.64 (m, 2H), 7.51 (s, 1H), 7.28−6.99 (m, 2H), 6.89 (dd, J = 7.53, 4.52 Hz, 1H), 6.40 (d, J = 7.03 Hz, 1H), 2.45 (s, 3H).

***N*-(3-(4-Amino-6-methyl-1,3,5-triazin-2-yl)pyridin-2-yl)-1*H*-indazol-4-amine (10).** A solution of **71a** (300 mg, 0.15 mmol) and 1*H*-indazol-4-amine (292 mg, 2.19 mmol) in 1,4-dioxane (5 mL) was treated with 2 M aqueous HCl (0.73 mL, 1.46 mmol), and the reaction vessel was heated at 150 °C for 40 min in a microwave reactor. After cooling, the reaction mixture was concentrated and purified by silica gel column chromatography (gradient: 0% → 10% MeOH/CH_2Cl_2) to give **10** (21.5 mg, 4.6%) as a yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.10 (s, 1H), 12.26 (s, 1H), 8.80 (d, J = 7.82 Hz, 1H), 8.42 (d, J = 4.50 Hz, 1H), 8.19 (s, 1H), 8.13 (d, J = 7.43 Hz, 1H), 7.75 (br s, 2H), 7.31 (t, J = 8.02 Hz, 1H), 7.16 (d, J = 8.41 Hz, 1H), 7.07−6.89 (m, 1H), 2.56 (s, 3H).

***N*-(3-(4-Amino-6-methyl-1,3,5-triazin-2-yl)pyridin-2-yl)-1*H*-indol-4-amine (11).** Aqueous HCl (2 M, 0.42 mL, 0.83 mmol) was added to a stirred mixture of **71a** (171 mg, 0.83 mmol) and 1*H*-indol-4-amine (132 mg, 1.00 mmol) in 1,4-dioxane (4 mL), and the mixture was heated at 100 °C for 16 h. After cooling, the reaction mixture was concentrated and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2) to give **11** (58 mg, 22%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.00 (s, 1H), 11.15 (br s, 1H), 8.77 (dd, J = 7.78, 1.76 Hz, 1H), 8.38 (dd, J = 4.52, 1.51 Hz, 1H), 8.09 (d, J = 6.02 Hz, 1H), 7.81−7.53 (m, 2H), 7.35 (t, J = 2.76 Hz, 1H), 7.19−6.99 (m, 2H), 6.90 (dd, J = 7.78, 4.77 Hz, 1H), 6.66 (br s, 1H), 2.55 (s, 3H).

4-(2-(6-Methoxypyridin-3-ylamino)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (12). A solution of **71a** (50 mg, 0.24 mmol) and 3-amino-6-methoxypyridine (30 mg, 0.24 mmol) in 1,4-dioxane (1 mL) was treated with 2 M aqueous HCl (0.12 mL, 0.24 mmol), and the mixture was heated at 150 °C for 16 h. After cooling, the reaction mixture was concentrated and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2) to give **12** (60 mg, 80%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.74 (br s, 1H), 8.77 (dd, J = 5.02, 2.51 Hz, 1H), 8.53 (br s, 1H), 8.29 (br s, 1H), 8.23−8.08 (m, 1H), 7.84 (br s, 1H), 7.71 (br s, 1H), 6.88 (ddd, J = 7.78, 4.27, 4.02 Hz, 1H), 6.82 (dd, J = 8.78, 4.27 Hz, 1H), 3.84 (d, J = 5.02 Hz, 3H), 2.42 (d, J = 4.02 Hz, 3H).

3-(3-(6-Amino-2-methylpyrimidin-4-yl)pyridin-2-ylamino)phenol (13). A solution of **71b** (121 mg, 0.59 mmol) and 3-aminophenol (78 mg, 0.71 mmol) in 1,4-dioxane (1 mL) was treated with 2 M aqueous HCl (0.30 mL, 0.60 mmol), and the mixture was heated at 100 °C for 16 h. After cooling, the reaction mixture was concentrated and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2) to give **13** (19.7 mg, 11%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.23 (s, 1H), 9.25 (d, J = 2.35 Hz, 1H), 8.35−8.18 (m, 1H), 8.02 (d, J = 7.63 Hz, 1H), 7.36 (br s, 1H), 7.16−6.95 (m, 4H), 6.93−6.84 (m, 1H), 6.74 (d, J = 1.76 Hz, 1H), 6.35 (dd, J = 6.65, 1.96 Hz, 1H), 2.62−2.51 (s, 3H).

***N*-(3-(6-Amino-2-methylpyrimidin-4-yl)pyridin-2-yl)-1*H*-indazol-4-amine (14).** A solution of **71b** (136 mg, 0.67 mmol) and 1*H*-indazol-4-amine (106 mg, 0.81 mmol) in 1,4-dioxane (1 mL) was treated with 2 M aqueous HCl (0.33 mL, 0.66 mmol), and the mixture was heated at 100 °C for 16 h. After cooling, the reaction mixture was concentrated and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2) to give **14** (32.9 mg, 16%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.09 (br s, 1H), 12.29 (s, 1H), 8.35 (d, J = 4.52 Hz, 1H), 8.22−7.89 (m, 3H), 7.29 (t, J = 7.78 Hz, 1H), 7.20−6.86 (m, 4H), 6.79 (s, 1H), 2.62 (s, 3H).

***N*-(3-(6-Amino-5-fluoro-2-methylpyrimidin-4-yl)-pyridin-2-yl)-1*H*-indazol-4-amine (15).** Aqueous HCl (2 M, 0.45 mL, 0.90 mmol) was added to a stirred mixture of **71c** (400 mg, 1.80 mmol) and 1*H*-indazol-4-amine (360 mg, 2.70 mmol) in 1,4-dioxane (3 mL), and the reaction vessel was heated at 150 °C for 40 min in a microwave reactor. After cooling, the mixture was concentrated and purified by silica gel column chromatography (gradient: 0% → 10% MeOH/CH_2Cl_2) to give **15** (134 mg, 22%) as a yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.07 (br s, 1H), 10.87 (s, 1H), 8.34 (d, J = 3.72 Hz, 1H), 8.18−7.82 (m, 3H), 7.47 (br s, 2H), 7.36−7.19 (m, 1H), 7.11 (d, J = 8.22 Hz, 1H), 7.05−6.75 (m, 1H), 2.56 (s, 3H).

***N*-(3-(6-Amino-2-(trifluoromethyl)pyrimidin-4-yl)-pyridin-2-yl)-1*H*-indazol-4-amine (16).** A mixture of **71d** (157 mg, 0.61 mmol) and 1*H*-indol-4-amine (162 mg, 1.22 mmol) in 1,4-dioxane (2 mL) and 2 M aqueous HCl (0.30 mL, 0.60 mmol) was heated at 100 °C for 16 h. After cooling, the reaction mixture was concentrated and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2) to give **16** as a yellow solid (14.4 mg, 6.4%). ^{1}H NMR (400

MHz, DMSO-d_6): δ 13.06 (br s, 1H), 10.82 (s, 1H), 8.36 (d, J = 4.52 Hz, 1H), 8.11 (d, J = 7.53 Hz, 1H), 7.99 (s, 1H), 7.89 (d, J = 7.53 Hz, 1H), 7.81 (br s, 2H), 7.29 (t, J = 7.53 Hz, 1H), 7.14 (d, J = 8.03 Hz, 1H), 7.07 (s, 1H), 7.05−6.95 (m, 1H).

4-(2-(1*H*-Indol-4-yloxy)pyridin-3-yl)-6-methylpyrimidin-2-amine (23). A stirred mixture of **71e** (57 mg, 0.28 mmol), 4-hydroxyindole (74 mg, 0.56 mmol), and K_2CO_3 (116 mg, 0.84 mmol) in DMF (2 mL) was heated at 180 °C for 30 min in a microwave reactor. The mixture was allowed to cool, concentrated, and purified by silica gel column chromatography (gradient: 0% → 10% MeOH/CH_2Cl_2) to give **23** (19.5 mg, 22%) as a gray powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.24 (br s, 1H), 8.37 (dd, J = 7.78, 1.76 Hz, 1H), 8.10 (dd, J = 4.77, 1.76 Hz, 1H), 7.48−7.16 (m, 4H), 7.08 (t, J = 7.78 Hz, 1H), 6.77 (d, J = 7.53 Hz, 1H), 6.63 (s, 2H), 6.03 (br s, 1H), 2.26 (s, 3H).

4-(2-((6-Methoxypyridin-3-yl)(methyl)amino)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine Trifluoroacetate (24). A solution of 6-methoxy-*N*-methylpyridin-3-amine (123 mg, 0.89 mmol) and **71f** (263 mg, 0.59 mmol) in THF (5 mL) was cooled to 0 °C in an ice−water bath and treated dropwise with 1.0 M LiHMDS in THF (1.8 mL, 1.8 mmol). The solution was stirred at 0 °C for 4 h. The reaction mixture was quenched with a saturated solution of NH_4Cl at 0 °C and extracted with EtOAc (30 mL), dried ($MgSO_4$), filtered, and concentrated to give **73f** (415 mg). LC−MS m/z: 564.0 $(M + H)^+$.

A solution of **73f** (94.6 mg, 0.168 mmol) in TFA (8 mL) was heated at 80 °C for 48 h. The mixture was concentrated to about 50% of the original volume under a stream of Ar. The remaining mixture was pipetted carefully into a saturated aqueous solution of $NaHCO_3$, which had been cooled in an ice−water bath. The resulting precipitate was removed by filtration and washed with H_2O. The aqueous layer (containing the product) was lyophilized to give a yellow solid. This was purified by silica gel column chromatography (EtOAc) followed by reversed-phase preparative HPLC (Phenomenex C18 column: 150 mm × 30 mm; 5 μm; 10% → 90% MeCN/H_2O; 0.1% TFA additive) to give **24** (20 mg, 26%) as a yellow film. ^{1}H NMR (400 MHz, CD_3OD): δ 8.44 (dd, J = 5.1, 1.8 Hz, 1H), 7.83 (dd, J = 7.5, 1.9 Hz, 1H), 7.79 (d, J = 2.7 Hz, 1H), 7.42 (dd, J = 8.9, 2.8 Hz, 1H), 7.07 (dd, J = 7.5, 5.0 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 3.84 (s, 3H), 3.50 (s, 3H), 2.34 (s, 3H).

3-(3-(2-Amino-6-methylpyrimidin-4-yl)pyridin-2-ylamino)phenol (25). A mixture of **71e** (50 mg, 0.25 mmol) and 3-aminophenol (32 mg, 0.29 mmol) in 1,4-dioxane (1 mL) was treated with 2 M aqueous HCl (0.12 mL, 0.24 mmol) and heated at 100 °C for 16 h. The reaction mixture was concentrated and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2) to give **25** (3.0 mg, 4%) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD): δ 8.30−8.19 (m, 1H), 8.17 (d, J = 7.53 Hz, 1H), 7.38 (d, J = 2.01 Hz, 1H), 7.19−6.97 (m, 4H), 6.92−6.72 (m, 1H), 6.47 (d, J = 8.03 Hz, 1H), 2.41 (s, 3H).

4-(3-(6-Methoxypyridin-3-ylamino)pyridin-4-yl)-6-methyl-1,3,5-triazin-2-amine (27). A mixture of **71g** (32 mg, 0.069 mmol), 3-amino-6-methoxypyridine (17 μL, 0.14 mmol), chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2′-4′-6′-tri-iso-propyl-1,1′-biphenyl][2-(2-aminoethyl)phenyl]-palladium(II) (BrettPhos precatalyst, 2 mg), and *t*-BuONa (17 mg, 0.17 mmol) in 1,4-dioxane (1 mL) was heated at 100 °C for 16 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (2 × 20 mL). The organic extract was washed with saturated brine (5 mL) and dried (Na_2SO_4). The solution was filtered, concentrated, and purified by silica gel column chromatography (20% THF/CH_2Cl_2) to give **73g** (9 mg, 24%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.32 (s, 1H), 8.68−8.49 (m, 1H), 8.33 (s, 1H), 8.24 (d, J = 5.12 Hz, 2H), 8.03 (d, J = 5.12 Hz, 2H), 7.95 (d, J = 1.61 Hz, 1H), 7.38 (dd, J = 8.70, 2.41 Hz, 2H), 7.21 (d, J = 8.33 Hz, 2H), 7.14 (d, J = 8.33 Hz, 2H), 6.98 (s, 1H), 6.87 (d, J = 8.33 Hz, 2H), 6.79 (d, J = 8.33 Hz, 2H), 6.72 (d, J = 8.77 Hz, 1H), 4.86 (s, 2H), 4.79 (s, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 2.56 (s, 3H).

A solution of **73g** (7 mg, 0.013 mmol) and TfOH (3.4 μL, 0.04 mmol) in TFA (0.1 mL) was stirred at 22 °C for 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with saturated brine (5 mL) and dried (Na_2SO_4). The solution was filtered, concentrated, and purified by silica gel column chromatography (EtOAc) to give **27** (3.2 mg, 81%) as a yellow film. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.38 (s, 1H), 8.38 (s, 1H), 8.24 (d, J = 5.12 Hz, 1H), 8.13 (s, 1H), 8.07 (d, J = 4.97 Hz, 1H), 7.58 (dd, J = 8.77, 2.05 Hz, 1H), 6.81 (d, J = 8.77 Hz, 1H), 5.41 (s, 2H), 3.96 (s, 3H), 2.54 (s, 3H).

4-(3-(6-Methoxypyridin-3-ylamino)pyrazin-2-yl)-6-methyl-1,3,5-triazin-2-amine (30). A mixture of **71h** (61 mg, 0.26 mmol), 3-amino-6-methoxypyridine (38 μL, 0.31 mmol), CuI (5 mg, 0.03 mmol), and *i*-Pr_2NEt (89 μL, 0.51 mmol) in 1,4-dioxane (1 mL) was heated at 100 °C for 24 h. The mixture was concentrated and purified by silica gel column chromatography (20% EtOAc/CH_2Cl_2) to give *N*-(6-methoxypyridin-3-yl)-3-(4-methyl-6-(methylthio)-1,3,5-triazin-2-yl)-pyrazin-2-amine (**73h**) (67 mg, 76%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.34 (s, 1H), 8.36 (d, J = 1.90 Hz, 1H), 8.26 (s, 2H), 8.00 (dd, J = 8.99, 2.56 Hz, 1H), 6.80 (d, J = 8.77 Hz, 1H), 3.96 (s, 3H), 2.77 (s, 3H), 2.68 (s, 3H).

A mixture of **73h** (44 mg, 0.129 mmol), concentrated aqueous NH_3 (1 mL), and 1,4-dioxane (1 mL) was heated at 100 °C for 16 h and then concentrated and purified by silica gel column chromatography (10% MeOH/EtOAc) to give **30** (34 mg, 85%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.83 (s, 1H), 8.37 (d, J = 2.05 Hz, 1H), 8.24 (s, 1H), 8.20 (s, 1H), 8.04 (dd, J = 8.92, 2.48 Hz, 1H), 6.80 (d, J = 8.77 Hz, 1H), 5.71 (s, 2H), 3.95 (s, 3H), 2.62 (s, 3H).

6-(3-(6-Methoxypyridin-3-ylamino)pyrazin-2-yl)-2-methylpyrimidin-4-amine (31). A mixture of **71i** (21 mg, 0.09 mmol), 3-amino-6-methoxypyridine (22 μL, 0.18 mmol), CuI (2 mg, 9 μmol), and *i*-Pr_2NEt (23 mg, 0.18 mmol) in 1,4-dioxane (1 mL) was heated at 100 °C for 24 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with saturated brine (5 mL) and dried (Na_2SO_4). The solution was filtered, concentrated, and purified by silica gel column chromatography (30% EtOAc/hexanes) to give *N*-(6-methoxypyridin-3-yl)-3-(2-methyl-6-(methylthio)pyrimidin-4-yl)pyrazin-2-amine (**73i**) (14 mg, 46%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.20 (s, 1H), 8.42 (d, J = 2.05 Hz, 1H), 8.22 (s, 1H), 8.18 (s, 1H), 8.09 (dd, J = 8.92, 2.63 Hz, 1H), 8.02 (d, J = 1.90 Hz, 1H), 6.79 (d, J = 8.77 Hz, 1H), 3.95 (s, 3H), 2.78 (s, 3H), 2.63 (s, 3H).

A solution of **73i** (11 mg, 0.032 mmol) and in 1,4-dioxane (1 mL) was treated with *m*-CPBA (11 mg, 0.065 mmol) and stirred at 22 °C for 1 h. The mixture was then treated with concentrated aqueous NH_3 (0.5 mL, 13 mmol) and 1,4-dioxane

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(1 mL). The reaction mixture was heated at 100 °C for 2 h. The mixture was concentrated and purified by silica gel column chromatography (80% EtOAc/hexanes) to give **31** (8.2 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.46 (s, 1H), 8.42 (s, 1H), 8.15 (s, 1H), 8.10 (dd, J = 8.77, 2.48 Hz, 1H), 7.98 (d, J = 1.32 Hz, 1H), 7.47 (s, 1H), 6.78 (d, J = 8.62 Hz, 1H), 4.95 (s, 2H), 3.95 (s, 3H), 2.64 (s, 3H).

4-(5-Chloro-2-(6-methoxypyridin-3-ylamino)pyridin-3-yl)-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-1,3,5-triazin-2-amine (73j). A solution of 3-amino-6-methoxypyridine (1.41 g, 11.3 mmol) and **71j** (3.62 g, 7.54 mmol) in THF (15 mL) was cooled to 0 °C and treated dropwise with 1.0 M LiHMDS in THF (22.6 mL, 22.6 mmol). The resulting reaction mixture was stirred for 30 min and then quenched with a saturated aqueous solution of NH_4Cl (50 mL). The mixture was extracted with EtOAc (50 mL), dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column chromatography (gradient: 20% → 100% EtOAc/hexanes) to give **73j** (3.77 g, 86%) as a bright-yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.64 (s, 1H), 8.73 (d, J = 2.74 Hz, 1H), 8.25 (d, J = 2.54 Hz, 1H), 8.19 (d, J = 2.74 Hz, 1H), 7.83 (dd, J = 9.00, 2.74 Hz, 1H), 7.19 (dd, J = 16.43, 8.61 Hz, 4H), 6.92−6.78 (m, 4H), 6.70 (d, J = 8.80 Hz, 1H), 4.86 (s, 2H), 4.81 (s, 2H), 3.92 (s, 3H), 3.80 (d, J = 9.19 Hz, 6H), 2.57 (s, 3H).

4-(5-Chloro-2-(6-methoxypyridin-3-ylamino)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (32). A solution of **73j** (110 mg, 0.19 mmol) in TFA (10 mL) was heated at 80 °C for 16 h. The mixture was concentrated to a slurry, diluted with saturated aqueous $NaHCO_3$ (5 mL), and filtered. The solid was washed with H_2O, MeOH, and 25% EtOAc/hexanes to give **32** as a brown solid (65 mg, 100%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.69 (br s, 1H), 8.72 (br s, 1H), 8.50 (d, J = 3.33 Hz, 1H), 8.31 (br s, 1H), 8.09 (br s, 1H), 7.94 (br s, 1H), 7.80 (br s, 1H), 6.84 (br s, 2H), 3.85 (br s, 3H), 2.43 (br s, 3H).

4-(5-Bromo-2-(4-methoxyphenylamino)pyridine-3-yl)-6-methyl-1,3,5-triazin-2-amine (33). A mixture of **71k** (645 mg, 2.27 mmol) and 3-amino-6-methoxypyridine (282 mg, 2.27 mmol) in THF (5 mL) was cooled in an ice−water bath and treated dropwise with 1.0 M LiHMDS in THF (13.6 mL, 13.6 mmol). The mixture was stirred for 30 min and then quenched with H_2O (60 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (5% 2 M NH_3 in MeOH/CH_2Cl_2) to give **33** (450 mg, 51%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.70 (d, J = 1.17 Hz, 1H), 8.84 (br s, 1H), 8.49 (d, J = 4.30 Hz, 1H), 8.37 (br s, 1H), 8.07 (dd, J = 4.21, 1.86 Hz, 1H), 7.81 (br s, 1H), 6.84 (d, J = 2.35 Hz, 1H), 3.84 (br s, 3H), 2.50 (d, J = 0.98 Hz, 3H).

4-(2-(6-Methoxypyridin-3-ylamino)-5-methylpyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (34). NaH (60% dispersion in mineral oil) (410 mg, 10 mmol) was carefully added to a solution of **71m** (905 mg, 4.1 mmol) and Boc_2O (2.70 g, 12 mmol) in DMF (3.0 mL), and the mixture was stirred at 22 °C for 16 h. The solution was quenched with ice and diluted with H_2O (50 mL), and the resulting precipitate was collected by filtration to give di-*tert*-butyl 4-(2-fluoro-5-methylpyridin-3-yl)-6-methyl-1,3,5-triazin-2-yl-dicarbamate (**72m**) (1.13 g, 65%) as a yellow solid. LC−MS m/z: 420 $(M + H)^+$.

1.0 M LiHMDS in THF (0.80 mL, 0.80 mmol) was added dropwise to a stirred mixture of **72m** (112 mg, 0.27 mmol) and 3-amino-6-methoxypyridine (50 mg, 0.40 mmol) in THF (3 mL) at 22 °C. The mixture was stirred for 1 h and then diluted with saturated aqueous NH_4Cl (5 mL) and H_2O (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated brine, dried (Na_2SO_4), and concentrated to give crude **73m**. This was dissolved in CH_2Cl_2 (2 mL) and treated with TFA (2 mL). The mixture was stirred for 1 h. The reaction mixture was concentrated, H_2O (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated brine, dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2) followed by another silica gel column chromatography purification (gradient: 0% → 80% EtOAc/hexanes) to give **34** (11 mg, 13%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.53 (br s, 1H), 8.66 (br s, 1H), 8.35 (br s, 1H), 8.16 (br s, 1H), 8.09 (d, J = 10.37 Hz, 1H), 6.79 (d, J = 9.19 Hz, 1H), 5.38 (br s, 2H), 3.95 (s, 3H), 2.56 (s, 3H), 2.29 (s, 3H).

4-(5-Methoxy-2-(6-methoxypyridin-3-ylamino)-pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (35). 1,4-Dioxane (0.1 mL) and 2 M aqueous HCl (0.22 mL, 0.44 mmol) were added to a mixture of **71n** (110 mg, 0.44 mmol) and 3-amino-6-methoxypyridine (81 mg, 0.66 mmol), and the mixture was heated at 140 °C for 60 min in a microwave reactor. The resulting mixture was concentrated and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2). The product was washed with methanol (3 × 5 mL) and recrystallized from MeOH to give **35** (21 mg, 14%) as a yellow-green powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.47 (s, 1H), 8.52 (d, J = 2.74 Hz, 1H), 8.39 (d, J = 3.33 Hz, 1H), 8.18−8.13 (m, 1H), 8.12 (d, J = 3.13 Hz, 1H), 7.86 (br s, 1H), 7.73 (br s, 1H), 6.79 (d, J = 8.80 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.44 (s, 3H).

6-Chloro-2-methyl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (76). A mixture of 2-methyl-4,6-dichloro-5-aminopyrimidine (**74**) (1.05 g) and aqueous NH_3 (~25% w/v) (3 mL) was heated in a microwave reactor at 120 °C for 25 min. This procedure was performed nine times to process a total of 9.94 g (55.8 mmol) of **74**. The reaction mixtures were combined and concentrated, and the residue (**75**; 8.89 g) was suspended in triethyl orthoformate (100 mL, 600 mmol) and heated at 100 °C for 75 min. The mixture was concentrated and treated with hexanes (100 mL), and the resulting solid was collected by filtration (9.45 g). The solid was suspended in CH_2Cl_2 (100 mL), and TsOH (12% in acetic acid, 0.90 mL, 5.6 mmol) and 3,4-dihydro-2*H*-pyran (6.6 mL, 73 mmol) were added. The mixture was heated at 50 °C for 30 min and then stirred at 22 °C for 16 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous $NaHCO_3$ (75 mL). The organic extract was dried (Na_2SO_4) and concentrated to give **76** (13.73 g, 97% over 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 5.78 (d, J = 10.56 Hz, 1H), 4.19 (d, J = 11.93 Hz, 1H), 3.84−3.76 (m, 1H), 2.80 (s, 3H), 2.20−1.96 (m, 3H), 1.89−1.64 (m, 3H).

6-(2-Fluoropyridin-3-yl)-2-methyl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (77a). A mixture of **76** (532 mg, 2.10 mmol), 2-fluoropyridin-3-ylboronic acid (596 mg, 4.23 mmol), KOAc (629 mg, 6.41 mmol), and $Pd(Amphos)_2Cl_2$ (37 mg, 53 μmol) under N_2 was suspended in EtOH (5 mL) and H_2O (1 mL), degassed, and heated at reflux for 2 h. The mixture was poured into saturated aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were dried ($MgSO_4$), concentrated, and purified by

silica gel column chromatography (EtOAc) to give **77a** (519 mg, 79%) as a pale-yellow oil which crystallized to give a white solid upon trituration with Et_2O. ^1H NMR (400 MHz, DMSO-d_6): δ 8.79 (s, 1H), 8.53−8.46 (m, 1H), 8.46−8.43 (m, 1H), 7.62−7.55 (m, 1H), 5.85−5.78 (m, 1H), 4.08−4.00 (m, 1H), 3.80−3.70 (m, 1H), 2.78 (s, 3H), 2.40−2.26 (m, 1H), 2.06−1.95 (m, 2H), 1.87−1.72 (m, 1H), 1.67−1.56 (m, 2H).

***N*-(3-(2-Methyl-9*H*-purin-6-yl)pyridin-2-yl)-1*H*-indazol-4-amine (17).** A mixture of **77a** (320 mg, 1.02 mmol) and 1*H*-indazol-4-amine (187 mg, 1.41 mmol) was suspended in EtOH (10 mL), and 5 M aqueous HCl (0.25 mL, 1.25 mmol) was added. The mixture was heated at 100 °C for 75 min, cooled to 22 °C, and treated with 2 M NH_3 in MeOH (5 mL). The reaction mixture was concentrated and purified by reversed-phase preparative HPLC (Phenomenex C18 column: 150 mm × 30 mm; 5 μm; 10% → 90% MeCN/H_2O; 0.1% TFA additive). The resulting product was dissolved in CH_2Cl_2, filtered through a short silica gel plug, washing with 2 M NH_3 in MeOH, and concentrated to give **17** (33.9 mg, 10%). ^1H NMR (400 MHz, DMSO-d_6): δ 13.12 (s, 1H), 12.72 (s, 1H), 9.78 (s, 1H), 8.62 (s, 1H), 8.41 (dd, J = 4.50 Hz, 1.76 Hz, 1H), 8.27 (s, 1H), 8.10 (d, J = 7.43 Hz, 1H), 7.33 (t, J = 8.02 Hz, 1H), 7.17 (d, J = 8.22 Hz, 1H), 7.09 (dd, J = 7.83 Hz, 4.69 Hz, 1H), 2.94 (s, 3H).

***N*-(3-(2-Methyl-9*H*-purin-6-yl)pyridin-2-yl)-1*H*-indol-4-amine (18).** A mixture of **77a** (270 mg, 0.86 mmol) and 4-aminoindole (159 mg, 1.21 mmol) in EtOH (5 mL) was treated with 5 M aqueous HCl (0.21 mL, 1.1 mmol) and heated at 100 °C for 3 h. The mixture was allowed to cool and was then diluted with 2 M NH_3 in MeOH (4 mL) and allowed to stand for 16 h. The mixture was concentrated, treated with DMF (5 mL), and filtered. The solid was washed with CH_2Cl_2, and the filtrate was concentrated and purified by reversed-phase preparative HPLC (Phenomenex C18 column: 150 mm × 30 mm; 5 μm; 10% → 90% MeCN/H_2O; 0.1% TFA additive). The resulting product was dissolved in CH_2Cl_2, filtered through a short silica gel plug, washing with 2 M NH_3 in MeOH, and concentrated to give **18** (13.7 mg, 5%). ^1H NMR (400 MHz, DMSO-d_6): δ 13.60 (s, 1H), 12.44 (s, 1H), 11.16 (s, 1H), 9.77 (d, J = 7.04 Hz, 1H), 8.61 (s, 1H), 8.37 (dd, J = 4.69 Hz, 1.76 Hz, 1H), 8.05 (dd, J = 6.85 Hz, 1.56 Hz, 1H), 7.37 (t, J = 2.64 Hz, 1H), 7.11−7.04 (m, 2H), 7.01 (dd, J = 7.82 Hz, 4.69 Hz, 1H), 6.72 (s, 1H), 2.92 (s, 3H).

6-Methoxy-*N*-(3-(2-methyl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-yl)pyridin-2-yl)pyridin-3-amine (78a). A solution of **77a** (190 mg, 0.61 mmol) and 3-amino-6-methoxypyridine (94 mg, 0.76 mmol) in THF (2 mL) was cooled in an ice−water bath and treated with 1.0 M LiHMDS in THF (3.0 mL, 3.0 mmol). The mixture was stirred for 1 h and then quenched with H_2O (0.1 mL). The mixture was extracted into EtOAc (3 × 50 mL) from saturated aqueous $NaHCO_3$ (50 mL), concentrated, and purified by silica gel column chromatography (gradient: 25% → 50% EtOAc/hexane; yellow band from column) to give **78a** (96.3 mg, 38%) as a yellow crystalline solid. ^1H NMR (400 MHz, DMSO-d_6): δ 12.50 (s, 1H), 9.72 (dd, J = 7.82, 1.71 Hz, 1H), 8.87 (s, 1H), 8.53 (d, J = 2.69 Hz, 1H), 8.32 (dd, J = 4.65, 1.96 Hz, 1H), 8.18 (dd, J = 8.93, 2.81 Hz, 1H), 7.01 (dd, J = 7.82, 4.65 Hz, 1H), 6.85 (d, J = 9.05 Hz, 1H), 5.89−5.80 (m, 1H), 4.12−3.97 (m, 1H), 3.85 (s, 3H), 3.82−3.67 (m, 1H), 2.89 (s, 3H), 2.38−2.27 (m, 1H), 2.12−1.93 (m, 2H), 1.88−1.72 (m, 1H), 1.70−1.55 (m, 2H).

***N*-(6-Methoxypyridin-3-yl)-3-(2-methyl-9*H*-purin-6-yl)pyridin-2-amine (19).** A solution of **78a** (95 mg, 0.23 mmol) in 2 M aqueous HCl (2 mL, 4 mmol) was heated briefly at 100 °C in an oil bath, and then the heater was turned off and the mixture was allowed to slowly cool to 22 °C. The solution was concentrated and purified by strong cation-exchange chromatography[44] (gradient: MeOH → 2 M NH_3/MeOH) to give **19** (72 mg, 95%) as an orange solid. ^1H NMR (400 MHz, DMSO-d_6): δ 13.60 (br s, 1H), 12.68 (s, 1H), 9.80 (dd, J = 7.82, 1.96 Hz, 1H), 8.60 (s, 1H), 8.54 (d, J = 2.69 Hz, 1H), 8.31 (dd, J = 4.65, 1.96 Hz, 1H), 8.20 (dd, J = 8.92, 2.81 Hz, 1H), 7.00 (dd, J = 7.95, 4.77 Hz, 1H), 6.85 (d, J = 8.80 Hz, 1H), 3.85 (s, 3H), 2.86 (s, 3H).

6-Methoxy-*N*-(3-(9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-yl)pyridin-2-yl)pyridin-3-amine (78b). A solution of **77b** (197 mg, 0.66 mmol) and 3-amino-6-methoxypyridine (102 mg, 0.82 mmol) in THF (2 mL) was cooled in an ice−water bath and treated with 1.0 M LiHMDS in THF (3.0 mL, 3.0 mmol). The mixture was stirred for 1 h and then quenched with H_2O (0.1 mL). The mixture was extracted into EtOAc from saturated aqueous $NaHCO_3$, concentrated, and purified by silica gel column chromatography (50% EtOAc/hexane; yellow band from column) to give **78b** (190 mg, 72%) as a yellow crystalline solid. ^1H NMR (400 MHz, $CDCl_3$): δ 12.06 (s, 1H), 9.68 (dd, J = 7.82, 1.76 Hz, 1H), 8.99 (s, 1H), 8.44 (d, J = 2.54 Hz, 1H), 8.28 (dd, J = 4.69, 1.76 Hz, 1H), 8.34 (s, 1H), 8.05 (dd, J = 8.90, 2.64 Hz, 1H), 6.88 (dd, J = 7.82, 4.69 Hz, 1H), 6.77 (d, J = 8.80 Hz, 1H), 5.86 (dd, J = 10.37, 2.35 Hz, 1H), 4.25−4.16 (m, 1H), 3.95 (s, 3H), 3.82 (s, 1H), 2.24−1.98 (m, 3H), 1.89−1.61 (m, 3H).

***N*-(6-Methoxypyridin-3-yl)-3-(9*H*-purin-6-yl)pyridin-2-amine (21).** A solution of **78b** (190 mg, 0.47 mmol) in 2 M aqueous HCl (2 mL, 4 mmol) was heated for 5 min at 100 °C and then allowed to slowly cool to 22 °C and stand for 16 h. The solution was neutralized with aqueous NH_3, and the precipitated product was collected by filtration, washing with a small volume of H_2O and dried under vacuum. **21** (120 mg, 80%) was obtained as an orange solid. ^1H NMR (400 MHz, DMSO-d_6): δ 13.80 (br s, 1H), 12.33 (br s, 1H), 9.73 (br s, 1H), 9.10 (s, 1H), 8.70 (s, 1H), 8.58−8.50 (m, 1H), 8.34−8.25 (m, 1H), 8.20−8.08 (m, 1H), 7.07−6.95 (m, 1H), 6.90−6.79 (m, 1H), 3.85 (s, 3H).

4-Nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (80a) and 4-Nitro-2-(tetrahydro-2*H*-pyran-2-yl)-2*H*-indazole (80b). A suspension of 4-nitro-1*H*-indazole (4.07 g, 25 mmol) in EtOAc (50 mL) was treated with 3,4-dihydro-2*H*-pyran (6.8 mL, 75 mmol) and MP-TsOH resin (Biotage) (380 mg, 4.3 mmol/g, 0.06 equiv) and heated at reflux for 2 h. The mixture was filtered, concentrated, and purified by silica gel column chromatography (gradient: 5% EtOAc/hexane →10% EtOAc/10% CH_2Cl_2/hexane) to give **80a** (3.04 g, 49%) as a pale-yellow crystalline solid (recrystallized from EtOAc/hexane) followed by **80b** (2.34 g, 38%) as a pale-yellow oil. Structural assignments were confirmed by NOESY (N−CH−O to aromatic protons).

80a: ^1H NMR (400 MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.32 (d, J = 8.53 Hz, 1H), 8.21 (d, J = 7.53 Hz, 1H), 7.69 (t, J = 8.03 Hz, 1H), 6.04 (dd, J = 9.54, 2.01 Hz, 1H), 3.93−3.84 (m, 1H), 3.83−3.74 (m, 1H), 2.46−2.36 (m, 1H), 2.12−1.98 (m, 2H), 1.84−1.70 (m, 1H), 1.67−1.56 (m, 2H).

80b: ^1H NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 8.26−8.22 (m, 2H), 7.54 (t, J = 8.03 Hz, 1H), 5.93 (dd, J = 9.54, 2.51

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Hz, 1H), 4.01 (m, 1H), 3.83−3.71 (m, 1H), 2.30−2.18 (m, 1H), 2.15−1.34 (m, 5H).

1-(Tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-amine (81a). A solution of **80a** (1.05 g, 4.25 mmol) in EtOAc (100 mL) was treated with 10% Pd/C (60 mg) and stirred under an atmosphere of H_2 for 22 h. The reaction was filtered and concentrated. The residue was triturated with Et_2O to give **81a** (892 mg, 97%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.11 (s, 1H), 7.03 (t, J = 7.82 Hz, 1H), 6.74 (d, J = 8.22 Hz, 1H), 6.18 (d, J = 7.43 Hz, 1H), 5.78 (s, 2H), 5.67−5.59 (m, 1H), 3.92−3.82 (m, 1H), 3.74−3.63 (m, 1H), 2.45−2.30 (m, 1H), 2.08−1.96 (m, 1H), 1.94−1.84 (m, 1H), 1.80−1.65 (m, 1H), 1.55 (br s, 2H).

2-(Tetrahydro-2*H*-pyran-2-yl)-2*H*-indazol-4-amine (81b). A solution of **80b** (2.34 g, 9.45 mmol) was dissolved in EtOAc (100 mL) and treated with 10% Pd/C (100 mg). The resulting suspension was stirred under an atmosphere of H_2 for 16 h and then was filtered, concentrated, and purified by silica gel column chromatography (50% EtOAc/hexane) to give **81b** (584 mg, 29%) as an orange foam. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 6.92 (t, J = 7.82 Hz, 1H), 6.72 (d, J = 8.61 Hz, 1H), 5.99 (d, J = 7.04 Hz, 1H), 5.69−5.54 (m, 3H), 3.98 (d, J = 11.74 Hz, 1H), 3.78−3.63 (m, 1H), 2.13−2.02 (m, 2H), 2.00−1.87 (m, 1H), 1.80−1.65 (m, 1H), 1.59 (br s, 2H).

4-Chloro-6-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (82). LDA was prepared by dropwise addition of 2.5 M *n*-BuLi in hexanes (14.7 mL, 36.8 mmol) to *i*-Pr_2NH (5.42 mL, 38.4 mmol) in THF (40 mL) cooled in an ice−water bath. The LDA solution was cooled to −78 °C, and a solution of 4,6-dichloro-2-methylpyrimidine (**64b**) (5.45 g, 33.4 mmol) in THF (50 mL) was added dropwise over 1 h. A solution of *N*-methyl-*N*-(2-pyridyl)formamide (4.8 mL, 40 mmol) in THF (20 mL) was added dropwise to the solution at −78 °C over 20 min. The resulting solution was stirred for 30 min and then quenched with a solution of acetic acid (2.1 mL, 37 mmol) in THF (20 mL) added dropwise at −78 °C over 10 min. The solution was stirred at −78 °C for 30 min.

The resulting solution of 4,6-dichloro-2-methylpyrimidine-5-carbaldehyde was treated dropwise with anhydrous hydrazine (1.1 mL, 35 mmol) at −78 °C. The mixture was stirred for 15 min, and then the cooling bath was removed and the mixture stirred at 22 °C for 1 h. The mixture was concentrated and partitioned between H_2O (110 mL) and EtOAc (110 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL), separated, dried ($MgSO_4$), treated with activated charcoal, and filtered through a plug of silica gel, washing with EtOAc. The filtrate was concentrated and purified by silica gel column chromatography (gradient: 5% acetone/CH_2Cl_2 → 25% EtOAc/hexane). The residue was suspended in CH_2Cl_2 (3 mL) and cooled in a freezer for 16 h (−20 °C), and the solid was collected by filtration to give **82** (330 mg, 5.9%) as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.25 (br s, 1H), 8.35 (s, 1H), 2.68 (s, 3H).

4-Chloro-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (83). A suspension of **82** (325 mg, 1.93 mmol) in EtOAc (3 mL) was treated with 3,4-dihydro-2*H*-pyran (0.53 mL, 5.8 mmol) and MP-TsOH resin (Biotage) (72 mg, 4.3 mmol/g, 0.15 equiv), and the resulting suspension was heated at 90 °C for 3 h. The solution was filtered, washed with EtOAc, and concentrated to give a pale-yellow oil. Purification by silica gel column chromatography (gradient: 5% → 20% EtOAc/hexanes) gave **83** (482 mg, 99%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (s, 1H), 6.02−5.91 (m, 1H), 3.99−3.91 (m, 1H), 3.77−3.67 (m, 1H), 2.72 (s, 3H), 2.48−2.36 (m, 1H), 2.08−1.96 (m, 1H), 1.95−1.87 (m, 1H), 1.84−1.32 (m, 3H).

4-(2-Fluoropyridin-3-yl)-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (84). A mixture of **83** (108 mg, 0.43 mmol), 2-fluoropyridin-3-ylboronic acid (120 mg, 0.85 mmol), and KOAc (105 mg, 1.07 mmol) in EtOH (1.25 mL) and H_2O (0.25 mL) was placed under vacuum for 5 min and then flushed with nitrogen for 5 min and treated with $Pd(Amphos)_2Cl_2$ (8.0 mg, 11 μmol). The suspension was heated at 80 °C for 60 min. The reaction mixture was poured into EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) and extracted. The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column chromatography (gradient: 25% → 50% EtOAc/hexanes) to give **84** (105 mg, 79%) as a pale-yellow oil which slowly crystallized upon standing. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.57−8.46 (m, 2H), 8.41 (d, J = 3.51 Hz, 1H), 7.64 (s, 1H), 6.04 (d, J = 8.03 Hz, 1H), 4.02−3.92 (m, 1H), 3.79−3.68 (m, 1H), 2.82 (s, 3H), 2.48−2.41 (m, 1H), 2.10−2.00 (m, 1H), 1.99−1.88 (m, 1H), 1.87−1.72 (m, 1H), 1.59 (d, J = 3.51 Hz, 2H).

2-(Tetrahydro-2*H*-pyran-2-yl)-*N*-(3-(9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-yl)pyridin-2-yl)-2*H*-indazol-4-amine (85a). A solution of **81b** (37.4 mg, 0.17 mmol) and **77b** (51.5 mg, 0.17 mmol) in THF (1 mL) was cooled in an ice−water bath and treated dropwise with 1.0 M LiHMDS in THF (0.55 mL, 0.55 mmol). The mixture was stirred for 60 min and then quenched with H_2O (50 μL). The mixture was extracted with EtOAc (100 mL) from saturated aqueous $NaHCO_3$ (100 mL), dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (50% EtOAc/hexane) to give **85a** (36.6 mg, 43%) as a yellow oil which crystallized upon standing. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.75 (br s, 1H), 9.77 (d, J = 7.82 Hz, 1H), 9.12 (s, 1H), 8.44 (d, J = 3.52 Hz, 1H), 8.38 (s, 2H), 8.06 (d, J = 7.04 Hz, 1H), 7.41 (d, 1H), 7.35 (d, J = 7.63 Hz, 1H), 7.03−6.92 (m, 1H), 5.88 (d, 1H), 5.73 (d, 1H), 4.30−4.13 (m, 2H), 3.84 (br s, 2H), 2.35−2.17 (m, 3H), 2.16−2.00 (m, 3H), 1.79 (br s, 6H).

***N*-(3-(9*H*-Purin-6-yl)pyridin-2-yl)-1*H*-indazol-4-amine (±)-10-Camphorsulfonate (20).** A solution of **85a** (34.8 mg, 70 μmol) in CH_2Cl_2/MeOH (4 mL; 1:1) was treated with CSA (38 mg, 2.2 equiv), and the mixture was stirred at 40 °C for 3 h. The volume of the reaction mixture was reduced by ∼50% under a stream of N_2 to remove CH_2Cl_2, and the solution was triturated with Et_2O, resulting in the formation of a precipitate that was collected by filtration, washed with Et_2O, and dried under vacuum to give **20** (33.7 mg, 86%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.17 (br s, 1H), 9.89 (d, 1H), 9.33 (s, 1H), 8.76 (s, 1H), 8.46−8.41 (m, 1H), 8.31 (s, 1H), 8.24 (d, 1H), 7.35 (t, 1H), 7.21 (d, 1H), 7.14 (t, 1H), 2.88 (d, 1H), 2.73−2.63 (m, 1H), 2.42−2.34 (d, 1H), 2.29−2.18 (m, 1H), 1.97−1.90 (m, 1H), 1.90−1.74 (m, 2H), 1.27 (m, 2H), 1.05 (s, 3H), 0.75 (s, 3H).

***N*-(3-(6-Methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)pyridin-2-yl)-2-(tetrahydro-2*H*-pyran-2-yl)-2*H*-indazol-4-amine (85b).** A solution of **81b** (80 mg, 0.37 mmol) and **84** (112 mg, 0.36 mmol) in THF (1 mL) was stirred in an ice−water bath and treated dropwise with a 1.0 M solution of LiHMDS in THF (1.1 mL, 1.1 mmol). The mixture was stirred for 45 min and then quenched with H_2O (0.1 mL). The mixture was extracted into EtOAc (100 mL) from saturated aqueous $NaHCO_3$ (100 mL),

dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (gradient: 25% → 30% EtOAc/hexanes) to give **85b** (56.9 mg, 31%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.97 (br s, 1H), 8.53−8.43 (m, 1H), 8.42−8.30 (m, 3H), 7.96 (br s, 1H), 7.48−7.38 (m, 1H), 7.34 (d, J = 7.43 Hz, 1H), 7.03−6.94 (m, 1H), 6.16 (d, J = 10.17 Hz, 1H), 5.71 (d, J = 9.00 Hz, 1H), 4.14 (d, J = 9.98 Hz, 2H), 3.95−3.73 (m, 2H), 3.04 (s, 3H), 2.76−2.58 (m, 1H), 2.39−2.26 (m, 1H), 2.25−1.94 (m, 4H), 1.93−1.59 (m, 6H).

***N*-(3-(6-Methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-pyridin-2-yl)-1*H*-indazol-4-amine (22).** A solution of **85b** (57 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) and MeOH (2 mL) was treated with CSA (114 mg, 4.4 equiv) and stirred at 60 °C for 1 h. The mixture was concentrated and purified by strong cation-exchange chromatography[44] (gradient: MeOH → 2 M NH_3/MeOH) to give **22** (35 mg, 87%) as a brown solid. The ^{1}H NMR of the free base thus obtained gave very broad signals, and so ∼2 mg of **22** was converted to the HCl salt for better ^{1}H NMR analysis by dissolving **22** in MeOH (1 mL) containing 2 drops of 2 M aqueous HCl followed by concentration to dryness. HCl salt: ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.18 (br s, 1H), 11.38 (s, 1H), 10.43 (s, 1H), 9.76 (s, 1H), 9.42 (d, 1H), 9.04 (s, 1H), 8.64 (d, 1H), 8.46 (s, 1H), 7.98−7.85 (m, 2H), 7.69 (d, J = 9.54 Hz, 1H), 2.14 (s, 3H).

4-(2-Aminophenyl)-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-1,3,5-triazin-2-amine (87). A mixture of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**86**) (292 mg, 1.33 mmol), $Pd(PPh_3)_4$ (59 mg, 0.05 mmol), **66** (395 mg, 1.03 mmol), $Na_2CO_3 \cdot H_2O$ (218 mg, 2.05 mmol), DME (5 mL), and H_2O (1.5 mL) was purged with Ar and then heated at 90 °C for 2 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (20 mL), and the extract was dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (gradient: 0% → 1% MeOH/CH_2Cl_2) to give **87** (244 mg, 54%) as a light-yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (dd, J = 8.02, 1.57 Hz, 1H), 7.28−7.06 (m, 8H), 6.89 (t, J = 8.12 Hz, 4H), 6.72 (d, J = 7.63 Hz, 1H), 5.47 (s, 1H), 4.78 (s, 2H), 4.74 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 2.44 (s, 3H).

***N*,*N*-Bis(4-methoxybenzyl)-4-(2-(6-methoxypyridin-3-ylamino)phenyl)-6-methyl-1,3,5-triazin-2-amine (88).** A mixture of **87** (540 mg, 1.22 mmol), $Cu(OAc)_2$ (330 mg, 1.83 mmol), 6-methoxypyridin-3-ylboronic acid (561 mg, 3.67 mmol), and *i*-Pr_2NEt (0.85 mL, 4.89 mmol) in CH_2Cl_2 (15 mL) was stirred at 22 °C for 16 h, filtered through a pad of diatomaceous earth, concentrated, and purified by silica gel column chromatography (gradient: 0% → 2% 2 M NH_3 in MeOH/CH_2Cl_2), to give **88** (384 mg, 57%) as a dark-yellow oil. LC−MS m/z: 548.8 $(M + H)^+$.

4-(2-(6-Methoxypyridin-3-ylamino)phenyl)-6-methyl-1,3,5-triazin-2-amine (26). A solution of **88** (384 mg, 0.70 mmol) in TFA (3 mL) was treated with 3 drops of TfOH and heated at 80 °C for 3 h. The solvent was removed in vacuo, and the residue was purified by reversed-phase preparative HPLC (Phenomenex C18 column: 150 mm × 30 mm; 5 μm; 10% → 90% MeCN/H_2O; 0.1% TFA additive) to give **26** (47 mg, 22%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.92 (s, 1H), 8.44 (dd, J = 8.12, 1.66 Hz, 1H), 8.12 (d, J = 2.74 Hz, 1H), 7.68 (dd, J = 8.80, 2.74 Hz, 2H), 7.53 (br s, 1H), 7.28 (ddd, J = 8.46, 6.99, 1.57 Hz, 1H), 6.88 (dd, J = 12.81, 8.51 Hz, 2H), 6.82−6.69 (m, 1H), 3.86 (s, 3H), 2.38 (s, 3H).

***tert*-Butyl 2-(2-Methyl-6-(methylthio)pyrimidin-4-yl)-pyridin-3-ylcarbamate (90).** A mixture of *tert*-butyl 2-bromopyridin-3-ylcarbamate (**89**) (481 mg, 1.76 mmol) and $Pd(PPh_3)_4$ (170 mg, 0.15 mmol) under N_2 was treated with a solution of **70b** (630 mg, 1.47 mmol) in toluene (7 mL). The mixture was heated at 120 °C for 16 h, concentrated, and purified by silica gel column chromatography (gradient: 0% → 25% EtOAc/hexanes) to give **90** (462 mg, 95%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.61 (s, 1H), 8.82−8.76 (m, 1H), 8.30 (dd, J = 4.30, 1.56 Hz, 1H), 8.21 (s, 1H), 7.33 (dd, J = 8.61, 4.30 Hz, 1H), 2.73 (s, 3H), 2.62 (s, 3H), 1.56 (s, 9H).

2-(2-Methyl-6-(methylthio)pyrimidin-4-yl)pyridin-3-amine (91). A mixture of **90** (462 mg, 1.39 mmol), 4.0 M HCl in 1,4-dioxane (7.0 mL, 28 mmol), and MeOH (8 mL) was heated at 60 °C for 16 h. The reaction mixture was concentrated, and the yellow residue was partitioned between CH_2Cl_2 (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to give **91** (380 mg, 100%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H), 8.06 (dd, J = 4.30, 1.57 Hz, 1H), 7.14 (dd, J = 8.22, 4.30 Hz, 1H), 7.04 (dd, J = 8.31, 1.47 Hz, 1H), 6.48 (br s, 1H), 2.70 (s, 3H), 2.61 (s, 3H).

6-Methoxy-*N*-(2-(2-methyl-6-(methylthio)pyrimidin-4-yl)pyridin-3-yl)pyridin-3-amine (92). A mixture of **91** (380 mg, 1.64 mmol), 6-methoxypyridin-3-ylboronic acid (751 mg, 4.91 mmol), $Cu(OAc)_2$ (446 mg, 2.45 mmol), and *i*-Pr_2NEt (1.1 mL, 6.5 mmol) in CH_2Cl_2 (10 mL) was stirred for 72 h at 22 °C. The mixture was filtered through diatomaceous earth, concentrated, and purified by silica gel column chromatography (gradient: 5% → 50% EtOAc/hexane) to give **92** (76 mg, 14%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.23 (s, 1H), 8.22 (s, 1H), 8.15−8.06 (m, 2H), 7.52 (dd, J = 8.71, 2.84 Hz, 1H), 7.32 (dd, J = 8.51, 1.47 Hz, 1H), 7.13 (dd, J = 8.51, 4.21 Hz, 1H), 6.80 (d, J = 8.61 Hz, 1H), 3.97 (s, 3H), 2.70 (s, 3H), 2.62 (s, 3H).

6-(3-(6-Methoxypyridin-3-ylamino)pyridin-2-yl)-2-methylpyrimidin-4-amine (28). A solution of **92** (76 mg, 0.22 mmol) in CH_2Cl_2 (6 mL) was treated with *m*-CPBA (103 mg, 0.45 mmol) at 22 °C and stirred for 90 min. The reaction mixture was partitioned between CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to give crude 6-methoxy-*N*-(2-(2-methyl-6-(methylsulfonyl)pyrimidin-4-yl)-pyridin-3-yl)pyridin-3-amine (113 mg) as an orange oil. LC−MS m/z: 372.0 $(M + H)^+$.

NH_3 gas was bubbled through a solution of crude 6-methoxy-*N*-(2-(2-methyl-6-(methylsulfonyl)pyrimidin-4-yl)pyridin-3-yl)pyridin-3-amine (83 mg, 0.22 mmol) in 1,4-dioxane (7 mL) for 5 min, and then the vessel was heated at 100 °C for 18 h. The reaction mixture was concentrated and purified by silica gel column chromatography (gradient: 10% → 60% EtOAc/hexanes). The product was further purified by trituration with Et_2O to give **28** (22 mg, 22%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.38 (br s, 1H), 8.12 (dd, J = 2.54, 0.39 Hz, 1H), 8.06 (dd, J = 4.30, 1.37 Hz, 1H), 7.52 (dd, J = 8.80, 2.74 Hz, 1H), 7.47 (s, 1H), 7.36−7.29 (m, 1H), 7.11 (dd, J = 8.41, 4.30 Hz, 1H), 6.79 (d, J = 8.80 Hz, 1H), 4.94 (br s, 2H), 3.96 (s, 3H), 2.57 (s, 3H).

5-Bromo-*N*-(6-methoxypyridin-3-yl)pyrimidin-4-amine (95). A mixture of 5-bromopyrimidin-4-amine (**94**) (344 mg, 1.98 mmol), 6-methoxypyridin-3-ylboronic acid (**93**) (907 mg, 5.93 mmol), *i*-Pr_2NEt (1.4 mL, 7.9 mmol), and anhydrous $Cu(OAc)_2$ (539 mg, 2.97 mmol) in CH_2Cl_2 (2 mL) was stirred at 22 °C for 16 h. The solid was filtered off and

washed with CH_2Cl_2. The filtrate was concentrated and purified by silica gel column chromatography (50% EtOAc/hexanes) to give **95** (36 mg, 6.5%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.46 (s, 1H), 8.28 (s, 1H), 7.85 (dd, J = 8.77, 2.48 Hz, 1H), 6.98 (s, 1H), 6.80 (d, J = 8.92 Hz, 1H), 3.95 (s, 3H).

***N*-(6-Methoxypyridin-3-yl)-5-(4-methyl-6-(methylthio)-1,3,5-triazin-2-yl)pyrimidin-4-amine (96).** A mixture of 5-bromo-*N*-(6-methoxypyridin-3-yl)pyrimidin-4-amine (**95**) (23 mg, 0.08 mmol), **70a** (35.2 mg, 0.08 mmol), CuI (15 mg, 0.08 mmol), CsF (206 mg, 0.82 mmol), and $Pd(PPh_3)_4$ (9.5 mg, 8.2 μmol) in THF (1 mL) was heated at 140 °C in a microwave reactor for 30 min. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with saturated brine (5 mL), dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (60% EtOAc/hexanes) to give **96** (15 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.58 (s, 1H), 9.65 (s, 1H), 8.74 (s, 1H), 8.35 (d, J = 2.19 Hz, 1H), 8.07 (dd, J = 8.84, 2.56 Hz, 1H), 6.82 (d, J = 8.92 Hz, 1H), 3.96 (s, 3H), 2.67 (s, 3H), 2.65 (s, 3H).

4-(4-(6-Methoxypyridin-3-ylamino)pyrimidin-5-yl)-6-methyl-1,3,5-triazin-2-amine (29). A mixture of **96** (14 mg, 0.04 mmol), 28% aqueous NH_3 (0.5 mL, 12.8 mmol), and 1,4-dioxane (1 mL) was heated at reflux for 1 h. The solid formed was collected by filtration and washed with EtOAc (2 mL) to give **29** (10 mg, 79%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.78 (s, 1H), 9.37 (s, 1H), 8.65 (s, 1H), 8.48 (s, 1H), 8.10 (d, J = 8.33 Hz, 1H), 7.94 (s, 1H), 7.79 (s, 1H), 6.88 (d, J = 8.77 Hz, 1H), 3.87 (s, 3H), 2.43 (s, 3H).

5-(1,3-Dioxolan-2-yl)-2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (100). 6-Fluoronicotinaldehyde (**97**) (21.96 g, 176 mmol) was suspended in toluene (340 mL), and ethylene glycol (10.4 mL, 186 mmol) and TsOH (15% in acetic acid, 1.10 mL) were added. The mixture was heated at 120 °C for 45 min, cooled to 22 °C, diluted with saturated aqueous $NaHCO_3$ (50 mL) and H_2O (150 mL), and extracted with EtOAc (2 × 150 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (gradient: 0% → 2.5% MeOH/CH_2Cl_2) to give 5-(1,3-dioxolan-2-yl)-2-fluoropyridine (**98**) (19.06 g, 64%) as a pale-yellow liquid. LC−MS m/z: 170 $(M + H)^+$.

Compound **98** (18.80 g, 111 mmol) was dissolved in THF (300 mL) and cooled in a dry ice−acetone bath under N_2. A 2.0 M solution of LDA in heptane/THF/ethylbenzene (89 mL, 178 mmol) was added via syringe over 20 min. After 75 min, (i-PrO)$_3$B (40.8 mL, 178 mmol) was added via syringe over 5 min, and then the reaction was allowed to slowly warm to 22 °C. After 4.5 h, the reaction mixture was treated with 1 M aqueous NaOH (300 mL) and stirred for 15 min. The layers were separated, and the organic layer was discarded. The stirred aqueous phase was treated with concentrated aqueous HCl to lower the pH to ∼5 and was then extracted with 10:1 CH_2Cl_2/MeOH (3 × 250 mL). The aqueous phase was treated with 5 M aqueous HCl during the extractions to maintain the pH at ∼5−6, and saturated brine was also added to the aqueous phase to aid extraction. The combined organic extracts were concentrated to give 5-(1,3-dioxolan-2-yl)-2-fluoropyridin-3-ylboronic acid (**99**) (14.56 g, 62%). LC−MS m/z: 214 $(M + H)^+$.

Compound **99** (14.56 g, 68.4 mmol) was suspended in toluene (300 mL), and anhydrous $MgSO_4$ (41.20 g, 342 mmol) and pinacol (8.27 g, 70.0 mmol) were added. The reaction was stirred under N_2 at 22 °C for 72 h. The suspension was filtered, and the solid was washed with EtOAc. The filtrate was washed with saturated brine (2 × 200 mL) and dried (Na_2SO_4), filtered, and concentrated to give **100** (19.19 g, 100%) as a light-yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, J = 2.54 Hz, 1H), 8.28 (dd, J = 8.02 Hz, 2.54 Hz, 1H), 5.84 (s, 1H), 4.17−4.04 (m, 4H), 1.37 (s, 12H).

4-(5-(1,3-Dioxolan-2-yl)-2-fluoropyridin-3-yl)-*N*,*N*-bis-(4-methoxybenzyl)-6-methyl-1,3,5-triazin-2-amine (101a). A mixture of **66** (2.10 g, 5.46 mmol), **100** (1.90 g, 6.44 mmol), $Pd(Amphos)_2Cl_2$ (201 mg, 0.28 mmol), and KOAc (1.51 g, 15.4 mmol) was suspended in H_2O (4 mL) and 1,4-dioxane (20 mL), and N_2 was bubbled through the suspension for 30 s. The mixture was heated at 100 °C for 4 h, cooled to 22 °C, treated with H_2O (40 mL), and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered through a diatomaceous earth, concentrated, and purified by silica gel column chromatography (gradient: 0% → 2% MeOH/CH_2Cl_2) to give **101a** (3.18 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (dd, J = 8.90 Hz, 2.45 Hz, 1H), 8.42 (d, J = 1.37 Hz, 1H), 7.23 (dd, J = 8.41 Hz, 5.87 Hz, 4H), 6.87 (dd, J = 10.27 Hz, 8.71 Hz, 4H), 5.93 (s, 1H), 4.83 (s, 2H), 4.81 (s, 2H), 4.17−4.04 (m, 4H), 3.82 (s, 3H), 3.80 (s, 3H), 2.55 (s, 3H).

2-(5-(1,3-Dioxolan-2-yl)-2-fluoropyridin-3-yl)-4-methyl-6-(methylthio)-1,3,5-triazine (101b). A suspension of **100** (715 mg, 3.53 mmol), **68a** (682 mg, 3.88 mmol), $Pd(PPh_3)_4$ (408 mg, 0.35 mmol), and $Na_2CO_3{\cdot}H_2O$ (935 mg, 8.82 mmol) in 1,4-dioxane (16 mL) and H_2O (3.3 mL) was heated at 90 °C for 2 h. The mixture was filtered and washed with EtOAc (2 × 20 mL), and the combined organic phases were concentrated and purified by silica gel column chromatography (gradient: 0% → 30% EtOAc/hexanes) to give **101b** (526 mg, 48%) as a white solid. LC−MS m/z: 309 $(M + H)^+$.

5-(4-(Bis(4-methoxybenzyl)amino)-6-methyl-1,3,5-triazin-2-yl)-6-(6-methoxypyridin-3-ylamino)-nicotinaldehyde (103a). A mixture of **101a** (3.25 g, 6.28 mmol) and 3-amino-6-methoxypyridine (858 mg, 6.91 mmol) in THF (63 mL) was cooled to 0 °C and treated dropwise with 1.0 M LiHMDS in THF (19 mL, 19 mmol). The mixture was stirred at 0 °C for 2 h, and then 5 M aqueous HCl (10 mL, 50 mmol) was added and the mixture was stirred for 20 min. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with H_2O (2 × 100 mL), and the organic layer was dried (Na_2SO_4), filtered, and concentrated to give **103a** (3.25 g, 90%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (s, 1H), 9.90 (s, 1H), 9.14 (d, J = 2.35 Hz, 1H), 8.77 (d, J = 2.35 Hz, 1H), 8.31 (d, J = 2.74 Hz, 1H), 7.87 (dd, J = 8.80, 2.74 Hz, 1H), 7.28 (d, J = 8.61 Hz, 2H), 7.21 (d, J = 8.80 Hz, 2H), 6.94−6.87 (m, 2H), 6.87−6.78 (m, 3H), 4.83 (d, J = 7.24 Hz, 4H), 3.85 (s, 3H), 3.74 (s, 3H), 3.69 (s, 3H), 2.58 (s, 3H).

5-(1,3-Dioxolan-2-yl)-*N*-(6-methoxypyridin-3-yl)-3-(4-methyl-6-(methylthio)-1,3,5-triazin-2-yl)pyridin-2-amine (102b). A mixture of **101b** (425 mg, 1.38 mmol) and 3-amino-6-methoxypyridine (257 mg, 2.09 mmol) in THF (3 mL) was cooled to 0 °C and treated dropwise with 1.0 M LiHMDS in THF (4.1 mL, 4.1 mmol) and then stirred for 1 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with saturated brine (10 mL), dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (gradient: 0% → 50% EtOAc/hexanes) to give

102b (35 mg, 6%) as a yellow solid. LC−MS m/z: 413 $(M + H)^+$.

6-(6-Methoxypyridin-3-ylamino)-5-(4-methyl-6-(methylthio)-1,3,5-triazin-2-yl)nicotinaldehyde (103b). A solution of **102b** (35 mg, 0.09 mmol) in THF (3 mL) was treated with 2 M aqueous HCl (1.5 mL, 3.0 mmol), and the mixture was stirred at 22 °C for 2 h. A yellow precipitate gradually formed. The THF was removed in vacuo, and the precipitate was collected and dried to give **103b** (27 mg, 86%) as a yellow solid. LC−MS m/z: 369 $(M + H)^+$.

(5-(4-(Bis(4-methoxybenzyl)amino)-6-methyl-1,3,5-triazin-2-yl)-6-(6-methoxypyridin-3-ylamino)pyridin-3-yl)-methanol (104). $NaBH_4$ (103 mg, 2.72 mmol) was added to a suspension of **103a** (523 mg, 0.91 mmol) in MeOH (5 mL) and CH_2Cl_2 (5 mL) at 0 °C. The resulting solution was stirred at 0 °C for 5 min and then allowed to warm to 22 °C and stirred for 45 min. Saturated aqueous NH_4Cl (10 mL) and H_2O (20 mL) were added, and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give **104** (505 mg, 96%) as a yellow-orange solid. LC−MS m/z: 580 $(M + H)^+$.

(5-(4-(Bis(4-methoxybenzyl)amino)-6-methyl-1,3,5-triazin-2-yl)-6-(6-methoxypyridin-3-ylamino)pyridin-3-yl)-methyl Methanesulfonate (105). A suspension of **104** (1.00 g, 1.73 mmol) in CH_2Cl_2 (25 mL) was stirred at 0 °C and treated with Et_3N (1.1 mL, 7.9 mmol) followed by MsCl (0.50 mL, 6.4 mmol). The resulting solution was stirred for 30 min, diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL), and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give **105** (935 mg, 82%). LC−MS m/z: 658 $(M + H)^+$.

(5-(4-Amino-6-methyl-1,3,5-triazin-2-yl)-6-(6-methoxypyridin-3-ylamino)pyridin-3-yl)methanol (36). A solution of **104** (101 mg, 0.17 mmol) in TFA (3.5 mL) was treated with TfOH (70 μL) and stirred at 75 °C for 1 h. The mixture was allowed to cool to 22 °C and then concentrated. 1.0 M Aqueous NaOH (2.0 mL) followed by MeOH (1 mL) were added, and the mixture was stirred at 22 °C for 5 min. The MeOH was removed in vacuo, and the resulting solid was collected by filtration, washing with H_2O (20 mL) and then Et_2O (6 mL). Purification by silica gel column chromatography (gradient: 0% → 10% MeOH/CH_2Cl_2) gave **36** (41.8 mg, 71%) as a yellow solid. ^1H NMR (400 MHz, CD_3OD): δ 8.94 (d, J = 2.54 Hz, 1H), 8.48 (d, J = 2.35 Hz, 1H), 8.25 (d, J = 2.54 Hz, 1H), 8.07 (dd, J = 8.80, 2.74 Hz, 1H), 6.85 (d, J = 9.00 Hz, 1H), 4.60 (s, 2H), 3.94 (s, 3H), 3.38 (s, 2H), 2.52 (s, 3H).

4-(5-(Methoxymethyl)-2-(6-methoxypyridin-3-ylamino)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (37). A mixture of **73j** (109 mg, 0.19 mmol), potassium trifluoro(methoxymethyl)borate (34 mg, 0.22 mmol), X-Phos (8.9 mg, 0.019 mmol), $Pd(OAc)_2$ (2.1 mg, 9.3 μmol), and Cs_2CO_3 (182 mg, 0.56 mmol) in 1,4-dioxane (1.2 mL) and H_2O (0.12 mL) under N_2 was heated in a microwave reactor at 140 °C for 30 min. The mixture was filtered through a short plug of diatomaceous earth, washing with EtOAc, and the filtrate was concentrated and purified by silica gel column chromatography (gradient: 0% → 50% EtOAc/CH_2Cl_2) to give *N*,*N*-bis(4-methoxybenzyl)-4-(5-(methoxymethyl)-2-((6-methoxypyridin-3-yl)amino)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (**106a**) (37 mg, 33%) as a yellow solid. LC−MS m/z: 594 $(M + H)^+$.

The title compound was synthesized from **106a** (37 mg, 0.06 mmol), following an analogous deprotection procedure to that described for compound **36**, and isolated (5.7 mg, 26%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 11.73 (br s, 1H), 8.85 (d, J = 2.35 Hz, 1H), 8.37 (d, J = 2.35 Hz, 1H), 8.28 (d, J = 2.35 Hz, 1H), 8.11 (dd, J = 8.90, 2.45 Hz, 1H), 6.80 (d, J = 8.80 Hz, 1H), 5.41 (br s, 2H), 4.42 (s, 2H), 3.96 (s, 3H), 3.39 (s, 3H), 2.57 (s, 3H).

4-(2-(6-Methoxypyridin-3-ylamino)-5-morpholinopyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (39). A mixture of **73j** (100 mg, 0.17 mmol), $Pd(OAc)_2$ (5.8 mg, 0.03 mmol), X-Phos (49 mg, 0.10 mmol), Cs_2CO_3 (167 mg, 0.51 mmol), and morpholine (0.10 mL, 1.2 mmol) in toluene (2 mL) was stirred under Ar at 160 °C for 24 h. The mixture was allowed to cool to 22 °C and purified by silica gel column chromatography (gradient: 0% → 90% EtOAc/hexanes) to give *N*,*N*-bis(4-methoxybenzyl)-4-(2-(6-methoxypyridin-3-ylamino)-5-morpholinopyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (**106b**) (95.6 mg, 88%) as an orange solid. ^1H NMR (400 MHz, $CDCl_3$): δ 11.32 (br s, 1H), 8.44 (d, J = 2.93 Hz, 1H), 8.25 (d, J = 2.54 Hz, 1H), 8.06 (d, J = 2.93 Hz, 1H), 7.86 (dd, J = 8.80, 2.74 Hz, 1H), 7.21 (d, J = 8.41 Hz, 2H), 7.17 (d, J = 8.61 Hz, 2H), 6.87 (d, J = 8.41 Hz, 2H), 6.83 (d, J = 8.61 Hz, 2H), 6.68 (d, J = 8.80 Hz, 1H), 4.87 (s, 2H), 4.80 (s, 2H), 3.92 (s, 3H), 3.87−3.83 (m, 4H), 3.81 (s, 3H), 3.78 (s, 3H), 3.06−3.00 (m, 4H), 2.57 (s, 3H).

The title compound was synthesized from **106b** (110 mg, 0.17 mmol) following an analogous deprotection procedure to that described for compound **36** and isolated as an orange solid (10.3 mg, 15%). ^1H NMR (400 MHz, $CDCl_3$): δ 11.39 (br s, 1H), 8.49 (d, J = 3.13 Hz, 1H), 8.34 (d, J = 2.54 Hz, 1H), 8.10 (d, J = 2.74 Hz, 1H), 8.10−8.07 (m, 1H), 6.76 (d, J = 8.80 Hz, 1H), 5.38 (br s, 2H), 3.94 (s, 3H), 3.86−3.92 (m, 4H), 3.16−3.09 (m, 4H), 2.56 (s, 3H).

4-(5-(3,6-Dihydro-2*H*-pyran-4-yl)-2-(6-methoxypyridin-3-ylamino)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (40). A mixture of 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (64 mg, 0.31 mmol), **73j** (162 mg, 0.28 mmol), Pd_2dba_3 (10 mg, 0.01 mmol), and X-Phos (11 mg, 0.02 mmol) in 1,4-dioxane (3 mL) was purged with Ar and treated with 1.0 M aqueous $Na_2CO_3 \cdot H_2O$ (0.69 mL, 0.69 mmol). The mixture was heated at 140 °C in a microwave reactor for 30 min and then treated with 1 M aqueous NaOH (30 mL) and extracted with EtOAc (30 mL). The organic extract was washed with saturated brine, dried ($MgSO_4$), filtered, and concentrated to give 4-(5-(3,6-dihydro-2*H*-pyran-4-yl)-2-(6-methoxypyridin-3-ylamino)pyridin-3-yl)-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-1,3,5-triazin-2-amine (**106c**) (175 mg) as a bright-yellow crystalline solid.

The title compound was synthesized from **106c** (175 mg) following an analogous deprotection procedure to that described for compound **36** as a bright-yellow amorphous solid (38 mg, 35%). ^1H NMR (400 MHz, DMSO-d_6): δ 11.76 (s, 1H), 8.83 (d, J = 2.5 Hz, 1H), 8.54 (d, J = 2.7 Hz, 1H), 8.44 (d, J = 2.5 Hz, 1H), 8.17 (dd, J = 8.8, 2.7 Hz, 1H), 7.87 (br s, 1H), 7.73 (br s, 1H), 6.83 (d, J = 8.8 Hz, 1H), 6.22 (br s, 1H), 4.24 (d, J = 2.5 Hz, 2H), 3.87−3.82 (m, 5H), 2.47 (m, 2H), 2.44 (s, 3H).

4-(2-(6-Methoxypyridin-3-ylamino)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (41). The title compound (17.2 mg, 49%) was synthesized as an orange solid following a similar two step procedure to that described for **39** using **73j** (50 mg, 0.09 mmol) and 1-

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methylpiperazine (20 μL, 0.18 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.41 (br s, 1H), 8.51 (d, *J* = 2.93 Hz, 1H), 8.34 (d, *J* = 2.54 Hz, 1H), 8.11 (d, *J* = 2.93 Hz, 1H), 8.11−8.07 (m, 1H), 6.76 (d, *J* = 8.80 Hz, 1H), 5.34 (br s, 2H), 3.93 (s, 3H), 3.22 (br s, 4H), 2.71 (br s, 4H), 2.56 (s, 3H), 2.45 (br s, 3H).

5-(4-Amino-6-methyl-1,3,5-triazin-2-yl)-*N*-(6-methoxypyridin-3-yl)-6′-methyl-3,3′-bipyridin-6-amine (42). The title compound was synthesized as a yellow crystalline solid (57 mg, 56%) following a similar two step procedure to that described for **40** using **73j** (144 mg, 0.25 mmol) and 6-methylpyridin-3-ylboronic acid (40.5 mg, 0.30 mmol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.85 (s, 1H), 9.03 (d, *J* = 2.7 Hz, 1H), 8.77 (d, *J* = 2.2 Hz, 1H), 8.67 (d, *J* = 2.5 Hz, 1H), 8.56 (d, *J* = 2.7 Hz, 1H), 8.20 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.99 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.91 (br s, 1H), 7.77 (br s, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 3.86 (s, 3H), 2.52 (s, 3H), 2.46 (s, 3H).

4-(2-(6-Methoxypyridin-3-ylamino)-5-(1-methyl-*1H*-pyrazol-4-yl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (43). The title compound was synthesized as an orange crystalline solid (72 mg, 83%) following a similar two step procedure to that described for **40** using **73j** (97 mg, 0.17 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*1H*-pyrazole (42 mg, 0.20 mmol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.69 (s, 1H), 8.87 (d, *J* = 2.5 Hz, 1H), 8.55 (t, *J* = 3.1 Hz, 2H), 8.18 (dd, *J* = 8.8, 2.7 Hz, 1H), 8.12 (s, 1H), 7.90 (s, 1H), 7.82 (s, 1H), 7.77 (s, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.46 (s, 3H).

4-(2-(6-Methoxypyridin-3-ylamino)-5-((4-methylpiperazin-1-yl)methyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (51). A mixture of **73j** (160 mg, 0.27 mmol), X-Phos (13 mg, 0.03 mmol), Cs_2CO_3 (268 mg, 0.82 mmol), potassium 1-methyl-4-trifluoroboratomethylpiperazine (66 mg, 0.30 mmol), and $Pd(OAc)_2$ (3.1 mg, 0.014 mmol) in THF (1 mL) and H_2O (0.1 mL) was purged with Ar and heated in a microwave reactor at 140 °C for 30 min. The mixture was filtered through a short plug of diatomaceous earth, washing with EtOAc, and the filtrate was concentrated and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2) to give *N*,*N*-bis(4-methoxybenzyl)-4-(2-(6-methoxypyridin-3-ylamino)-5-((4-methylpiperazin-1-yl)methyl)-pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (**106g**) (161 mg, 89%) as a viscous yellow oil. LC−MS *m*/*z*: 662 $(M + H)^+$.

The title compound was synthesized from **106g** (175 mg, 0.28 mmol) as a yellow solid (98 mg, 96%) following an analogous deprotection procedure to that described for compound **36**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.74 (s, 1H), 8.69 (d, *J* = 2.15 Hz, 1H), 8.54 (d, *J* = 2.74 Hz, 1H), 8.33−8.00 (m, 2H), 7.86 (br s, 1H), 7.71 (br s, 1H), 6.82 (d, *J* = 8.80 Hz, 1H), 3.84 (s, 3H), 3.81−3.49 (m, 4H), 3.40 (s, 2H), 2.44 (s, 3H), 2.35 (m, 4H), 2.14 (s, 3H).

4-(5-Benzyl-2-(6-methoxypyridin-3-ylamino)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (61). A mixture of 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (90 mg, 0.41 mmol), **73j** (160 mg, 0.27 mmol), Pd_2dba_3 (12 mg, 0.014 mmol), X-Phos (13 mg, 0.027 mmol), and $Na_2CO_3·H_2O$ (73 mg, 0.69 mmol) in 1,4-dioxane (2.5 mL) and H_2O (0.25 mL) was purged with Ar and heated in a microwave reactor at 140 °C for 30 min. The mixture was filtered through a short plug of diatomaceous earth, washing with EtOAc. The filtrate was concentrated and purified by silica gel column chromatography (gradient: 0% → 30% EtOAc/hexanes) to give 4-(5-benzyl-2-(6-methoxypyridin-3-ylamino)pyridin-3-yl)-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-1,3,5-triazin-2-amine (**106h**) (110 mg, 63%) as a viscous yellow oil. LC−MS *m*/*z*: 640 $(M + H)^+$.

A solution of **106h** (110 mg, 0.17 mmol) in TFA (265 μL, 3.44 mmol) was treated with TfOH (15 μL, 0.17 mmol), and the mixture was heated at 80 °C for 16 h. The mixture was concentrated and purified by silica gel column chromatography (gradient: 0% → 3% 2 M NH_3 in MeOH/CH_2Cl_2) to give **61** (15 mg, 22%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.68 (s, 1H), 8.61 (d, *J* = 2.15 Hz, 1H), 8.53 (d, *J* = 2.54 Hz, 1H), 8.23 (d, *J* = 2.15 Hz, 1H), 8.16 (dd, *J* = 8.80, 2.74 Hz, 1H), 7.83 (br s, 1H), 7.69 (br s, 1H), 7.11−7.45 (m, 5H), 6.81 (d, *J* = 8.80 Hz, 1H), 3.94 (s, 2H), 3.84 (s, 3H), 2.41 (s, 3H).

4-(5-((2-Methoxyethylamino)methyl)-2-(6-methoxypyridin-3-ylamino)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (38). A solution of **103a** (240 mg, 0.42 mmol) in CH_2Cl_2 (2 mL) and MeOH (2 mL) was treated with 2-methoxyethanamine (54 μL, 0.62 mmol) and $NaBH(OAc)_3$ (264 mg, 1.25 mmol). The mixture was stirred for 2 h, concentrated, diluted with CH_2Cl_2 (100 mL), washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), dried (Na_2SO_4), and concentrated to give *N*,*N*-bis(4-methoxybenzyl)-4-(5-(((2-methoxyethyl)amino)methyl)-2-((6-methoxypyridin-3-yl)-amino)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (**107a**), which was used without further purification.

The **107a** thus obtained was deprotected using the procedure described for **36** to give **38** (37 mg, 22%) as a yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.63 (s, 1H), 8.78 (d, *J* = 2.54 Hz, 1H), 8.35 (d, *J* = 2.54 Hz, 1H), 8.24 (d, *J* = 2.54 Hz, 1H), 8.12 (dd, *J* = 8.80, 2.74 Hz, 1H), 6.77 (d, *J* = 8.80 Hz, 1H), 5.63 (s, 2H), 3.94 (s, 3H), 3.78 (s, 2H), 3.57−3.52 (m, 2H), 3.36 (s, 3H), 2.86−2.80 (m, 2H), 2.55 (s, 3H).

4-(5-(Azetidin-1-ylmethyl)-2-(6-methoxypyridin-3-ylamino)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (44). The title compound was synthesized as a yellow crystalline solid (11 mg, 7%) following the two step procedure described for **38** using **103a** (228 mg, 0.40 mmol) and azetidine hydrochloride (48 mg, 0.51 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.75 (s, 1H), 8.90 (d, *J* = 2.35 Hz, 1H), 8.37 (d, *J* = 2.74 Hz, 1H), 8.17 (d, *J* = 2.35 Hz, 1H), 8.08 (dd, *J* = 8.90, 2.64 Hz, 1H), 6.77 (d, *J* = 8.80 Hz, 1H), 3.94 (s, 3H), 3.76 (s, 2H), 3.53 (t, *J* = 7.34 Hz, 4H), 2.53 (s, 3H), 2.28 (quin, *J* = 7.38 Hz, 2H).

4-(2-(6-Methoxypyridin-3-ylamino)-5-(pyrrolidin-1-ylmethyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (45). The title compound was synthesized as a yellow crystalline solid (81 mg, 46%) following the two step procedure described for **38** using **103a** (257 mg, 0.45 mmol) and pyrrolidine (48 mg, 0.67 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.64 (s, 1H), 8.71 (d, *J* = 2.35 Hz, 1H), 8.36 (d, *J* = 2.54 Hz, 1H), 8.20 (d, *J* = 2.35 Hz, 1H), 8.13 (dd, *J* = 8.80, 2.74 Hz, 1H), 6.76 (d, *J* = 8.80 Hz, 1H), 6.33 (br s, 2H), 3.94 (s, 3H), 3.58 (s, 2H), 2.57 (br s, 4H), 2.54 (s, 3H), 1.90−1.80 (m, 4H).

4-(2-(6-Methoxypyridin-3-ylamino)-5-(piperidin-1-ylmethyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (46). The title compound was synthesized as a yellow crystalline solid (52 mg, 28%) following the two step procedure described for **38** using **103a** (264 mg, 0.46 mmol) and piperidine (68 μL, 0.69 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.64 (s, 1H), 8.72 (d, *J* = 2.35 Hz, 1H), 8.35 (d, *J* = 2.54 Hz, 1H), 8.21 (d, *J* = 2.35 Hz, 1H), 8.14 (dd, *J* = 8.90, 2.84 Hz, 1H), 6.77 (d, *J* = 9.00 Hz, 1H), 5.56 (br s, 2H), 3.94 (s, 3H), 3.45 (s, 2H), 2.56 (s, 3H), 2.41 (br s, 3H), 1.60 (dt, *J* = 10.95, 5.48 Hz, 5H), 1.46−1.39 (m, 2H).

4-(2-(6-Methoxypyridin-3-ylamino)-5-(morpholinomethyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (47). Morpholine (18 μL, 0.20 mmol) and AcOH (4 μL, 0.07 mmol) were added to a suspension of **103b** (25 mg, 0.07 mmol) in EtOH (3 mL), the mixture was stirred at 22 °C for 1 h, and then $NaBH_3(CN)$ (4.3 mg, 0.07 mmol) was added. The mixture was stirred for 16 h, diluted with H_2O (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated brine, dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (gradient: 0% → 10% MeOH/CH_2Cl_2) to give *N*-(6-methoxypyridin-3-yl)-3-(4-methyl-6-(methylthio)-1,3,5-triazin-2-yl)-5-(morpholinomethyl)pyridin-2-amine (**107e**) (19 mg, 64%) as a yellow solid. LC–MS *m*/*z*: 440 $(M + H)^+$.

A mixture of **107e** (19 mg, 0.04 mmol) in 2.0 M NH_3/*i*-PrOH (3 mL) was heated at 90 °C for 24 h. The reaction mixture was concentrated and purified by silica gel column chromatography (gradient: 0% → 5% MeOH/CH_2Cl_2) to give **47** (6.0 mg, 34%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, with one drop of DMSO-d_6): δ 11.69 (br s, 1H), 8.76 (br s, 1H), 8.39 (br s, 1H), 8.23 (br s, 1H), 8.12 (br s, 1H), 6.77 (d, *J* = 9.00 Hz, 1H), 5.92 (br s, 2H), 3.93 (br s, 3H), 3.49 (br s, 2H), 2.55 (br s, 3H), 2.50 (br s, 4H), 2.23 (br s, 4H).

(*R*)-(1-((5-(4-Amino-6-methyl-1,3,5-triazin-2-yl)-6-(6-methoxypyridin-3-ylamino)pyridin-3-yl)methyl)-pyrrolidin-3-yl)methanol (49). The title compound was synthesized as a pale-yellow solid (65 mg, 28%) following the two step procedure described for **38** using **103a** (310 mg, 0.54 mmol) and (*R*)-pyrrolidin-3-yl-methanol (0.16 mL, 1.6 mmol). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.83 (s, 1H), 10.12–10.01 (dd, *J* = 5.28, 2.35 Hz, 1H), 8.91 (dd, *J* = 5.28, 2.35 Hz, 1H), 8.54 (dd, *J* = 2.54, 0.39 Hz, 1H), 8.42 (dd, *J* = 3.72, 2.35 Hz, 1H), 8.15 (dd, *J* = 8.90, 2.84 Hz, 1H), 7.93 (d, *J* = 1.17 Hz, 1H), 7.82 (d, *J* = 0.78 Hz, 1H), 6.85 (d, *J* = 9.00 Hz, 1H), 4.38 (dd, *J* = 6.85, 0.39 Hz, 2H), 3.85 (s, 3H), 3.51–3.31 (m, 4H), 3.29–3.07 (m, 2H), 2.86–2.55 (m, 1H), 2.44 (s, 3H), 2.14–1.92 (m, 1H), 1.82–1.61 (m, 1H).

4-(2-(6-Methoxypyridin-3-ylamino)-5-((4-(methylsulfonyl)piperidin-1-yl)methyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (56). The title compound was synthesized as a yellow crystalline solid (87 mg, 52%) following the two step procedure described for **38** using **103a** (200 mg, 0.35 mmol) and 4-(methylsulfonyl)piperidine (85 mg, 0.52 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.67 (s, 1H), 8.71 (d, *J* = 2.15 Hz, 1H), 8.36 (d, *J* = 2.54 Hz, 1H), 8.18 (d, *J* = 2.35 Hz, 1H), 8.11 (dd, *J* = 9.00, 2.74 Hz, 1H), 6.77 (d, *J* = 8.80 Hz, 1H), 5.76 (s, 2H), 3.94 (s, 3H), 3.49 (s, 2H), 3.10 (d, *J* = 11.35 Hz, 2H), 2.86–2.80 (m, 4H), 2.55 (s, 3H), 2.18–2.00 (m, 4H), 2.00–1.84 (m, 3H).

4-(2-(6-Methoxypyridin-3-ylamino)-5-((4-(methylsulfonyl)-1,4-diazepan-1-yl)methyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (58). The title compound was synthesized as a yellow crystalline solid (25 mg, 12%) following the two step procedure described for **38** using **103a** (242 mg, 0.42 mmol) and 1-(methylsulfonyl)-1,4-diazepane hydrochloride (135 mg, 0.63 mmol). ^{1}H NMR (400 MHz, CD_3OD): δ 8.90 (d, *J* = 2.35 Hz, 1H), 8.45 (d, *J* = 2.74 Hz, 1H), 8.22 (d, *J* = 2.35 Hz, 1H), 8.02 (dd, *J* = 8.80, 2.74 Hz, 1H), 6.80 (d, *J* = 8.80 Hz, 1H), 3.97 (s, 2H), 3.91 (s, 3H), 3.59–3.51 (m, 2H), 3.47 (t, *J* = 6.26 Hz, 2H), 3.14–3.03 (m, 4H), 2.91 (s, 3H), 2.09–2.00 (m, 2H).

(±)-4-(2-(6-Methoxypyridin-3-ylamino)-5-((3-(methylsulfonyl)pyrrolidin-1-yl)methyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (59). The title compound was synthesized as a yellow crystalline solid (78 mg, 42%) following the two step procedure described for **38** using **103a** (230 mg, 0.40 mmol) and 3-(methylsulfonyl)pyrrolidine (89 mg, 0.60 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.63 (s, 1H), 8.73 (d, *J* = 2.35 Hz, 1H), 8.36 (d, *J* = 2.54 Hz, 1H), 8.21 (d, *J* = 2.15 Hz, 1H), 8.10 (dd, *J* = 8.80, 2.74 Hz, 1H), 6.78 (d, *J* = 8.80 Hz, 1H), 5.55 (br s, 2H), 3.94 (s, 3H), 3.68–3.56 (m, 3H), 3.05–2.99 (m, 1H), 2.95–2.88 (m, 1H), 2.87 (s, 3H), 2.84–2.76 (m, 1H), 2.70–2.61 (m, 1H), 2.56 (s, 3H), 2.35–2.25 (m, 2H).

1-((5-(4-Amino-6-methyl-1,3,5-triazin-2-yl)-6-(6-methoxypyridin-3-ylamino)pyridin-3-yl)methyl)piperidin-4-ol (48). A solution of **105** (510 mg, 0.78 mmol) in CH_2Cl_2 (25 mL) was treated with 4-hydroxypiperidine (254 mg, 2.51 mmol) and Et_3N (0.49 mL, 3.5 mmol). The resulting suspension was stirred for 16 h, diluted with H_2O (20 mL), and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (gradient: 5% → 20% 2 M NH_3 in MeOH/CH_2Cl_2) to give 1-((5-(4-(bis(4-methoxybenzyl)amino)-6-methyl-1,3,5-triazin-2-yl)-6-(6-methoxypyridin-3-ylamino)pyridin-3-yl)methyl)piperidin-4-ol (**108a**) (385 mg, 75%) as a yellow gum.

A solution of **108a** (310 mg, 468 mmol) in TFA (1 mL) and TfOH (0.2 mL) was stirred at 90 °C for 1 h. The solution was allowed to cool, concentrated, and diluted with 2 M aqueous NaOH (10 mL). The mixture was stirred for 10 min and then extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried, concentrated, and purified by silica gel column chromatography (gradient: 5% → 20% 2 M NH_3 in MeOH/CH_2Cl_2) to give **48** (120 mg, 61%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.75 (s, 1H), 8.68 (d, *J* = 0.78 Hz, 1H), 8.54 (d, *J* = 2.74 Hz, 1H), 8.18 (d, *J* = 2.74 Hz, 1H), 8.16 (t, *J* = 2.35 Hz, 1H), 7.87 (d, *J* = 1.37 Hz, 1H), 7.71 (br s, 1H), 6.83–6.80 (d, *J* = 9.00 Hz, 1H), 4.54 (d, *J* = 4.11 Hz, 1H), 3.84 (s, 3H), 3.38 (br s, 3H), 2.67 (dd, *J* = 4.60, 2.64 Hz, 2H), 2.44 (s, 3H), 1.99 (m, 2H), 1.69 (d, *J* = 3.33 Hz, 2H), 1.38 (d, *J* = 10.76 Hz, 2H).

4-((5-(4-Amino-6-methyl-1,3,5-triazin-2-yl)-6-((6-methoxypyridin-3-yl)amino)pyridin-3-yl)methyl)-thiomorpholine 1,1-Dioxide (60). A mixture of **105** (126 mg, 0.19 mmol), thiomorpholine 1,1-dioxide (78 mg, 0.58 mmol), and Et_3N (0.11 mL, 0.77 mmol) in THF (4 mL) was stirred at 80 °C for 4 h. The reaction mixture was diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25 mL), and the combined organic layers were dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (gradient: 25% → 100% EtOAc/hexanes) to give 4-((5-(4-(bis(4-methoxybenzyl)amino)-6-methyl-1,3,5-triazin-2-yl)-6-((6-methoxypyridin-3-yl)amino)pyridin-3-yl)methyl)-thiomorpholine 1,1-dioxide (**108b**) (80 mg, 60%) as a yellow oil.

Compound **108b** (80 mg, 0.115 mmol) was deprotected using the procedure described for **36** to give **60** (35 mg, 57%) as a yellow crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.76 (s, 1H), 8.75–8.67 (m, 1H), 8.54 (dd, *J* = 2.25, 0.49 Hz, 1H), 8.28–8.21 (m, 1H), 8.21–8.12 (m, 1H), 7.93–7.83 (m, 1H), 7.74 (br s, 1H), 6.82 (d, *J* = 8.80 Hz, 1H), 3.84 (s, 3H), 3.64 (s, 2H), 3.15–3.08 (m, 4H), 2.94–2.86 (m, 4H), 2.44 (s, 3H).

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5-((4-(*tert*-Butoxycarbonyl)piperazin-1-yl)methyl)-2-fluoropyridin-3-ylboronic acid (112). Benzoyl peroxide (1.57 g, 6.48 mmol) and NBS (23.2 g, 130 mmol) were added to a stirred solution of 2-fluoro-5-methylpyridine (14.4 g, 130 mmol) in CCl_4 (125 mL), and the suspension was heated at reflux for 2 h. After cooling, the solution was filtered, concentrated, and purified by silica gel column chromatography (gradient: 0% → 10% EtOAc/hexanes) to give 5-(bromomethyl)-2-fluoropyridine (**110**) (15.10 g, 61%) as a yellow solid. LC−MS m/z: 191 $(M + H)^+$.

tert-Butyl piperazine-1-carboxylate (17.8 g, 95 mmol) was added to a stirred solution of **110** (15.1 g, 80 mmol) in DMF (120 mL) at 0 °C, and the suspension was stirred at room temperature for 16 h. The reaction was quenched with cold H_2O (50 mL), the resulting suspension was stirred for 30 min, and the resulting solid was collected by filtration, washing with cold H_2O (50 mL). The off-white precipitate was dried under vacuum to give *tert*-butyl 4-((6-fluoropyridin-3-yl)methyl)-piperazine-1-carboxylate (**111**) (19.8 g, 84%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.13 (s, 1H), 7.90 (dt, J = 8.02, 1.37 Hz, 1H), 7.15 (dd, J = 8.31, 2.05 Hz, 1H), 3.51 (s, 2H), 3.30 (br s, 4H), 2.40−2.10 (m, 4H), 1.39 (s, 9H).

2.5 M *n*-BuLi in hexanes (36 mL, 90 mmol) was added dropwise to a solution of *i*-Pr_2NH (12.8 mL, 90 mmol) in THF (150 mL, 75 mmol) at −40 °C, and the pale-yellow solution of LDA was stirred for 1 h and then cooled to −78 °C. A solution of **111** (22.2 g, 75 mmol) in THF (100 mL) was added dropwise via cannula into the LDA solution over 30 min. The brown mixture was stirred at −78 °C for 1.5 h, and then a solution of $(i\text{-PrO})_3B$ (26 mL, 113 mmol) in THF (50 mL) was added slowly. The resulting mixture was stirred at −78 °C for 30 min, and then the cooling bath was removed. After the reaction mixture had warmed up to 22 °C, the yellow mixture was quenched with 1.0 M aqueous NaOH (50 mL) and stirred for an additional 30 min. The separated aqueous layer was carefully treated with 5 M aqueous HCl until acidic (pH ∼4−5), and the resulting cloudy mixture was diluted with EtOAc (150 mL). The separated aqueous layer was extracted with EtOAc (2 × 150 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated to give **112** (21.9 g, 86%) as a pale-yellow solid. LC−MS m/z: 340 $(M + H)^+$.

***tert*-Butyl 4-((5-(4-(Bis(4-methoxybenzyl)amino)-6-methyl-1,3,5-triazin-2-yl)-6-fluoropyridin-3-yl)methyl)-piperazine-1-carboxylate (113a).** A mixture of **66** (27.0 g, 70 mmol), **112** (28.6 g, 84 mmol), KOAc (17.2 g, 175 mmol), and $Pd(Amphos)_2Cl_2$ (2.59 g, 3.65 mmol) in 1,4-dioxane (300 mL) and H_2O (60 mL) was stirred at 100 °C for 16 h under N_2. The mixture was concentrated to remove most of the 1,4-dioxane and then partioned between H_2O (250 mL) and EtOAc (500 mL). The organic layer was washed with H_2O (250 mL), dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (gradient: 10% → 50% EtOAc/hexanes) to give **113a** (37.3 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (dt, J = 9.05, 1.34 Hz, 1H), 8.24 (d, J = 1.37 Hz, 1H), 7.22 (dd, J = 7.82, 7.24 Hz, 4H), 6.86 (t, J = 8.90 Hz, 4H), 4.81 (d, J = 4.30 Hz, 4H), 3.80 (d, J = 7.43 Hz, 6H), 3.41 (dd, J = 5.18, 4.79 Hz, 4H), 2.54 (s, 4H), 2.40 (d, J = 5.09 Hz, 4H), 1.45 (s, 9H).

***tert*-Butyl 4-((6-Fluoro-5-(4-methyl-6-(methylthio)-1,3,5-triazin-2-yl)pyridin-3-yl)methyl)piperazine-1-carboxylate (113b).** 1,4-Dioxane (15 mL) and H_2O (3 mL) were added to a mixture of **68a** (560 mg, 3.19 mmol), **112** (1.03 g, 3.04 mmol), $Na_2CO_3{\cdot}H_2O$ (805 mg, 7.59 mmol), and $Pd(Ph_3P)_4$ (175 mg, 0.15 mmol). The suspension was heated at 80 °C for 16 h and filtered through a short plug of solid Na_2SO_4, washing with EtOAc, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (gradient: 0% → 30% EtOAc/hexanes) to give **113b** (968 mg, 74%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, J = 9.00 Hz, 1H), 8.30 (s, 1H), 3.58 (s, 2H), 3.44 (br s, 4H), 2.66 (s, 3H), 2.64 (s, 3H), 2.43 (d, J = 4.50 Hz, 4H), 1.46 (s, 9H).

***N*,*N*-Bis(4-methoxybenzyl)-4-(2-(6-methoxypyridin-3-ylamino)-5-(piperazin-1-ylmethyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (115a).** A 1.0 M solution of LiHMDS in THF (46.6 mL, 46.6 mmol) was added dropwise to a solution of **113a** (10.0 g, 15.5 mmol) and 3-amino-6-methoxypyridine (2.9 mL, 23 mmol) in THF (150 mL) at 0 °C. The mixture was stirred for 1 h and then quenched with H_2O (200 mL), diluted with saturated aqueous NH_4Cl (200 mL), and extracted with CH_2Cl_2 (1 × 400 mL; 3 × 200 mL). The combined organic extracts were washed with saturated brine (500 mL) and then dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (gradient: 5% → 50% EtOAc/hexanes) to give *tert*-butyl 4-((5-(4-(bis(4-methoxybenzyl)amino)-6-methyl-1,3,5-triazin-2-yl)-6-(6-methoxypyridin-3-ylamino)pyridin-3-yl)methyl)-piperazine-1-carboxylate (**114a**) (9.50 g, 82%). LC−MS m/z: 748 $(M + H)^+$.

A solution of **114a** (57.0 g, 76 mmol) in CH_2Cl_2 (200 mL) and TFA (200 mL) was stirred for 2 h and concentrated, and the residue was dissolved in CH_2Cl_2 (400 mL) and neutralized by slow addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give **115a** (45.6 g, 92%). This material was used without further purification. LC−MS m/z: 648 $(M + H)^+$.

4-(2-((6-Methoxypyridin-3-yl)amino)-5-(piperazin-1-ylmethyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (50). *Method A.* A 1.0 M solution of LiHMDS in THF (1.5 mL, 1.5 mmol) was added to a solution of **113b** (220 mg, 0.51 mmol) and 3-amino-6-methoxypyridine (94 mg, 0.76 mmol) in THF (3 mL) at 0 °C, and the mixture was stirred for 1 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (10 mL), H_2O (10 mL), and EtOAc (10 mL). The separated aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic layers were washed with saturated brine, dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (gradient: 0% → 50% EtOAc/hexanes) to give *tert*-butyl 4-((6-(6-methoxypyridin-3-ylamino)-5-(4-methyl-6-(methylthio)-1,3,5-triazin-2-yl)pyridin-3-yl)methyl)piperazine-1-carboxylate (**114b**) (133 mg, 49%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.42 (s, 1H), 8.81 (br s, 1H), 8.36 (d, J = 2.74 Hz, 1H), 8.27 (br s, 1H), 8.10 (dd, J = 8.71, 2.64 Hz, 1H), 6.79 (d, J = 8.80 Hz, 1H), 3.95 (s, 3H), 3.50 (s, 2H), 3.43 (br s, 4H), 2.67 (s, 3H), 2.66 (br s, 3H), 2.42 (br s, 4H), 1.45 (s, 9H).

TFA (2 mL) was added to a stirred mixture of **114b** (66 mg, 0.12 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at 22 °C for 1 h. The reaction mixture was concentrated, diluted with saturated aqueous $NaHCO_3$ (20 mL each), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated brine, dried (Na_2SO_4), and concentrated to give **115b**. This material was treated with a 2.0 M solution of NH_3 in *i*-PrOH (2 mL, 4 mmol), and the reaction vessel was sealed and heated at 90 °C for 16 h. The mixture was

concentrated and purified by silica gel column chromatography (gradient: 0% → 10% MeOH/CH_2Cl_2), followed by washing the isolated solid with Et_2O and EtOAc, to give **50** (2.5 mg, 13%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.74 (br s, 1H), 8.69 (br s, 1H), 8.55 (br s, 1H), 8.19 (br s, 1H), 8.16 (br s, 1H), 7.87 (br s, 1H), 7.72 (br s, 1H), 6.82 (d, J = 8.41 Hz, 1H), 4.21−3.94 (m, 2H), 3.84 (br s, 3H), 3.42 (d, J = 13.50 Hz, 4H), 2.84 (br s, 4H), 2.45−2.40 (m, 3H), 2.32 (br s, 1H).

4-(2-((6-Methoxypyridin-3-yl)amino)-5-(piperazin-1-ylmethyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (50). *Method B.* The title compound was alternatively prepared (250 mg, 79%) from **115a** (500 mg, 0.77 mmol) following the deprotection procedure described for **36**.

Methyl 4-((5-(4-Amino-6-methyl-1,3,5-triazin-2-yl)-6-(6-methoxypyridin-3-ylamino)pyridin-3-yl)methyl)-piperazine-1-carboxylate (52). A solution of **50** (500 mg, 1.23 mmol) and Et_3N (0.51 mL, 3.7 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C and treated with methyl chloroformate (0.19 mL, 2.45 mmol), and the suspension was stirred at 0 °C for 1 h. The mixture was concentrated and purified by silica gel column chromatography (gradient: 2% → 10% 2 M NH_3 in MeOH/CH_2Cl_2) to give **52** (160 mg, 28%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.75 (s, 1H), 8.70 (d, J = 1.96 Hz, 1H), 8.54 (d, J = 2.54 Hz, 1H), 8.18 (s, 1H), 8.16 (d, J = 2.74 Hz, 1H), 7.87 (s, 1H), 7.71 (s, 1H), 6.82 (d, J = 8.80 Hz, 1H), 3.84 (s, 3H), 3.58 (s, 3H), 3.44 (s, 2H), 3.39−3.33 (m, 4H), 2.44 (s, 3H), 2.38−2.30 (m, 4H).

4-((5-(4-Amino-6-methyl-1,3,5-triazin-2-yl)-6-((6-methoxypyridin-3-yl)amino)pyridin-3-yl)methyl)-*N*,*N*-dimethylpiperazine-1-carboxamide (53). A solution of **115a** (320 mg, 0.50 mmol) in CH_2Cl_2 (25 mL) was treated with Et_3N (0.69 mL, 5.0 mmol) and dimethylcarbamyl chloride (0.14 mL, 1.5 mmol). The solution was stirred at 22 °C for 16 h and then concentrated to give **116** as a yellow oil, which was used directly without further purification.

The crude **116** was deprotected following the procedure described for **36** to give **53** (315 mg) as a green solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.75 (s, 1H), 8.72−8.67 (m, 1H), 8.56−8.50 (m, 1H), 8.20−8.16 (m, 1H), 8.15 (dd, J = 2.25, 0.49 Hz, 1H), 7.88−7.83 (m, 1H), 7.73−7.66 (m, 1H), 6.81 (d, J = 9.00 Hz, 1H), 3.84 (s, 3H), 3.43 (br s, 2H), 3.09 (dd, J = 4.89, 4.30 Hz, 4H), 2.71 (s, 6H), 2.43 (s, 3H), 2.40−2.26 (m, 4H).

4-(2-((6-Methoxypyridin-3-yl)amino)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (54). A solution of **115a** (3.20 g, 4.94 mmol) and Et_3N (6.9 mL, 49 mmol) in CH_2Cl_2 (65 mL) was stirred at −15 to −10 °C and treated dropwise with MsCl (1.2 mL, 15 mmol). The resulting solution was stirred at −10 °C for 1 h. The solution was concentrated and purified by silica gel column chromatography (gradient: 0% → 10% 2 M NH_3 in MeOH/CH_2Cl_2) to give *N*,*N*-bis(4-methoxybenzyl)-4-(2-(6-methoxypyridin-3-ylamino)-5-((4-(methylsulfonyl)-piperazin-1-yl)methyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (**117**) (3.01 g, 84%) as light-yellow solid.

A solution of **117** (2.70 g, 3.72 mmol) in TFA (2 mL, 27 mmol) and TfOH (50 μL, 3.7 mmol) was stirred at 80 °C for 4 h. The dark solution was concentrated to a slurry and neutralized with saturated aqueous $NaHCO_3$. The resulting precipitate was collected by filtration and washed with H_2O (50 mL). The aqueous washings were extracted with CH_2Cl_2 (3 × 50 mL), dried (Na_2SO_4), filtered, and concentrated. The combined solids were purified by silica gel column chromatography (gradient: 0% → 10% MeOH/CH_2Cl_2), and the resulting product was suspended in *i*-PrOH (20 mL) and sonicated for 35 min. The solid was collected by filtration and dried to give **54** (1.41 g, 78%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.76 (d, J = 1.96 Hz, 1H), 8.70 (d, J = 1.76 Hz, 1H), 8.54 (br s, 1H), 8.19 (b, 2H), 7.87 (br s, 1H), 7.73 (d, J = 3.13 Hz, 1H), 6.83 (br s, 1H), 3.84 (br s, 3H), 3.48 (d, J = 2.15 Hz, 2H), 3.33 (d, J = 2.15 Hz, 3H), 3.10 (dd, J = 4.60, 2.25 Hz, 4H), 2.87 (d, J = 2.15 Hz, 3H), 2.44 (d, J = 0.78 Hz, 3H).

4-((5-(4-Amino-6-methyl-1,3,5-triazin-2-yl)-6-((6-methoxypyridin-3-yl)amino)pyridin-3-yl)methyl)-*N*,*N*-dimethylpiperazine-1-sulfonamide (55). A mixture of **115a** (520 mg, 0.80 mmol) and Et_3N (1.1 mL, 8.0 mmol) in CH_2Cl_2 (50 mL) was stirred at 0 °C and treated dropwise with dimethylsulfamoyl chloride (0.26 mL, 2.4 mmol). The mixture was stirred for 2 h, concentrated, and purified by silica gel column chromatography (gradient: 5% → 50% EtOAc/hexanes) to give 4-((5-(4-(bis(4-methoxybenzyl)amino)-6-methyl-1,3,5-triazin-2-yl)-6-(6-methoxypyridin-3-ylamino)-pyridin-3-yl)methyl)-*N*,*N*-dimethylpiperazine-1-sulfonamide (**118**) (250 mg, 41%). LC−MS m/z: 755 $(M + H)^+$.

Compound **118** (210 mg, 0.28 mmol) was deprotected following the procedure described for **36** to give **55** (110 mg, 77%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.75 (s, 1H), 8.70 (d, J = 2.15 Hz, 1H), 8.55 (d, J = 0.39 Hz, 1H), 8.19 (d, J = 2.54 Hz, 2H), 8.17 (dd, J = 8.90, 2.84 Hz, 1H), 7.86 (d, J = 0.98 Hz, 1H), 7.71 (d, J = 1.76 Hz, 1H), 6.82 (d, J = 8.80 Hz, 1H), 3.84 (s, 3H), 3.47 (s, 2H), 3.31 (s, 2H), 3.16 (d, J = 4.89 Hz, 3H), 2.75 (s, 6H), 2.47 (s, 2H), 2.44 (s, 3H).

4-(2-((6-Methoxypyridin-3-yl)amino)-5-((1-(methylsulfonyl)piperidin-4-yl)methyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (57). *tert*-Butyl 4-methylene-piperidine-1-carboxylate (**119**) (117 mg, 0.59 mmol) was treated with a 0.5 M solution of 9-BBN in THF (1.18 mL, 0.59 mmol), and the mixture was heated at reflux for 4 h. The resulting solution was transferred into a stirred mixture of **73j** (288 mg, 0.49 mmol), $Pd_2(dba)_3$ (23 mg, 0.03 mmol), X-Phos (24 mg, 0.05 mmol), and $Na_2CO_3 \cdot H_2O$ (131 mg, 1.23 mmol) in 1,4-dioxane (1 mL) and H_2O (0.25 mL). The mixture was heated in a microwave reactor at 140 °C for 30 min. The resulting mixture was filtered through a short plug of diatomaceous earth, washing with EtOAc (3 × 10 mL). The filtrate was concentrated and purified by silica gel column chromatography (gradient: 0% → 30% EtOAc/hexanes) to give *tert*-butyl 4-((5-(4-(bis(4-methoxybenzyl)amino)-6-methyl-1,3,5-triazin-2-yl)-6-(6-methoxypyridin-3-ylamino)pyridin-3-yl)methyl)piperidine-1-carboxylate (**120**) (261 mg, 71% yield) as a viscous yellow oil. LC−MS m/z: 747 $(M + H)^+$.

TFA (4 mL, 52 mmol) was slowly added to a solution of **120** (261 mg, 0.35 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at 22 °C for 1 h. The mixture was concentrated to remove as much TFA as possible. The sticky residue (**121**) was dissolved in CH_2Cl_2 (10 mL), and Et_3N (0.49 mL, 3.5 mmol) followed by MsCl (82 μL, 1.05 mmol) were slowly added at 0 °C. The mixture was stirred for 1 h and then concentrated. The crude product was partitioned between 1 M aqueous NaOH (20 mL) and CH_2Cl_2 (20 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with saturated brine (20 mL), dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (gradient: 10% → 50%

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EtOAc/hexanes) to give *N*,*N*-bis(4-methoxybenzyl)-4-(2-(6-methoxypyridin-3-ylamino)-5-((1-(methylsulfonyl)piperidin-4-yl)methyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (**122**) (192 mg, 76%) as a yellow film. LC−MS *m*/*z*: 725 $(M + H)^+$.

Compound **57** (88 mg, 69%) was prepared as a yellow solid from **122** (192 mg, 0.26 mmol) following the deprotection procedure described for **36**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.66 (s, 1H), 8.60 (d, J = 2.54 Hz, 1H), 8.54 (d, J = 2.54 Hz, 1H), 8.17 (dd, J = 8.90, 2.64 Hz, 1H), 8.14 (d, J = 2.15 Hz, 1H), 7.84 (br s, 1H), 7.71 (br s, 1H), 6.81 (d, J = 8.80 Hz, 1H), 3.84 (s, 3H), 3.62−3.45 (m, 2H), 2.82 (s, 3H), 2.72−2.61 (m, 2H), 2.43 (s, 3H), 1.68−1.67 (m, 2H), 1.64−1.46 (m, 1H), 1.32−1.15 (m, 2H).

4-(2-(6-Methoxypyridin-3-ylamino)-5-(4-(methylsulfonyl)benzyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (62). Magnesium turnings (214 mg, 8.79 mmol) in a minimal amount of THF were treated with 1,2-dibromoethane (50 μL, cat.), and the mixture was allowed to stand until effervescence was observed (1 min). A solution of 4-bromothioanisole (1.71 g, 8.39 mmol) in THF (20 mL) was added dropwise, and the mixture was stirred for 2 h, occasionally heating to reflux with a heat gun, to give a cloudy pale-yellow solution. The resulting Grignard solution was added dropwise over 10 min to a solution of 6-fluoronicotinaldehyde (**67**) (1.00 g, 7.99 mmol) in THF (10 mL) cooled in a dry ice−acetone bath. The mixture was stirred at −78 °C for 30 min, and then the reaction was quenched by the dropwise addition of 2 M aqueous HCl (9 mL, 18 mmol). The cooling bath was removed, and the mixture was allowed to warm to ambient temperature. The mixture was extracted into EtOAc (3 × 200 mL) from H_2O (500 mL), dried ($MgSO_4$), and concentrated to give (6-fluoropyridin-3-yl)(4-(methylthio)-phenyl)methanol (**123**) (1.86 g, 93%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (s, 1H), 7.87 (t, J = 8.22 Hz, 1H), 7.32 (d, J = 8.02 Hz, 2H), 7.22 (d, J = 7.82 Hz, 2H), 7.11 (d, J = 8.41 Hz, 1H), 6.11 (br s, 1H), 5.78 (s, 1H), 2.44 (s, 3H).

A solution of **123** (1.86 g, 7.96 mmol) in CH_2Cl_2 (3 mL) was treated with TFA (2.6 mL, 34 mmol), resulting in a green solution. The mixture was stirred for 5 min, and then Et_3SiH (3.3 mL, 21 mmol) was added dropwise. The green color dissipated rapidly to give a straw-colored solution, and a brief exotherm was observed. The mixture was stirred for 30 min and then extracted into CH_2Cl_2 (3 × 100 mL) from saturated aqueous $NaHCO_3$ (100 mL). The organic extracts were dried ($MgSO_4$) and purified by silica gel column chromatography (gradient: 5% → 7.5% EtOAc/hexanes) to give 2-fluoro-5-(4-(methylthio)benzyl)pyridine (**124**) (1.67 g, 89%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.81 (t, J = 8.22 Hz, 1H), 7.20 (s, 4H), 7.10 (d, J = 8.41 Hz, 1H), 3.94 (s, 2H), 2.44 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6): δ −72.37 (s, 1F).

A solution of LiTMP was generated by dropwise addition of a 1.6 M solution of *n*-BuLi in hexanes (7.4 mL, 11.8 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (2.1 mL, 12 mmol) in THF (24 mL) cooled in an ice−water bath. The resulting yellow solution was stirred for 15 min. A solution of **124** (2.26 g, 9.67 mmol) and (*i*-PrO)$_3$B (4.5 mL, 20 mmol) in THF (30 mL) was cooled in a dry ice−acetone bath and treated dropwise via cannula with the above LiTMP solution over 15 min to give a yellow/brown solution. The solution was stirred at −78 °C for 1 h, and then it was slowly allowed to warm up to 22 °C over 1.5 h. The solution was stirred for an additional 1 h at 22 °C before being quenched with H_2O (50 mL) and stirred for 15 min. The layers were separated, and the organic phase was extracted with 1 M aqueous NaOH (3 × 50 mL). The organic phase was discarded, and the combined aqueous phases were treated with concentrated HCl to lower the pH to 5. Then, the aqueous phase was extracted with 10:1 CH_2Cl_2/MeOH (3 × 50 mL). The organic extracts were combined and concentrated to give 2-fluoro-5-(4-(methylthio)benzyl)pyridin-3-ylboronic acid (**125**) (1.89 g, 71%) as a waxy solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (br s, 2H), 8.14−8.11 (m, 1H), 7.90−7.85 (m, 1H), 7.20 (s, 4H), 3.91 (s, 2H), 2.44 (s, 3H). ^{19}F NMR (377 MHz, DMSO-d_6): δ −64.21 (s, 1F).

A mixture of **66** (2.37 g, 6.15 mmol), **125** (1.89 g, 6.83 mmol), $Pd(Amphos)_2Cl_2$ (224 mg, 0.32 mmol), and KOAc (2.72 g, 27.7 mmol) was suspended in EtOH (30 mL) and H_2O (7.5 mL). N_2 was bubbled through the suspension for about 20 s, and the mixture was then heated at 88 °C for 2.75 h. The reaction was allowed to cool to 22 °C, treated with H_2O (90 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (gradient: 80% CH_2Cl_2/hexanes → CH_2Cl_2 → 3.5% MeOH/CH_2Cl_2) to give 4-(2-fluoro-5-(4-(methylthio)benzyl)pyridin-3-yl)-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-1,3,5-triazin-2-amine (**126**) (2.84 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (dd, J = 9.00 Hz, 2.35 Hz, 1H), 8.14 (dd, J = 1.56 Hz, 1H), 7.24−7.18 (m, 6H), 7.13−7.09 (m, 2H), 6.90−6.83 (m, 4H), 4.81 (s, 2H), 4.78 (s, 2H), 3.99 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 2.53 (s, 3H), 2.46 (s, 3H).

A solution of **126** (625 mg, 1.07 mmol) in CH_2Cl_2 (11 mL) was cooled in an ice−water bath and treated with a solution of *m*-CPBA (557 mg, 3.23 mmol) in CH_2Cl_2 (17.5 mL). The reaction was allowed to warm to 22 °C and stirred for 35 min. The mixture was treated with saturated aqueous $NaHCO_3$ (25 mL) and saturated aqueous $Na_2S_2O_3$ (6 mL) and stirried for an additional 50 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (gradient: 0% → 2% MeOH/CH_2Cl_2) to give 4-(2-fluoro-5-(4-(methylsulfonyl)-benzyl)pyridin-3-yl)-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-1,3,5-triazin-2-amine (**127**) (540 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (dd, J = 8.90 Hz, 2.45 Hz, 1H), 8.16 (d, J = 1.76 Hz, 1H), 7.89 (d, J = 8.41 Hz, 2H), 7.40 (d, J = 8.22 Hz, 2H), 7.21 (d, J = 8.61 Hz, 4H), 6.90−6.82 (m, 4H), 4.82 (s, 2H), 4.79 (s, 2H), 4.13 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.03 (s, 3H), 2.54 (s, 3H).

A solution of **127** (503 mg, 0.82 mmol) and 3-amino-6-methoxypyridine (112 mg, 0.91 mmol) in THF (8 mL) was cooled to 0 °C, treated dropwise with a 1.0 M solution of LiHMDS in THF (2.5 mL, 2.5 mmol), and stirred for 40 min. The mixture was treated with ice−water (0.60 mL), diluted with CH_2Cl_2 (100 mL), dried (Na_2SO_4), filtered, concentrated, and purified by silica gel column chromatography (gradient: 0% → 2% MeOH/CH_2Cl_2) to give *N*,*N*-bis(4-methoxybenzyl)-4-(2-(6-methoxypyridin-3-ylamino)-5-(4-(methylsulfonyl)-benzyl)pyridin-3-yl)-6-methyl-1,3,5-triazin-2-amine (**128**) (412 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.58 (s, 1H), 8.61 (d, J = 2.35 Hz, 1H), 8.26 (d, J = 2.54 Hz, 1H), 8.13 (d, J = 2.35 Hz, 1H), 7.87 (dd, J = 8.90 Hz, 2.64 Hz, 1H), 7.81 (d, J = 8.22 Hz, 2H), 7.37 (d, J = 8.22 Hz, 2H), 7.21 (d, J = 8.61 Hz, 2H), 7.15 (d, J = 8.61 Hz, 2H), 6.87 (d, J = 8.61 Hz, 2H), 6.82 (d, J = 8.41 Hz, 2H), 6.70 (d, J = 8.80 Hz, 1H), 4.85 (s, 2H),

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4.77 (s, 2H), 4.00 (s, 2H), 3.93 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 2.98 (s, 3H), 2.57 (s, 3H).

A suspension of **128** (412 mg, 0.57 mmol) in TFA (6 mL, 78 mmol) was heated at 75 °C for 16 h. The mixture was concentrated and diluted first with saturated aqueous $NaHCO_3$ and then with 5 M aqueous NaOH to raise the pH to ∼8−9. The suspension was filtered, and the solid was washed with H_2O and purified by silica gel column chromatography (gradient: 3% → 5% MeOH/CH_2Cl_2). The resulting solid was suspended in MeOH (5 mL), filtered, and dried to give **62** (126 mg, 46%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.64 (s, 1H), 8.65 (d, J = 2.15 Hz, 1H), 8.36 (d, J = 2.35 Hz, 1H), 8.17 (d, J = 1.56 Hz, 1H), 8.11 (dd, J = 8.90 Hz, 2.25 Hz, 1H), 7.88 (d, J = 8.22 Hz, 2H), 7.42 (d, J = 7.82 Hz, 2H), 6.78 (d, J = 8.80 Hz, 1H), 5.36 (br s, 2H), 4.04 (s, 2H), 3.95 (s, 3H), 3.04 (s, 3H), 2.56 (s, 3H).

In Vitro Assays. Enzyme assays for PI3Kα, PI3Kβ, PI3Kγ, PI3Kδ, mTOR, hVPS34, and B-Raf, as well as the U-87 MG pAKT-inhibition cellular assay were performed as previously described.[14,37]

In Vivo Assays. A mouse liver PD assay and a mouse U-87 MG tumor xenograft efficacy study were performed in CD1 nude mice (Charles Rivers Laboratories) with compound **54** at the indicated doses and analyzed following the procedures previously described.[14]

Crystallography: Determination of p110γ Crystal Structures. Human p110γ (144−1102) was expressed, purified, and crystallized according to published procedures.[45] The inhibitor complex was obtained by soaking apo crystals for 20 h at room temperature in cryo solutions (mother liquor plus 20% glycerol) containing 1 mM compound (5% DMSO). Crystals were then flash frozen in liquid nitrogen prior to data collection. Diffraction data for p110γ + **54** was collected at the Advanced Photon Source, beamline 22-BM using λ = 1.0000 Å and a MAR 225 mm CCD detector. Data were reduced using the HKL software suite,[46] and the structures were solved by molecular replacement using apo human p110γ as a search model (PDB ID 1E8Y). Structures were refined using REFMAC,[47,48] and model building was performed with COOT.[49]

■ ASSOCIATED CONTENT

Supporting Information

Tabulated structure, enzyme, cell, and rat/human microsomal stability data; cell permeability and kinase selectivity data for select compounds; analytical HPLC methods; kinase selectivity data for compounds **5**, **7**, **8**, **10**−**12**, and **54**; and X-ray cocrystal data for compound **54** with PI3Kγ. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

Amphos, di-*tert*-butyl(4-dimethylaminophenyl)phosphine; *m*-CPBA, 3-chloroperoxybenzoic acid; CSA, (±)-camphorsulfonic acid; DMSO, methyl sulfoxide; HGF, hepatocyte growth factor; HPLC, high performance liquid chromatography; LC−MS, liquid chromatography−mass spectrometry; LDA, lithium diisopropylamide; LiHMDS, lithium bis(trimethylsilyl)amide; MP-TsOH, macroporous polystyrene-supported *p*-toluenesulfonic acid; mTOR, mammalian target of rapamycin; NBS, *N*-bromosuccinimide; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homologue; PTFE, polytetrafluoroethylene; TFA, trifluoroacetic acid; TfOH, trifluoromethanesulfonic acid; THP, tetrahydro-2*H*-pyranyl; TLC, thin layer chromatography; TsOH, *p*-toluenesulfonic acid; X-Phos, dicyclohexyl(2′,4′,6′-triisopropylbiphenyl-2-yl)phosphine

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