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Discovery and Optimization of a Novel Series of Potent Mutant B-Raf^{V600E} Selective Kinase Inhibitors

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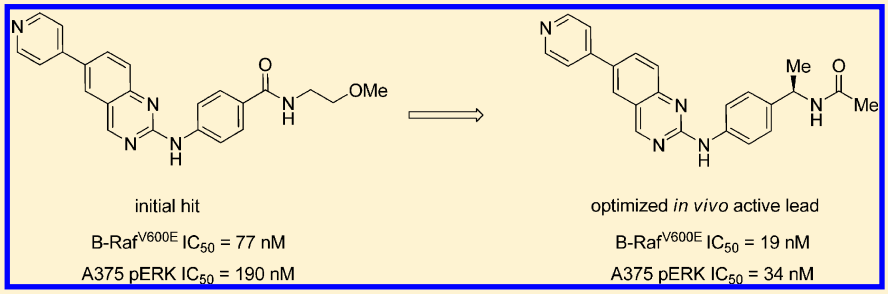
Supporting Information



ABSTRACT: B-Raf represents an attractive target for anticancer therapy and the development of small molecule B-Raf inhibitors has delivered new therapies for metastatic melanoma patients. We have discovered a novel class of small molecules that inhibit mutant B-Raf^{V600E} kinase activity both in vitro and in vivo. Investigations into the structure−activity relationships of the series are presented along with efforts to improve upon the cellular potency, solubility, and pharmacokinetic profile. Compounds selectively inhibited B-Raf^{V600E} in vitro and showed preferential antiproliferative activity in mutant B-Raf^{V600E} cell lines and exhibited selectivity in a kinase panel against other kinases. Examples from this series inhibit growth of a B-Raf^{V600E} A375 xenograft in vivo at a well-tolerated dose. In addition, aminoquinazolines described herein were shown to display pERK elevation in nonmutant B-Raf cell lines in vitro.

INTRODUCTION

The Raf family of intracellular serine/threonine protein kinases is involved in the transmission of proliferative signals from cell surface receptors to the cell nucleus through the mitogen-activated protein kinase (MAPK) pathway.[1] The RAS/RAF/MEK/ERK pathway plays a key role in many cancers and is activated in approximately 30% of all human tumors.[2] B-Raf somatic missense mutations have been reported in 66% of malignant melanomas and in a lower occurrence in a wide range of human cancers, with the most prevalent mutation V600E found to be constitutively active in carcinoma cells.[3] Selectively targeting the mutant form of B-Raf with small molecule inhibitors has been of great interest as a potential therapeutic strategy. The 2011 FDA approval of vemurafenib (PLX4032/RG7204, Plexxikon/Roche)[4−7] for the treatment of metastatic melanoma bearing the B-Raf^{V600E} mutation confirmed the importance of B-Raf within the MAPK pathway and advanced the treatment options for melanoma patients. Numerous other clinical and preclinical small molecule inhibitors have been published contributing to this field, further supporting the interest by many in the broader therapeutic potential for B-Raf inhibitors.[8−10]

We have reported previously an amidoheteroaryl class of compounds to be potent inhibitors of mutant B-Raf^{V600E} with in vivo activity.[11] Compound **1** represents one such example that potently inhibits B-Raf^{V600E} both in vitro (B-Raf ^{V600E} IC_{50} = 16 nM and A375 pERK IC_{50} = 40 nM, Figure 1) and in vivo. We also identified additional compounds such as **2** (AZ628)[12] to be potent inhibitors of mutant B-Raf^{V600E} (B-Raf ^{V600E} IC_{50} = 34 nM and A375 pERK IC_{50} = 15 nM, Figure 1), and **2** has been reported by us and others for its ability to modulate the MAPK pathway.[13] Examples such as **1** and **2** are believed to bind to mutant B-Raf^{V600E} in its DFG-out conformation.[14] As part of our screening efforts within AstraZeneca to identify inhibitors of B-Raf, we screened a subset of our collection which was biased

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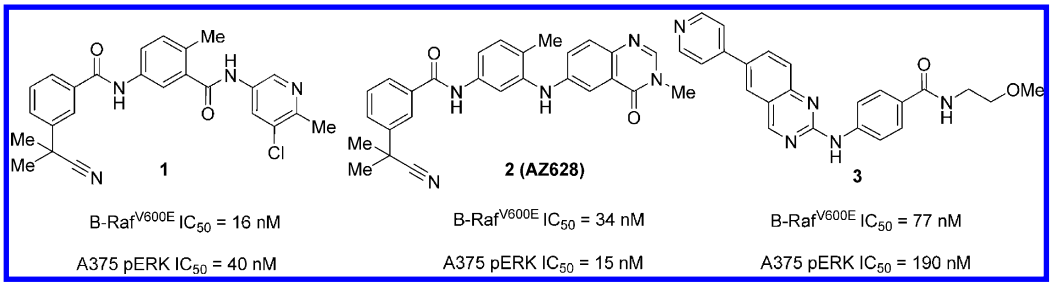
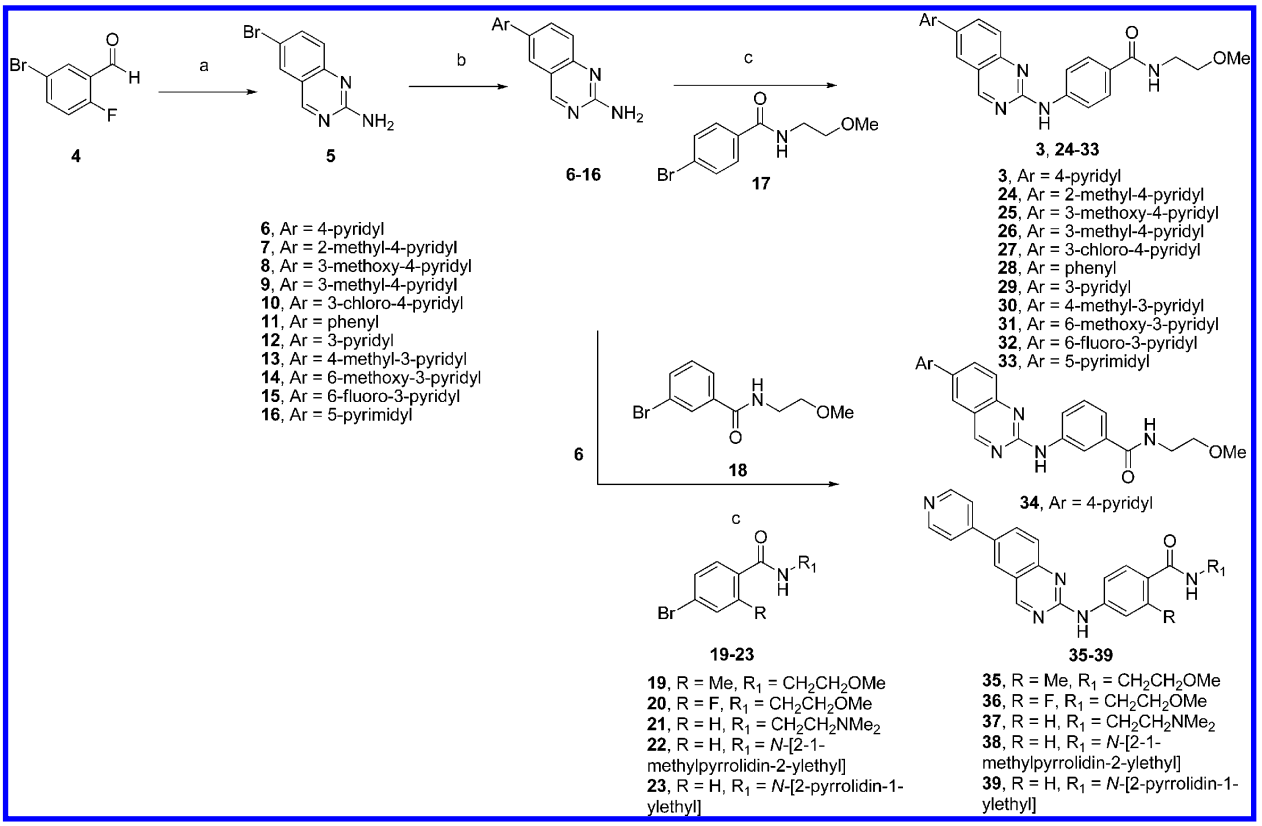


Figure 1. AstraZeneca B-Raf inhibitors **1**–**3**.

Scheme 1. Preparation of Aminoquinazolines 3 and 24–39[a]



[a]Reagents and conditions: (a) guanidine carbonate, DMA, 140 °C; (b) Pd(PPh$_3$)$_4$ (20 mol %), K$_2$CO$_3$, ArB(OH)$_2$, DME/water, 90 °C; (c) **17**–**23**, Pd$_2$(dba)$_3$ (5 mol %), BINAP (10 mol %), Cs$_2$CO$_3$, dioxane, 100 °C.

toward small molecules known or expected to contain kinase inhibitors. Aminoquinazoline **3** was identified as a singleton hit from this effort and displayed reasonable biochemical (B-Raf^{V600E} IC$_{50}$ = 77 nM) and cellular potency (A375 pERK IC$_{50}$ = 190 nM), as shown in Figure 1. In contrast to previous inhibitors **1** and **2**, the hit **3** was at least 5-fold less potent based on pERK cellular potency. However, we did believe **3** represented an excellent starting point for further optimization.

In this paper, we describe our efforts to further expand and optimize the aminoquinazoline hit **3** into a DFG-in binding inhibitor of mutant B-Raf^{V600E}. Examples from this inhibitor class were optimized for cellular potency, physical properties, and rat pharmacokinetics, resulting in examples with potent in vivo activity in A375 xenograft models. We likewise found that the aminoquinazoline compounds represented herein exhibited a mutant B-Raf^{V600E} selective profile based on biochemical activity and preferential cell panel antiproliferative activity over a range of cell lines. The B-Raf^{V600E} selective nature of the compounds was found to elevate pERK in nonmutant B-Raf cell lines in vitro, a phenomenon which has been previously documented by others in the literature as resulting from Raf dimerization events.[15] Aminoquinazolines presented herein represent a new class of B-Raf^{V600E} selective inhibitors that provide a complementary profile to those we had previously reported (**1** and **2**), thus serving as additional B-Raf^{V600E} selective tool compounds to further interrogate the important role of mutant B-Raf within the MAPK pathway.

Synthetic Chemistry. Aminoquinazolines were readily accessed using the following synthetic route (Scheme 1). Commercially available aldehyde **4** was converted to 6-bromoaminoquinazoline **5** by treatment with guanidine carbonate heating in DMA followed by Suzuki coupling with a variety of boronic acids to afford amino derivatives **6**–**16**. Palladium-catalyzed coupling with the corresponding aryl bromides generated the final aminoquinazoline analogs **3** and **24**–**39** (Tables 1 and 2).

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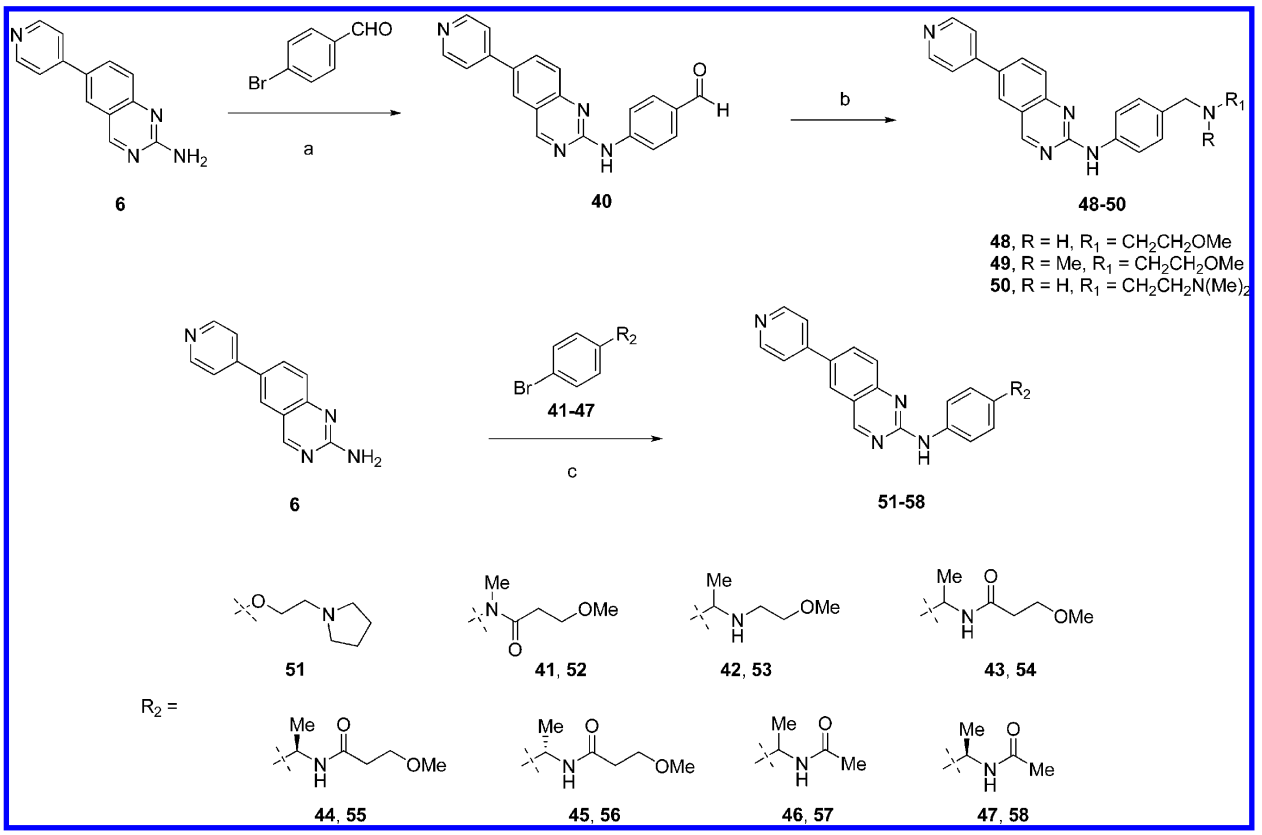
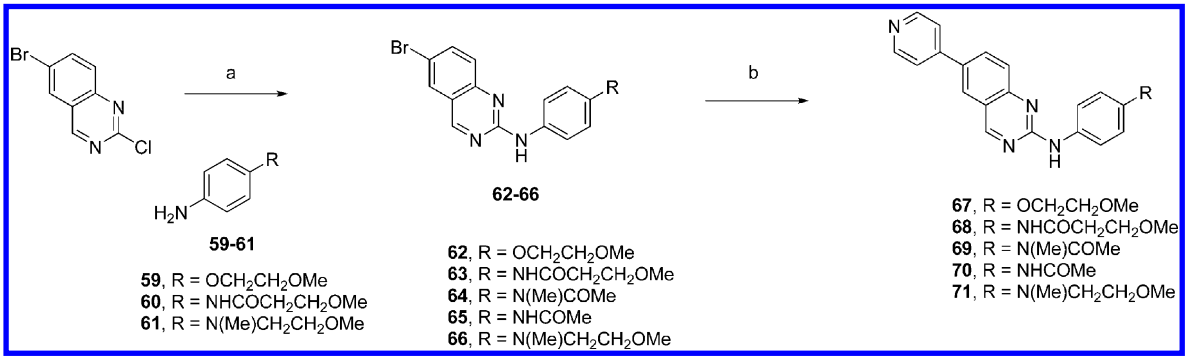
Scheme 2. Preparation of Aminoquinazolines 48−50 and 51−58[a]



[a]Reagents and conditions: (a) $Pd_2(dba)_3$ (10 mol %), BINAP (20 mol %), Cs_2CO_3, dioxane, 100 °C; (b) amine (1.1 equiv), MeOH, 3 Å MS, HOAc (catalytic amount), $NaBH_3CN$ (1.6 equiv), rt, 12 h then 1 N NaOH; (c) **41−47**, Xantphos (10 mol %), Cs_2CO_3 (3.0 equiv), dioxane, $Pd(OAc)_2$,160 °C, microwave. For preparation of **51** and **53**, see the Experimental Section. 1-[2-(4-Bromophenoxy)ethyl]pyrrolidine was commercially available.

Scheme 3. Preparation of Aminoquinazolines 67−71[a]



[a]Reagents and conditions: (a) method A or B [method A, *N*-(4-aminophenyl)-*N*-methylacetamide or *N*-(4-aminophenyl)acetamide (1.5 equiv), MeCN, 125 °C, microwave, 30 min; method B, **59−61**, propan-2-ol, 100 °C, 2 h]; (b) 4-pyridinylboronic acid (1.5 equiv), Cs_2CO_3 or K_2CO_3 (3.0 equiv), dioxane/water or DME/water (4/1), $Pd(PPh_3)_4$or $PdCI_2(dppf)$-CH_2CI_2 (0.1 equiv), 100 °C.

As described in Scheme 2, benzyl amine analogs **48−50** (Table 2) were generated via the corresponding aminoquinazoline aldehyde **40**, followed by reductive amination with commercially available amines. A variety of aryl bromides were utilized to generate additional target analogs, including those containing ethers (**51**, Table 2), reversed amides (**52**, Table 2), and α-methyl benzyl amines and amides (**53−58**, Table 3). Aryl bromides were either commercially available or readily synthesized by standard conditions (see the Experimental Section).

An alternative route to access similar aminoquinazoline compounds containing either ethers (**67**, Table 2), reversed amides (**68−70**, Table 2), or *N*-linked anilines (**71**, Table 3) was accomplished, as reported in Scheme 3. Readily accessible 6-bromo-2-chloroquinazoline[16] was treated under either microwave or thermal conditions (method A or B, respectively) with a variety of anilines to afford bromides **62−66**, which were then subjected to palladium-catalyzed Suzuki coupling conditions with 4-pyridinylboronic acid to afford **67−71**.

Additional efforts to explore the effects of further diversifying the α-methyl benzyl motif led to the generation of α-methyl

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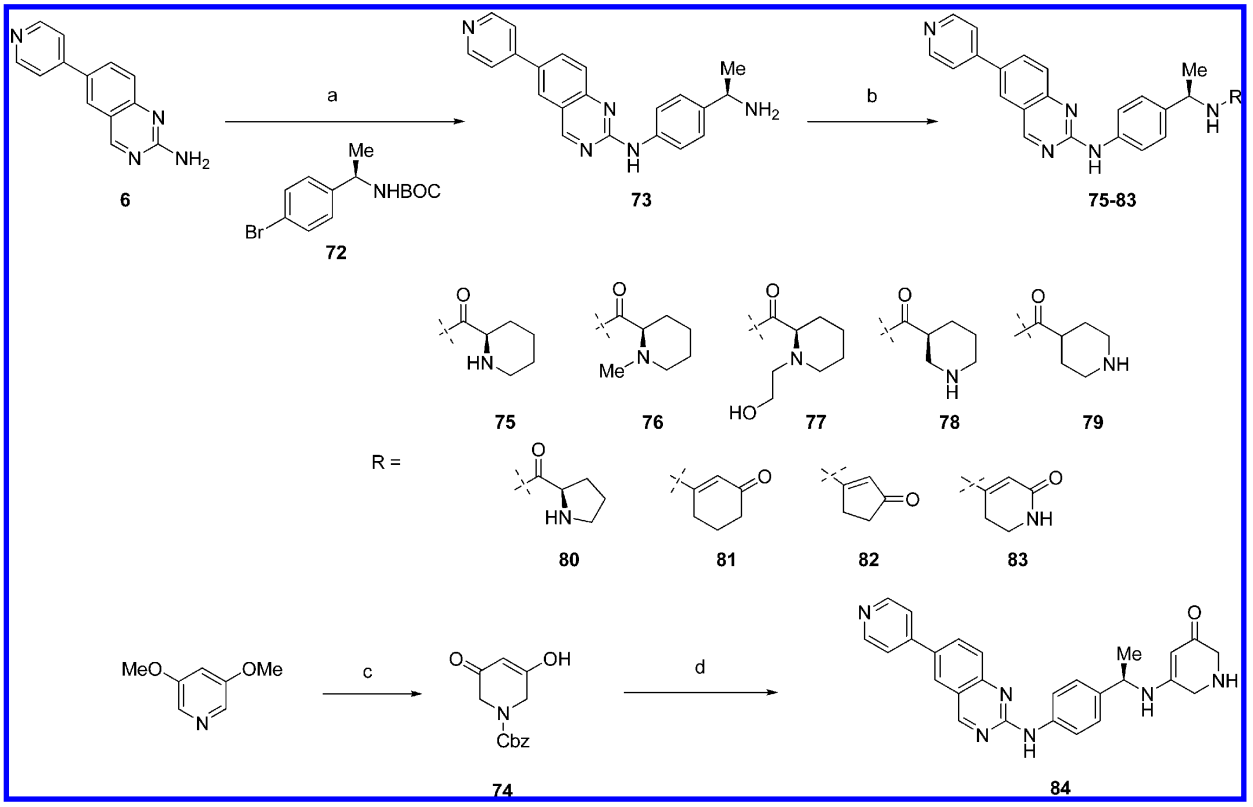
Scheme 4. Preparation of Aminoquinazoline Analogues 75−84[a]



[a]Reagents and conditions: (a) (i) **72**, Xantphos (10 mol %), Cs_2CO_3 (3.0 equiv), dioxane, $Pd(OAc)_2$ (5 mol %), 100 °C, 4 h; (ii) 2 N HCl in ether. (b) For compounds **75**−**76** and **78**−**80**, (i) carboxylic acid, DIPEA, HATU, DMF, 60 °C; (ii) 4 M HCl in dioxane or 2 N HCl in ether, rt; for compounds **81**, **82**, cyclohexane- or cyclopentane-1,3-dione (3 equiv), HOAc, DIPEA, MeOH, 60 °C, 12 h; for compound **83**, piperidine-2,4-dione, DMF, microwave, 150 °C; for preparation of **77**, see the Experimental Section. (c) (i) $NaBH_4$ (1.8 equiv), MeCN, benzyl carbonochloridate (1.2 equiv), 0 °C, dioxane; (ii) 4 M HCl in dioxane, rt. (d) (i) **73**, HOAc, NMP, 105 °C, 6 h; (ii) Pearlman's catalyst (15 mol %), MeOH, rt, H_2, 1 atm.

amine intermediate **73**, which was readily synthesized by palladium-catalyzed coupling of **6** and **72** followed by BOC-group deprotection. As described in Scheme 4, intermediate **73** served as a key building block for rapid synthesis of various α-methyl amides and vinylogous amides such as **75**−**84** (Table 4). The α-methyl amides (**75**−**80**) were prepared from coupling of the corresponding carboxylic acids with amine **73** followed by any required deprotection of BOC protecting groups to generate the desired analogs. Compounds **81** and **82** were generated by reacting **73** with cyclic 1,3-diketones such as cyclohexane-1,3-dione or cyclopentane-1,3-dione with a catalytic amount of acid or under microwave conditions in the presence of piperidine-2,4-dione to yield **83**. Vinylogous amide analog **84** was synthesized by reduction of commercially available 3,5-dimethoxypyridine followed by protection to afford intermediate **74**. Treatment of **74** in the presence of amine **73** under acid-mediated conditions followed by deprotection of the carbonylbenzyloxy protecting group generated the target compound **84** (Scheme 4).

The chemistry we employed to probe substitution at the 7- and 8-positions of the aminoquinazoline is described in Scheme 5. Readily accessible bromo chloride and amino intermediates such as **88**−**90** were generated in accordance with known literature procedures.[17] Treatment of aniline **85** with 6-bromo-2-chloro-8-methoxyquinazoline in the presence of refluxing propan-2-ol followed by base generated **86**, which after Suzuki coupling afforded **87**. Alternatively, the sequence of Suzuki coupling (generating **91**−**93**) followed by palladium-catalyzed coupling, deprotection of the BOC group, and acetylation led to the desired analogs (**97**−**99**). Further derivatization of **95** (R_1 = Cl, R = H) and **96** (R_1 = H, R = Cl) by coupling with methyl boronic acid followed by deprotection of the BOC group and acetylation resulted in **100** and **101**.

RESULTS AND DISCUSSION

Initial Hypothesis of Binding and Approach for Compound Design and Optimization. We obtained a cocrystal of compound **3** in kinase EphB4, which was used as a surrogate protein due to the high binding site homology to B-Raf^{V600E}. The structure confirmed **3** binding in a DFG-in manner, making the canonical hydrogen-bond interactions with the hinge region of the protein via the N3 of the quinazoline ring and the aniline hydrogen.[18] The binding mode oriented the 6-position 4-pyridyl group in the selectivity pocket at the back of the ATP site and the 4-substituent of the aniline ring directed into the solvent channel of the ATP site (Figure 2A).

On the basis of the knowledge of the binding mode of **3** in EphB4, the chemistry plan was focused on exploring the SAR of this class of compounds. Our approach was 3-fold and examined exploration of the A-, B-, and C-rings (Figure 2B). We prioritized A- and C-ring exploration, as we believed these regions of the molecule would influence most the cellular pERK potency and physical properties without interfering with the B-ring of the molecule, which was responsible for making the key interactions to the hinge region of the protein.

SAR Development. We began our exploration with modifications to the A-ring and found that a variety of steric

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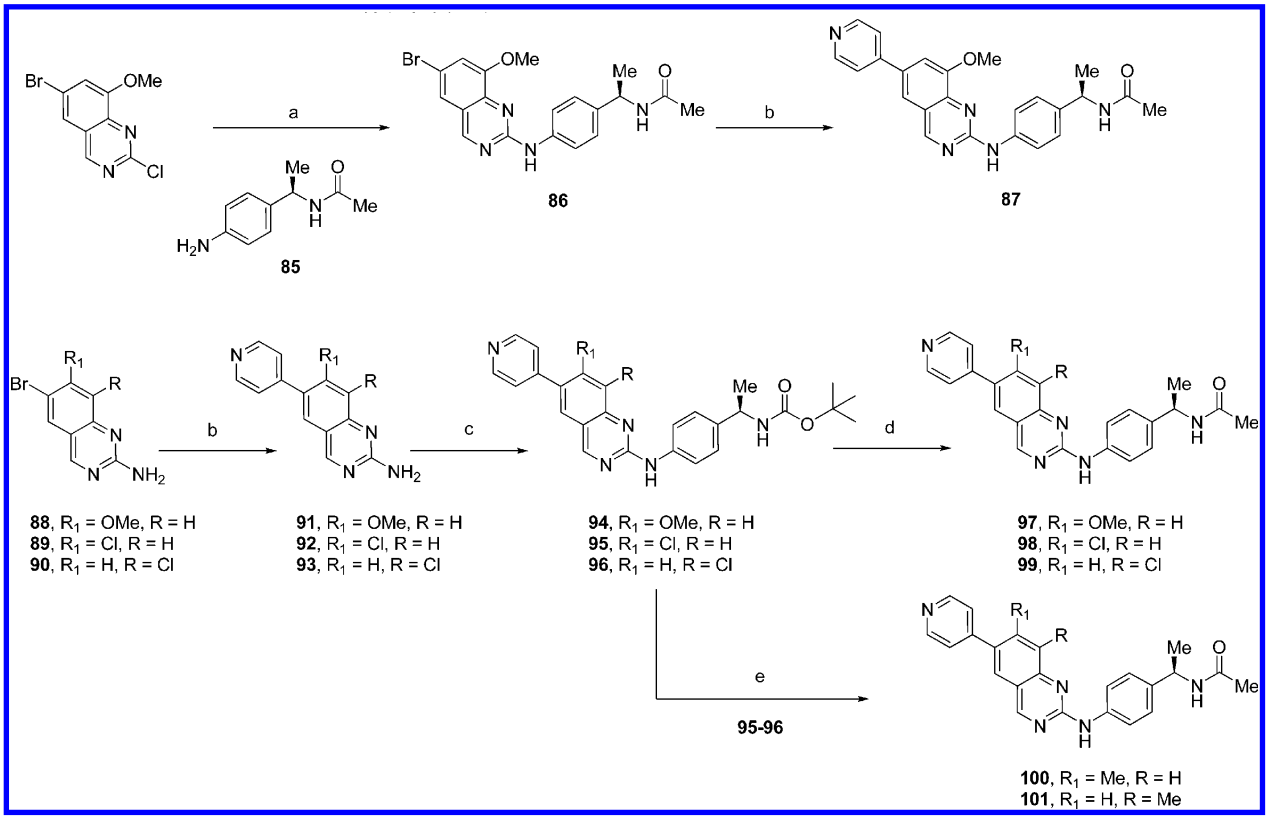
Scheme 5. Preparation of Aminoquinazolines 87 and 97−101[a]



[a]Reagents and conditions: (a) **85**, propan-2-ol, reflux, 3 h then DIPEA, reflux. (b) $Pd(PPh_3)_4$, Cs_2CO_3, 4-pyridinylboronic acid, dioxane/water (2/1), 90 °C. (c) **72**, $Pd(OAc)_2$ (5 mol %), Xantphos (10 mol %), Cs_2CO_3, dioxane, 100 °C. (d) (i) HCl/THF or 4 N HCl/dioxane; (ii) NEt_3, Ac_2O, rt. (e) (i) **95**, **96**, methyl boronic acid, K_2CO_3 (3.0 equiv), dioxane, $Pd(OAc)_2$(4 mol %), PCy_3-HBF_4 (10 mol %), 100 °C, 12 h; (ii) HCl/THF; (iii) NEt_3, Ac_2O, rt.

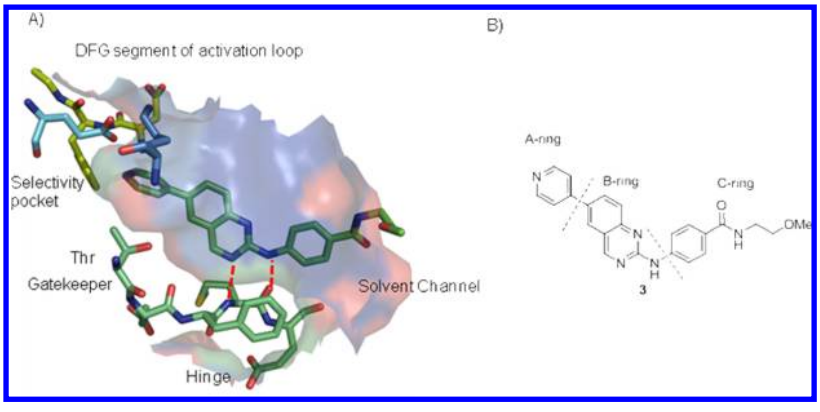


Figure 2. (A) Cocrystallization of **3** in EphB4, which was used as a surrogate to mutant B-Raf, illustrates the compound binding in a DFG-in manner in the ATP site of the kinase domain of the protein. The structure has been deposited in the Protein Data Bank (reference code 4bb4). (B) Proposed plan for aminoquinazoline exploration.

and electronic changes to the 4-pyridyl ring resulted in a significant loss in cell potency (**24**−**27**, Table 1). Likewise, replacing the 4-pyridyl with a phenyl group led to a much less potent compound (**28**, A375 pERK IC_{50} = 3.80 μM). We discovered that a 4-methyl-3-pyridyl group led to improvements in both biochemical and cell potency (**30**, B-Raf^{V600E} IC_{50} = 0.023 μM, A375 pERK IC_{50} = 0.089 μM), achieving a 2-fold improvement in cell potency vs the initial hit **3**. However, a 3-pyridyl or substituted 3-pyridyl ring was not tolerated (**29**, **31**, **32**). Further examples that explored the effects of various other nitrogen-containing six-membered ring heterocycles also resulted in a loss of cell potency, such as pyrimidine **33** (A375 pERK IC_{50} = 6.40 μM). Thus, while we identified tight SAR around the 6-position of the aminoquinazoline in the initial A-ring exploration, we were pleased to uncover the improvement in cell potency (i.e, **30**, Table 1).

We profiled the most potent analogs of this series (**3** and **30**) early on to better understand the kinase selectivity profile. Both compounds were screened against a Millipore panel of 83 kinases.[19] We concluded the selectivity profile of **3** to be superior to that of **30**, as demonstrated by visualization of inhibition profiles and $S(10)$ selectivity scores of 0.01 and 0.11, respectively

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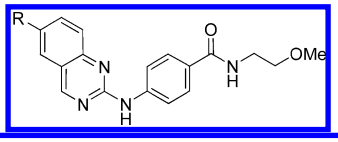
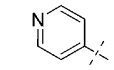
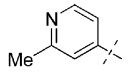
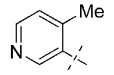
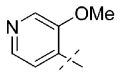
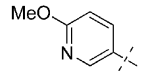
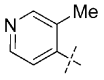
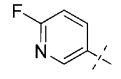
Table 1. A-Ring Exploration



Compound	R	B-Raf^{V600E} IC_{50} (μM)[a]	A375 pERK IC_{50} (μM)[b]	Compound	R	B-Raf^{V600E} IC_{50} (μM)[a]	A375 pERK IC_{50} (μM)[b]
3		0.077	0.190	**29**		0.601	7.04
24		0.399	>17	**30**		0.023	0.089
25		0.265	1.80	**31**		2.3	>32
26		0.132	0.96	**32**		5.4	>32
27		0.369	2.00	**33**		0.777	6.40
28		0.917	3.80				

[a]Measured at K_m ATP concentration. For experimental details, see the Supporting Information. [b]All values are an average of at least two independent dose−response curves. For experimental details, see the Supporting Information.

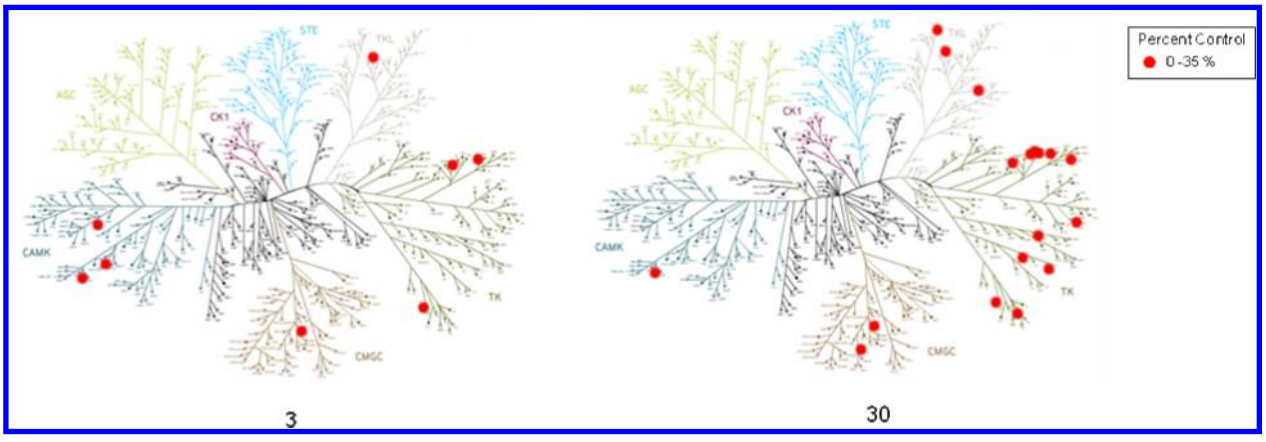


Figure 3. Millipore KinaseProfiler selectivity screening of a diverse kinase set ($n = 83$) at 1 μM of **3** and **30**, with hits overlaid on the kinome phylogenetic tree. Red circles indicate active hits ≤35% of control.

(Figure 3). The results revealed that the 4-pyridyl ring led to an overall more selective profile, in particular against other tyrosine and serine/threonine kinases. Therefore, based on the more promiscuous nature of **30**, we chose to continue our SAR optimization keeping the 4-pyridyl A-ring constant.

In addition to assessing the kinase selectivity profile, we also studied the biochemical and cell proliferation profile of **3**.[20] We hypothesized on the basis of our findings from both biochemical and cell proliferation data that aminoquinazoline **3** afforded a different profile to previous inhibitors such as **2**. Aminoquinazoline **3** was found to inhibit mutant B-Raf^{V600E} but was much less potent against C-Raf^{WT} or inactive against B-Raf^{WT} under saturated ATP conditions (Figure 4A), pointing to evidence for a more mutant B-Raf^{V600E} selective profile. Compound **2** resulted in a different biochemical profile affording a near equal inhibition of B-Raf^{V600E} and C-Raf and a drop off in the B-Raf^{WT} potency. We obtained similar results after comparing the cell proliferation profile of compounds **2** and **3** against a panel of various cell lines. Aminoquinazoline **3** resulted in preferential antiproliferative activity in the presence of mutant B-Raf^{V600E} cell lines (Figure 4B). Compound **2**, when treated under identical cell lines and conditions, inhibited additional nonmutant B-Raf cell lines. Thus, we identified early on the potential for the aminoquinazoline series to provide a different yet complementary profile to the previous inhibitors such as **2** that we had discovered.

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A)

Kinase	2	3
B-Raf^{V600E}	0.27	0.89
B-Raf^{WT}	2.64	>30
C-Raf^{WT}	0.38	5.84

Values represent IC_{50} values reported in μM units measured at 5 mM ATP concentration. For additional details around assay format, see the Supporting Information.

B)

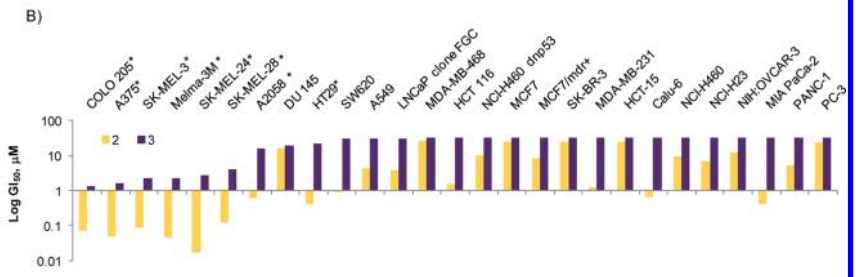
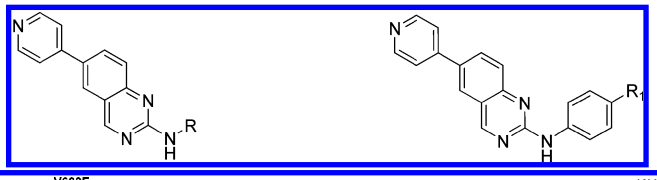
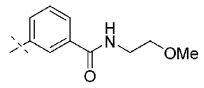
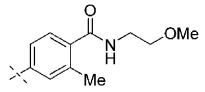
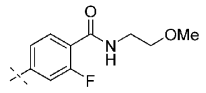
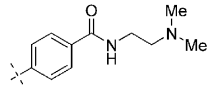
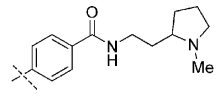
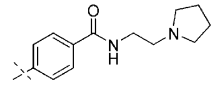
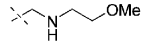
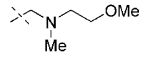
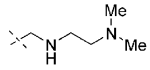
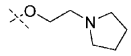
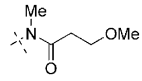
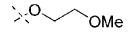
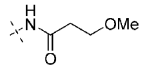
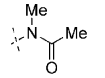
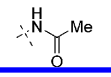


Figure 4. (A) Biochemical inhibitory profile of **2** and **3**. For a more detailed description of the biochemical differences of **2** and **3** with regard to substrate ATP concentration, see the Supporting Information. (B) Antiproliferative activity of B-Raf inhibitors **2** and **3** against a panel of various cell lines. Cells were incubated with DMSO or compounds **2** or **3** for 72 h and cell growth was determined by MTS assay, represented as log mean GI_{50} (average of three replicates). Cell lines denoted with an asterisk (*) harbor the B-Raf^{V600E} mutation. For a complete listing of cell line type, further observations around the proliferation profile, and additional MTS assay details, see the Supporting Information.

Table 2. C-Ring Modifications



Compound	R	B-Raf^{V600E} IC_{50} (μM)[a]	A375 pERK IC_{50} (μM)[b]	Solubility (μM) pH 7.4
34		0.33	>6	2
35		0.12	0.35	7
36		0.344	0.28	1
37		0.089	0.23	220
38		0.053	0.170	450
39		0.130	0.330	550

Compound	R_1	B-Raf^{V600E} IC_{50} (μM)[a]	A375 pERK IC_{50} (μM)[b]	Solubility (μM) pH 7.4
48		0.192	0.35	840
49		0.029	0.23	620
50		0.30	1.6	>1,000
51		0.101	0.41	>1,000
52		0.032	0.045	40
67		0.21	0.97	1
68		0.15	0.66	4
69		0.057	0.063	7
70		0.067	0.40	2

[a] Measured at K_m ATP. For experimental details, see Supporting Information.
[b] All values are an average of at least two independent dose-response curves. For experimental details, see Supporting Information.

Further exploration of the C-ring SAR involved modifications toward the solvent channel, a region of the molecule that would allow for optimization of the overall properties of the series. The solubility for **3** was found to be 3 μM, so a key focus of our optimization and SAR generation was around improving solubility. Meta-substitution of the amido group was not tolerated on the basis of the cellular potency; however, methyl or fluoro substitution adjacent to the *p*-amido group was acceptable, albeit with no improvement in solubility (Table 2, **34**−**36**). We incorporated various basic amines, both acyclic and cyclic, into the amide to serve as solubilizing groups. These changes significantly improved the solubility; however, they resulted in a slight decrease in potency (Table 2, analog **39**, A375 pERK IC_{50} = 330 nM) or had no effect on potency (such as **37** and **38**, with similar cellular potency to **3**). In order to better understand the functional group tolerance at the 2-position of the quinazoline, we investigated other groups in addition to amido-substituted phenyl. Diversifying beyond phenyl amides to benzyl amine derivatives **48**−**50**, while improving solubility, led to reduced potency, in particular with example **50**. Ethers such as **51** and **67** did not afford much benefit to potency, though improved solubility could be achieved with the inclusion of basic groups such as the pyrrolidine in **51**. We also explored reversing the amide with *N*-linked compounds such as **52** and **68**−**70**

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(Table 2) or removing the amide altogether with *N*-linked analog **71** (Table 3). While not all of these changes led to favorable improvements in cell potency, we were able to find some examples where cell potency below 100 nM was achieved and resulted in modest evidence for desirable solubility (**52**, A375 pERK IC_{50} = 45 nM, solubility 40 μM; **69**, A375 pERK IC_{50} 63 nM, solubility 7 μM; Table 2). It appeared from the SAR that *N*-methyl amides were >6-fold more potent in the A375 pERK cellular assay vs their desmethylated matched pairs (i.e., **52** vs **68** and **69** vs **70**, Table 2). In contrast, *N*-methyl linked analogs such as **71** were not tolerated on the basis of much weaker cell potency (Table 3, A375 pERK IC_{50} = 855 nM). From our initial exploration varying the functionality at the C-ring, we were able to identify compounds with good solubility and improved potency compared to initial hit **3**. Next, we further explored analogs **52** and **69** with the goal of maintaining the improvements in potency while increasing the solubility.

We were successful in obtaining a cocrystal structure of **48** in B-Raf^{V600E}, and our initial hypotheses from the cocrystallization of **3** in EphB4 were confirmed (Figure 5). The structure revealed

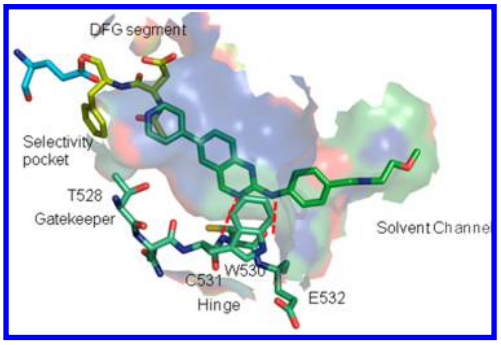

Figure 5. X-ray structure of **48** bound to the kinase domain of mutant B-Raf^{V600E}. The structure has been deposited in the Protein Data Bank (reference code 4H58), and detailed protein preparation, crystallization, and freezing protocols are included in the Supporting Information.

binding to the kinase domain in a DFG-in conformation, making the canonical hydrogen bond interaction to the N−H of C531 via the N3 of the quinazoline ring and the backbone carbonyl of E532 via the aniline hydrogen. The 4-substituent of the aniline ring was directed into the solvent channel of the ATP site, and the quinazoline and aniline rings were stacked against the indole side chain of W530. The 6-position 4-pyridyl group was located in the selectivity pocket at the back of the ATP site, above the T528 gatekeeper residue. We speculated on the basis of the structure that our observation of the 4-methyl-3-pyridyl analog (**30**, Table 1), which resulted in significantly more potent activity as compared to the desmethyl analog (**29**, Table 1), could be due to anchoring of the methyl group over the T528 gatekeeper residue to capitalize on a lipophilic interaction, thus locking into place the 6-position 3-pyridyl ring into the selectivity pocket. We also hypothesized that the preorganization gained by the lipophilic interaction of the T528 methyl and methyl group of the pyridyl ring in the selectivity pocket contributed to the broader kinase activity of analogs such as **30**, in particular by other threonine-containing gatekeeper kinases. The X-ray crystal structure of **48** thus helped support our plans to continue exploring the C-ring substituents in the solvent channel. The X-ray structure also suggested that additional exploration around the B-ring at either the 7- or 8-position of the quinazoline would be tolerated.

Additional exploration of what else could be tolerated in the solvent channel was instrumental to the optimization of this series. We expanded on our prior knowledge that *N*-methyl amides such as **52** and **69** improved potency while retaining modest solubility. We were also concerned that analogs such as **52** and **69** could carry a potential mutagenic liability due to the aromatic aniline functionality, and we sought to prioritize design ideas to remove this functionality.[21] We found that incorporating an additional atom between the arene and the nitrogen was tolerated, such as α-methyl amino derivative **53** (Table 3, A375 pERK IC_{50} = 49 nM). This compound had improved solubility (Table 3, solubility 830 μM and human plasma protein binding 9.4% free) as compared to the hit **3** (solubility 3 μM and human plasma protein binding 1.7% free).[22] Further expanding this theme to other α-methyl amides led to additional examples with promising cell potency. Analogs **54**−**58** highlight the stereochemical preference of the α-methyl group with respect to cellular potency. We discovered retention of potency in the (*R*)-enantiomer of each example (**55** and **58**, A375 pERK IC_{50} = 60 and 34 nM, respectively); however, these analogs suffered from poor physical properties (solubility <10 μM and human protein binding <2.3% free). On average, the (*R*)-enantiomers of both **54** and **57** were found to be 2−5 times more potent than the corresponding (*S*)-enantiomers (i.e., **56** vs **55**, A375 pERK IC_{50} = 160 vs 60 nM).[23] We were optimistic about the pharmacokinetic profiles of the α-methyl benzylic amino analogs because examples **53**, **55**, and **58** had favorable rat liver hepatocyte stabilities (Table 3, rat hepatocyte CL_{int} 16, 11, and 6 μL/min/1E6, respectively). Likewise, human microsomal stabilities for **53** and **58** were in a desirable range (Table 3). Encouraged by these results, we expanded upon the (*R*)-α-methyl amide motif.

Plans to improve upon the physical properties of analogs such as **55** and **58** centered around expanding the diversity of the (*R*)-α-methyl benzyl amides by incorporating solubilizing groups. We explored basic groups off the amide functionality in an attempt to improve solubility while the potency and in vitro PK profile that we believed would be desirable were maintained. We found amides containing cyclic amines to be most promising. A variety of ring sizes were explored, and positioning of the nitrogen was key for maintaining desirable cellular potency and solubility. For example, 4-piperidino carboxamide **79** resulted in a significant loss in cell potency (Table 4, A375 pERK IC_{50} = 688 nM), whereas the 2-piperidino carboxamide **75** maintained desirable cell potency (Table 4, A375 pERK IC_{50} = 45 nM). Compound **75** likewise had excellent solubility (>940 μM), human plasma protein binding (5.1% free), and moderate in vitro rat clearance. The 2-substituted piperidino carboxamide **75** was also found to be more potent than the 3-piperidino analog **78** (Table 4, A375 pERK IC_{50} = 140 nM), whereas the 2-pyrrolidino carboxamide **80** was of similar cellular potency to **75** (Table 4, A375 pERK IC_{50} = 74 nM).[24] We also explored further elaboration of **75** with various substituents to probe the importance of the free amine and build upon the SAR. We believed attenuation of the basic amine pK_a could be a strategy to address pharmacokinetic liabilities that may arise in vivo.[25] Methyl substitution as in **76** was tolerated, yielding an identical potency to **75** with reduced solubility (65 μM).[26] Substitution to generate what we believed would be a less basic moiety in hydroxyethyl analog **77** afforded a potent inhibitor (A375 pERK IC_{50} = 25 nM) though with poor solubility and higher predicted clearance as indicated by both rat liver hepatocytes and human liver microsomal data (Table 4).

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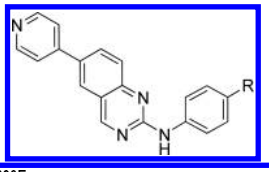
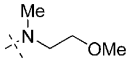
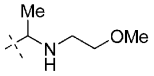
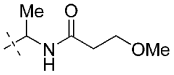
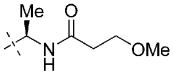
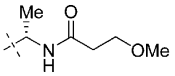
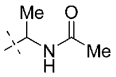
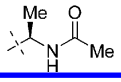
Table 3. Additional C-Ring Modifications



Compound	R	B-Raf^{V600E} IC_{50} (μM)[a]	A375 pERK IC_{50} (μM)[b]	Solubility (μM) pH 7.4	Hu PPB Fu (%)[c]	Rat Hep CL_{int} (μL/min/1E6)[c]	Hu Mic CL_{int} (μL/min/mg)[c]
71		0.168	0.855	2	<1	36	100
53		0.038	0.049	830	9.4	16	32
54		0.040	0.071	8	1.4	9	76
55		0.027	0.060	9	1.5	11	57
56		0.051	0.16	9	<1	<4	110
57		0.036	0.057	4	1.3	5	18
58		0.019	0.034	3	2.3	6	22

[a]Measured at K_m ATP concentration. For experimental details, see the Supporting Information. [b]All values are an average of at least two independent dose−response curves. For experimental details, see the Supporting Information. [c]Human PPB, rat hepatocyte, and human microsomal stability details can be found in the Supporting Information.

Inspired by reports of vinylogous amide pharmacophores in a series of pyrrolidine ether hNK_1 antagonists,[27] we found the carboxamide could be replaced by a vinylogous amide and derivatives such as **81** and **82** resulted in single digit nanomolar cell potency (Table 4, **81**−**82** A375 pERK IC_{50} = 4−5 nM). Both five- and six-membered rings were equally promising; however, both resulted in poor solubility (Table 4, 4 μM). We hypothesized the design and synthesis of close analogs such as dihydropyridinones **83** and **84** incorporating nitrogen atoms into the ring would improve the solubility with the expectation of maintaining single digit nanomolar cell potency. We discovered that analog **83** maintained potency however did little to improve upon the solubility of prior compounds (Table 4). Analog **84** was designed to combine features of the 2- and 3-piperidino carboxamide profiles of **75** and **78** with the vinylogous amide motif. Our hypothesis was that a combination of both features would maintain a desirable potency and solubility profile. However, **84** resulted in a less potent and still poorly soluble analog (Table 4, A375 pERK IC_{50} = 63 nM, solubility 10 μM). Our strategy to diversify beyond the (*R*)-α-methyl benzyl amides to uncover analogs such as piperidino carboxamide **75** and vinylogous amides **81** and **82** led to identification of promising leads with in vitro PK profiles that we believed would translate into an acceptable in vivo PK profile.

Modifications to the core aminoquinazoline B-ring were also examined to probe the SAR of this region. On the basis of our knowledge of the aminoquinazoline binding mode, we believed substitution at either the 7- or 8-position of the quinazoline would be tolerated. These positions were oriented away from the hinge binding region, whereas substitution of the aminoquinazoline at the 4- and 5-positions was expected to interfere with hinge binding. We explored the electronic distribution of the quinazoline ring as this might play a key role in modulating PK. A limited number of groups representing electron-donating and -withdrawing potential were investigated at the 7- and 8-positions of the aminoquinazoline. We discovered 7-substitution with chloro and methyl (Table 5, **98** and **100**, A375 pERK IC_{50} = 430 and 573 nM, respectively) were detrimental to pERK cell potency, resulting in a greater than 20-fold loss in potency as compared to their 8-substituted matched pairs (Table 5, **99** and **101**, respectively). Interestingly, both the 8- and 7-methoxy substitutions were tolerated and resulted in potency similar to that of **58** (Table 5, **87** and **97**, A375 pERK IC_{50} = 10 and 25 nM, respectively). These core substitutions did not lead to a desirable solubility range, as most analogs had <10 μM solubility and high human protein binding. Most examples exhibited acceptable rat hepatocyte and human microsomal intrinsic clearance values.

Pharmacokinetic Properties of Leads. Aminoquinazolines with desirable pERK cell potency (typically IC_{50} < 50 nM) and in vitro rat hepatocyte and human microsomal stability which should be predictive of modest clearance were progressed into in vivo rat PK studies. We were encouraged to find that the most potent analogs had low in vivo clearance and good bioavailability (**52** and **58**, F = 60 and 100%, respectively, Table

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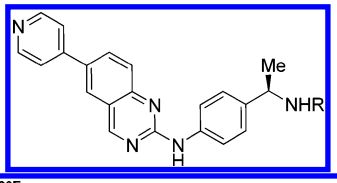
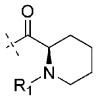
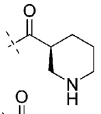
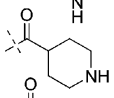
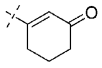
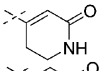
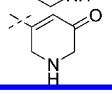
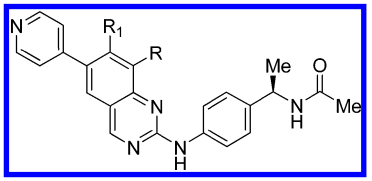
Table 4. Amide Modifications



Compound	R	B-Raf^{V600E} IC_{50} (μM)[a]	A375 pERK IC_{50} (μM)[b]	Solubility (μM) pH 7.4	Hu PPB Fu (%)[c]	Rat Hep CL_{int} (μL/min/1E6)[c]	Hu Mic CL_{int} (μL/min/mg)[c]
75	 R_1 = H	0.254	0.045	>940	5.1	14.2	49
76	R_1 = Me[d]	0.223	0.045	65	3.8	25	>100
77	R_1 = CH_2CH_2OH	0.102	0.025	1	3.4	>100	>100
78		0.256	0.140	34	1.7	13	16
79		0.230	0.688	34	3.4	2	27
80		0.214	0.074	410	1.4	11	53
81		0.037	0.004	4	1.3	16	35
82		0.094	0.005	4	2	10	13
83		0.158	0.008	3	2.3	ND[e]	<4
84		0.039	0.063	10	3.6	22	10

[a]Measured at 5 mM ATP concentration. For experimental details, see the Supporting Information. [b]All values are an average of at least two independent dose−response curves. For experimental details, see the Supporting Information. [c]Hu PPB, rat hepatocyte, and Hu microsomal stability details can be found in the Supporting Information. [d]**76** represents a mixture of diastereomers at the piperidinyl chiral center as the diasteromers proved to be inseparable after various attempts at separation. [e]Denotes not tested.

Table 5. B-Ring Core Modifications



			IC_{50} (μM)				CL_{int}	
compd	R	R_1	B-Raf^{V600E}[a]	A375 pERK[b]	solubility (μM) pH 7.4	Hu PPB Fu (%)[c]	rat Hep (μL/min/1E6)[c]	Hu Mic (μL/min/mg)[c]
87	OMe	H	0.057	0.01	5	3.4	2	8
97	H	OMe	0.14	0.025	<1	2.6	4	<4
98	H	Cl	2.29	0.43	2	<1	3	8
99	Cl	H	0.187	0.02	<1	<1	5	39
100	H	Me	2.6	0.573	5	1.9	2	11
101	Me	H	0.081	0.025	<1	<1	5	17

[a]Measured at 5 mM ATP concentration. For experimental details, see the Supporting Information. [b]All values are an average of at least two independent dose−response curves. For experimental details, see the Supporting Information. [c]Hu PPB, rat hepatocyte, and human microsomal stability details can be found in the Supporting Information.

6). However, a trend of short half-life and low volume of distribution was also seen, a profile that might not achieve the sustained exposure we would require to achieve target inhibition in vivo. Analogs such as benzyl amine **53**, which demonstrated improved solubility and desirable potency, showed moderate−high clearance in a manner similar to analog **84**. Interestingly, carboxamide **75** did lead to a desirable in vivo rat PK profile with a longer half-life over a 24 h iv dosing period and larger volume of distribution, though moderate clearance (Table 6). We believed compounds **58** and **75** were excellent candidates for additional in vivo evaluation.

Mutant B-Raf^{V600E} Selective Cell Profile Results in pERK Elevation in Nonmutant B-Raf Cells. Additional experiments to understand the effects of the mutant B-Raf^{V600E} selective

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Table 6. Rat PK of Lead Compounds[a]

compd	CL_{obs} (mL/min/kg)	V_{dss} (L/kg)	F (%)	$t_{1/2}$ (h)
52	9	0.7	60	1
53	56	4.9	31	1.5
58	11	0.8	100	0.9
75	43	13	28	4.4
81	19	0.67	17	1.1
84	120	7.9	ND[b]	0.42
97	15	0.67	ND[b]	0.61

[a]Han Wistar rat male; 10 mg/kg po (0.1% HPMC); 3 mg/kg iv (40% DMA/40% TEG/20% saline). $t_{1/2}$ represents the iv half-life. [b]Denotes not tested as a po dose, so F (%) was not determined.

profile are highlighted in Figure 6. An A549 cell line with B-Raf^{WT} KRAS mutant background was evaluated for pERK response to aminoquinazolines **3**, **58**, **69**, **75**, **81**, and **87**. Upon treatment of compounds at 0.1-, 1-, 10-, and 100-fold the A375 pERK IC_{50}, a dose-dependent elevation of pERK was seen with no clear margin to this effect, irrespective of the aminoquinazoline chosen. This observation is in stark contrast to the effects seen after a 75 min treatment with either **2** or Pfizer's known selective MEK1/2 inhibitor PD0325901 (**102**),[28] both of which resulted in a decreased pERK in a dose-dependent manner (Figure 6).

We wanted to understand how general this trend for elevated pERK was in a variety of other B-Raf^{WT} and KRAS cellular contexts, and thus selected lead aminoquinazoline **58** for additional studies. Both cancer (melanoma, lung, and breast), normal, and fibroblast cell lines were treated with **58** at 1-, 10-, and 100-fold the A375 pERK IC_{50}. Elevation of pERK was observed in all cell lines after a 75 min treatment with **58**. No clear margin to the elevation of pERK in nonmutant B-Raf cell lines, relative to decrease in pERK in A375 cell lines, was seen over the range of doses investigated (Figure 7). In contrast to aminoquinazoline compounds, **2** did not show pERK elevation in any of the cell lines tested. MEK1/2 inhibitor **102** led to an expected decrease, or near complete inhibition, of pERK in all cell lines. Consistent with observations by others in this field, there are differences in the ability of the various classes of B-Raf^{V600E} inhibitors to lead to elevated pERK and MAPK pathway activation in nonmutant B-Raf cells, an observation now well documented to result from Raf dimerization.[15,29]

In Vivo Activity of Lead Aminoquinazolines. Lead compound **58** was progressed for additional in vivo profiling. A dose-dependent decrease in pERK was observed in an A375 mouse xenograft PD study with **58** starting at the 10 mg/kg dose as observed by Western blot and quantitation of the percent reduction in pERK (Figure 8A,B). In addition, a dose-dependent increase in drug concentration in the plasma was observed (see the Supporting Information). Compound **58** was progressed further into an in vivo efficacy study in an A375 mutant B-Raf^{V600E} xenograft model dosed 25 mg/kg orally twice daily for 10.5 days. **58** demonstrated significant tumor growth inhibition

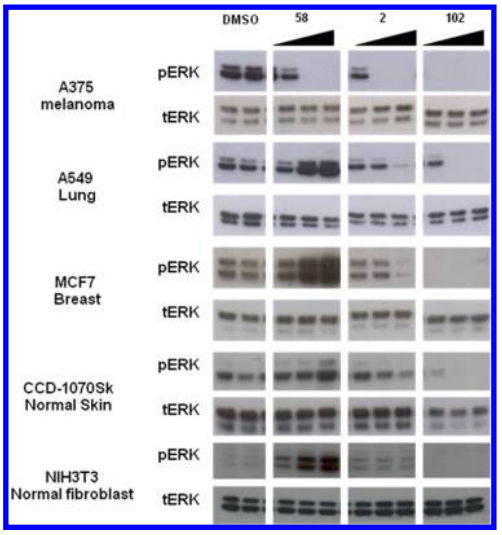

Figure 7. In vitro pERK evaluation in multiple nonmutant B-Raf cell lines. Cells were collected following 75 min treatment with DMSO or compound at the indicated doses (1-, 10-, and 100-fold the A375 pERK IC_{50}). Western blotting analysis was performed using antibodies against the indicated proteins. pERK refers to phospho-ERK levels and tERK represents total-ERK levels. **102** was used as a positive control in this study.

(Figure 8C) and displayed excellent tolerability with no significant body weight loss.[30]

CONCLUSION

The aminoquinazoline DFG-in class of compounds were shown to be potent and selective B-Raf^{V600E} inhibitors that evolved from a singleton hit identified from a kinase subset screening effort. Aminoquinazolines were optimized for B-Raf^{V600E} cellular potency, physical properties, and in vivo rat pharmacokinetics. We have demonstrated that a lead compound from this series, **58**, exhibits in vivo tumor growth inhibition in an A375 xenograft model. A key finding from this class of compounds was the B-Raf^{V600E} selective profile, which, similar to previous reports by others in the field, resulted in the elevation of pERK, thus highlighting the potential for multiple novel chemotypes to generate such a profile. Compounds such as the aminoquinazoline series described herein, in addition to the complementary profile afforded by analogs such as **2**, provide useful tools to further interrogate the important role of B-Raf within the MAPK pathway.[31]

EXPERIMENTAL SECTION

Chemistry. ^{1}H NMR spectra were recorded on either Bruker 300 or 400 MHz NMR spectrometers using deuterated DMSO (DMSO-d_6) unless otherwise stated. Temperatures are given in degrees Celsius (°C); operations were carried out at room temperature or ambient temperature, that is, in the range 18−25 °C. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are

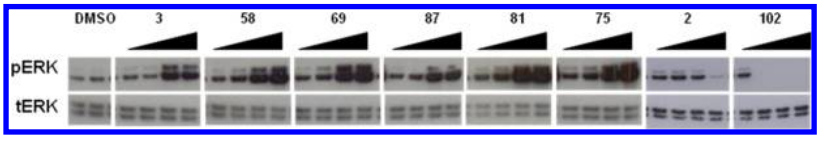

Figure 6. Evaluation of pERK in A549 cell lines. Cells were collected following a 75 min treatment with DMSO or compound at the indicated doses (0.1-, 1-, 10-, and 100-fold the A375 pERK IC_{50}). pERK refers to phospho-ERK levels and tERK represents total-ERK levels. Western blotting analyses were performed using antibodies against the indicated proteins. **102** was used as a positive control in this study.

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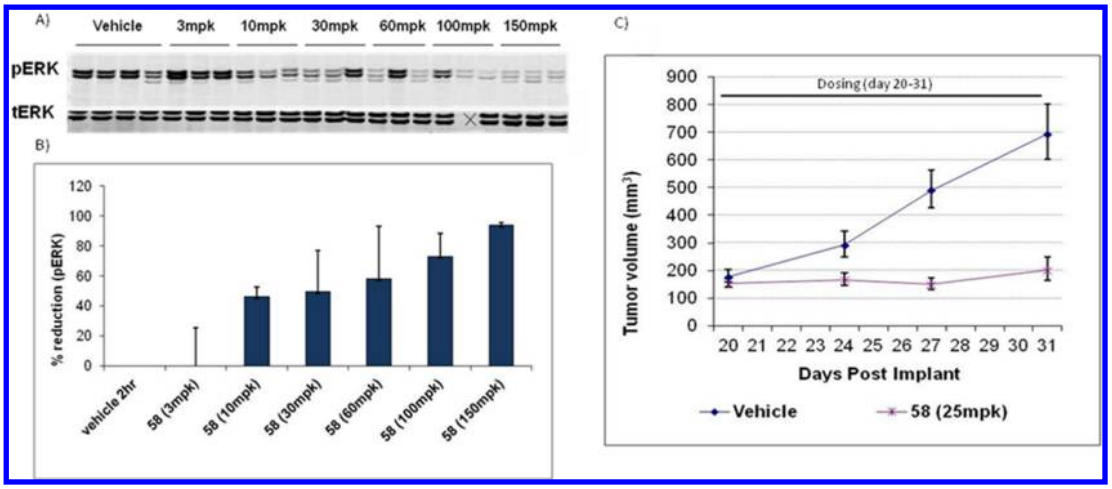

Figure 8. (A) A375 xenograft dose−response mouse PD of compound **58** at 2 h post po single dose. Tumors and plasma were harvested 2 h after dosing. Western blotting was performed on tumor samples to determine pERK inhibition. An equal amount of protein was loaded into each well and total ERK (tERK) was used for further normalization. (B) Percent reduction in pERK from the A375 xenograft dose−response mouse PD. For additional details including plasma concentration information, see the Supporting Information. (C) A375 mouse xenograft tumor growth inhibition study with **58** ($n = 5$) dosed at 25 mg/kg po BID for 10.5 days. The vehicle group ($n = 8$) received 0.5% HPMC. Tumor volume and body weights were measured twice weekly. For additional details, see the Supporting Information.

given in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), dd (doublet−doublet), t (triplet), q (quartet), m (multiplet), and br s (broad singlet). Mass spectroscopy analyses were performed with an Agilent 1100 equipped with Waters columns (Atlantis T3, 2.1 × 50 mm, 3 μm or Atlantis dC18, 2.1 × 50 mm, 5 μm) eluted with a gradient mixture of H_2O−acetonitrile with formic acid or ammonium acetate. The purity determination of all reported compounds was performed with an Agilent 1100 equipped with Waters columns (Atlantis T3, 2.1 × 50 mm, 3 μm; or Atlantis dC18, 2.1 × 50 mm, 5 μm) eluted for >10 min with a gradient mixture of H_2O−acetonitrile with formic or trifluoroacetic acid at wavelengths of 220, 254, and 280 nm. All final compounds analyzed were >95% pure unless otherwise indicated. Reverse-phase chromatography was performed with Gilson systems using a YMC-AQC18 reverse-phase HPLC column with dimension 20 mm/100 and 50 mm/250 in water/MeCN with 0.1% TFA, 0.1% ammonium acetate, or 0.1% formic acid as mobile phase. Most of the reactions described were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light or LC−MS. Flash column chromatography was performed on an ISCO system MPLC Combi-flash systems (4700 Superior Street, Lincoln, NE) unless otherwise mentioned using silica gel cartridges.

***N*-(2-Methoxyethyl)-4-[(6-pyridin-4-ylquinazolin-2-yl)-amino]benzamide (3).** 6-Pyridin-4-ylquinazolin-2-amine (**6**, 50 mg, 0.225 mmol), 4-bromo-*N*-(2-methoxyethyl)benzamide (**17**, 58 mg, 0.225 mmol), Cs_2CO_3 (220 mg, 0.675 mmol, 3.0 equiv), and BINAP (14 mg, 0.023 mmol, 10 mol %) in dioxane (2 mL) were treated with $Pd_2(dba)_3$ (11 mg, 0.012 mmol, 5 mol %). The reaction mixture was heated to 100 °C for 12 h. The reaction was then quenched with 10% NaOH (aq) and extracted with EtOAc. The organics were dried with NaCl (satd) and then Na_2SO_4 (solid). The solvent was removed under reduced pressure and the resulting solid was purified by a Gilson HPLC (0.1% TFA in CH_3CN and water) to afford 60 mg (52%) of the title compound. ^{1}H NMR: 10.38 (s, 1H), 9.45 (s, 1H), 8.86 (d, 2H), 8.61 (d, 1H), 8.38 (m, 2H), 8.22 (d, 2H), 8.07 (d, 2H), 7.87 (m, 3H), 3.44 (m, 4H), 3.27 (s, 3H). LC−MS: *m*/*z* 400.

6-Bromoquinazolin-2-amine (5). 2-Fluoro-5-bromobenzaldehyde (**4**, 1.0 g, 4.9 mmol) and guanidine carbonate (1.3 g, 7.4 mmol, 1.5 equiv) were dissolved in DMA and heated to 140 °C for 5 h. The reaction was treated with H_2O and the resulting precipitate was collected by vacuum filtration. LC−MS: *m*/*z* 225.

6-Pyridin-4-ylquinazolin-2-amine (6). 6-Bromoquinazolin-2-amine (**5**, 200 mg, 0.89 mmol), 4-pyridinylboronic acid (165 mg, 1.34 mmol, 1.5 equiv), and K_2CO_3 (370 mg, 2.68 mmol, 3.0 equiv) in DME/H_2O (5:1, 4 mL) were treated with $Pd(Ph_3P)_4$ (206 mg, 0.179 mmol, 20 mol %). The reaction was stirred at 90 °C for 12 h. The reaction was quenched with 10% NaOH and extracted with EtOAc. The combined organics were dried with NaCl (satd) and then Na_2SO_4 (s). The solvents were removed under reduced pressure. The crude product was purified by column chromatography utilizing an ISCO system (EtOAc−MeOH) to yield 100 mg (51%) of the title compound. LC−MS: *m*/*z* 223.

Following a similar procedure to that of **6**, **7**−**16** were synthesized.

6-(2-Methylpyridin-4-yl)quinazolin-2-amine (7). The title compound was synthesized from 6-bromoquinazolin-2-amine (**5**) and (2-methylpyridin-4-yl)boronic acid. LC−MS: *m*/*z* 237.

6-(3-Methoxypyridin-4-yl)quinazolin-2-amine (8). The title compound was synthesized from 6-bromoquinazolin-2-amine (**5**) and (3-methoxypyridin-4-yl)boronic acid. LC−MS: *m*/*z* 253.

6-(3-Methylpyridin-4-yl)quinazolin-2-amine (9). The title compound was synthesized from 6-bromoquinazolin-2-amine (**5**) and (3-methylpyridin-4-yl)boronic acid. LC−MS: *m*/*z* 237.

6-(3-Chloropyridin-4-yl)quinazolin-2-amine (10). The title compound was synthesized from 6-bromoquinazolin-2-amine (**5**) and (3-chloropyridin-4-yl)boronic acid. ^{1}H NMR: 7.71−7.65 (m, 4H), 7.58−7.45 (m, 5H).

6-Phenylquinazolin-2-amine (11). The title compound was synthesized from 6-bromoquinazolin-2-amine (**5**) and phenyl boronic acid. LC−MS: *m*/*z* 222.

6-Pyridin-3-ylquinazolin-2-amine (12). The title compound was synthesized from 6-bromoquinazolin-2-amine (**5**) and pyridin-3-ylboronic acid. LC−MS: *m*/*z* 223.

6-(4-Methylpyridin-3-yl)quinazolin-2-amine (13). The title compound was synthesized from 6-bromoquinazolin-2-amine (**5**) and (4-methylpyridin-3-yl)boronic acid. LC−MS: *m*/*z* 237.

6-(6-Methoxypyridin-3-yl)quinazolin-2-amine (14). The title compound was synthesized from 6-bromoquinazolin-2-amine (**5**) and (6-methoxypyridin-3-yl)boronic acid. LC−MS: *m*/*z* 253.

6-(6-Fluoropyridin-3-yl)quinazolin-2-amine (15). The title compound was synthesized from 6-bromoquinazolin-2-amine (**5**) and (6-fluoropyridin-3-yl)boronic acid. LC−MS: *m*/*z* 256.

6-(Pyrimidin-5-yl)quinazolin-2-amine (16). The title compound was synthesized from 6-bromoquinazolin-2-amine (**5**) and pyrimidin-5-ylboronic acid. LC−MS: *m*/*z* 224.

4-Bromo-*N*-(2-methoxyethyl)benzamide (17). 2-Methoxyethylamine (10 mL) at 0 °C was treated with 4-bromobenzoyl chloride (2.0 g, 9.1 mmol). After 15 min, 10% HCl was added to the reaction mixture. The resulting white solid (2.00 g, 85%) was collected by vacuum

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filtration. ^{1}H NMR: 8.59 (t, 1H), 7.78 (d, 2H), 7.66 (d, 2H), 3.42 (m, 4H), 3.25 (s, 3H).

3-Bromo-*N*-(2-methoxyethyl)benzamide (18). 2-Methoxyethylamine (0.435 mL, 5.0 mmol), 3-bromobenzoic acid (1.00 g, 5.0 mmol), and DIPEA (1.31 mL, 7.5 mmol) were dissolved in DMF (10 mL) followed by the addition of HATU (2.85 g, 7.5 mmol). The reaction mixture was stirred for 12 h at rt whereupon the mixture was extracted with saturated NH_4Cl solution and washed with EtOAc three times. The organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to afford the crude mixture that after purification using an ISCO system (EtOAc−MeOH) provided the title compound. LC−MS: *m*/*z* 259.

4-Bromo-*N*-(2-methoxyethyl)-2-methylbenzamide (19). The title compound was synthesized from 4-bromo-2-methylbenzoic acid and 2-methoxyethylamine using a method analogous to that of **18**. LC−MS: *m*/*z* 273.

4-Bromo-2-fluoro-*N*-(2-methoxyethyl)benzamide (20). The title compound was synthesized from 4-bromo-2-fluorobenzoic acid and 2-methoxyethylamine using a method analogous to that of **18**. LC−MS: *m*/*z* 277.

4-Bromo-*N*-[2-(dimethylamino)ethyl]benzamide (21). The title compound was synthesized from 4-bromobenzoyl chloride and *N*,*N*-dimethylethane-1,2-diamine using a method analogous to that of **17**. LC−MS: *m*/*z* 272.

4-Bromo-*N*-[2-(1-methylpyrrolidin-2-yl)ethyl]benzamide (22). The title compoumd was synthesized from 4-bromobenzoyl chloride and [2-(1-methylpyrrolidin-2-yl)ethyl]amine using a method analogous to that of **17**. LC−MS: *m*/*z* 312.

4-Bromo-*N*-(2-pyrrolidin-1-ylethyl)benzamide (23). The title compound was synthesized from 4-bromobenzoic acid and (2-pyrrolidin-1-ylethyl)amine using a method analogous to that of **18**. LC−MS: *m*/*z* 298.

***N*-(2-Methoxyethyl)-4-{[6-(2-methylpyridin-4-yl)quinazolin-2-yl]amino}benzamide (24).** The title compound was synthesized from 4-bromo-*N*-(2-methoxyethyl)benzamide (**17**) and 6-(2-methylpyridin-4-yl)quinazolin-2-amine (**7**) following a similar procedure to that of **3**. ^{1}H NMR: 10.30 (s, 1H), 9.42 (s, 1H), 8.54 (d, 1H), 8.44 (s, 1H), 8.38 (m, 1H), 8.27 (d, 1H), 8.08 (m, 2H), 7.84 (m, 2H), 7.72 (s, 1H), 7.62 (m, 2H), 3.44 (m, 4H), 3.27 (s, 3H), 2.56 (s, 3H). LC−MS: *m*/*z* 414. Purity: 94%.

***N*-(2-Methoxyethyl)-4-{[6-(3-methoxypyridin-4-yl)quinazolin-2-yl]amino}benzamide (25).** The title compound was synthesized from 4-bromo-*N*-(2-methoxyethyl)benzamide (**17**) and 6-(3-methoxypyridin-4-yl)quinazolin-2-amine (**8**) following a similar procedure to that of **3**. ^{1}H NMR: 10.27 (s, 1H), 9.41 (s, 1H), 8.52 (s, 1H), 8.38 (m, 1H), 8.33 (d, 1H), 8.19 (m, 1H), 8.07 (d, 3H), 7.85 (d, 2H), 7.78 (d, 1H), 7.49 (d, 1H), 3.94 (s, 3H), 3.44 (m, 4H), 3.27 (s, 3H). LC−MS: *m*/*z* 430.

***N*-(2-Methoxyethyl)-4-{[6-(3-methylpyridin-4-yl)quinazolin-2-yl]amino}benzamide (26).** The title compound was synthesized from 4-bromo-*N*-(2-methoxyethyl)benzamide (**17**) and 6-(3-methylpyridin-4-yl)quinazolin-2-amine (**9**) following a similar procedure to that of **3**. ^{1}H NMR: 10.28 (s, 1H), 9.41 (s, 1H), 8.55 (s, 1H), 8.50 (d, 1H), 8.42−8.35 (m, 1H), 8.10−8.02 (m, 3H), 7.93−7.78 (m, 4H), 7.36 (d, 1H), 3.47−3.41 (m, 4H), 3.27 (s, 3H), 2.32 (s, 3H). LC−MS: *m*/*z* 414.

4-{[6-(3-Chloropyridin-4-yl)quinazolin-2-yl]amino}-*N*-(2-methoxyethyl)benzamide (27). The title compound was synthesized from 4-bromo-*N*-(2-methoxyethyl)benzamide (**17**) and 6-(3-chloropyridin-4-yl)quinazolin-2-amine (**10**) following a similar procedure to that of **3**. ^{1}H NMR: 10.34 (s, 1H), 9.47 (s, 1H), 8.80 (s, 1H), 8.65 (d, 1H), 8.46−8.35 (m, 1H), 8.22−8.15 (m, 1H), 8.09 (d, 2H), 8.01 (dd, 1H), 7.91−7.81 (m, 3H), 7.64 (d, 1H), 3.50−3.40 (m, 4H), 3.28 (s, 3H). LC−MS: *m*/*z* 434. Purity: 90%.

N-(2-Methoxyethyl)-4-(6-phenylquinazolin-2-ylamino)-benzamide (28). The title compound was synthesized from 4-bromo-*N*-(2-methoxyethyl)benzamide (**17**) and 6-phenylquinazolin-2-amine (**11**) following a similar procedure to that of **3**. ^{1}H NMR: 10.23 (s, 1H), 9.42 (s, 1H), 8.37 (m, 1H), 8.28 (m, 1H), 8.21 (m, 1H), 8.08 (d, 2H), 7.87−7.80 (m, 5H), 7.53 (t, 2H), 7.42 (t, 1H), 3.44 (m, 4H), 3.28 (s, 3H). LC−MS: *m*/*z* 399.

***N*-(2-Methoxyethyl)-4-[(6-pyridin-3-ylquinazolin-2-yl)-amino]benzamide (29).** The title compound was synthesized from 4-bromo-*N*-(2-methoxyethyl)benzamide (**17**) and 6-pyridin-3-ylquinazolin-2-amine (**12**) following a similar procedure to that of **3**. ^{1}H NMR: 10.29 (s, 1H), 9.42 (s, 1H), 9.03 (s, 1H), 8.61 (m, 1H), 8.40 (m, 1H), 8.36 (m, 1H), 8.23 (m, 2H), 8.08 (d, 2H), 7.84 (m, 3H), 7.54 (m, 1H), 3.44 (m, 4H), 3.27 (s, 3H). LC−MS: *m*/*z* 400.

***N*-(2-Methoxyethyl)-4-{[6-(4-methylpyridin-3-yl)quinazolin-2-yl]amino}benzamide (30).** The title compound was synthesized from 4-bromo-*N*-(2-methoxyethyl)benzamide (**17**) and 6-(4-methylpyridin-3-yl)quinazolin-2-amine (**13**) following a similar procedure to that of **3**. ^{1}H NMR: 10.26 (s, 1H), 9.40 (s, 1H), 8.47 (m, 2H), 8.38 (m, 1H), 8.07 (m, 2H), 8.00 (s, 1H), 7.84 (m, 4H), 7.37 (d, 1H), 3.44 (m, 4H), 3.27 (s, 3H), 2.32 (s, 3H). LC−MS: *m*/*z* 414.

***N*-(2-Methoxyethyl)-4-{[6-(6-methoxypyridin-3-yl)-quinazolin-2-yl]amino}benzamide (31).** The title compound was synthesized from 4-bromo-*N*-(2-methoxyethyl)benzamide (**17**) and 6-(6-methoxypyridin-3-yl)quinazolin-2-amine (**14**) following a similar procedure to that of **3**. ^{1}H NMR: 10.23 (s, 1H), 9.38 (s, 1H), 8.61 (m, 1H), 8.37 (m, 1H), 8.25 (m, 1H), 8.16 (m, 2H), 8.08 (m, 2H), 7.83 (m, 3H), 6.98 (d, 1H), 3.91 (s, 3H), 3.45 (m, 4H), 3.27 (s, 3H). LC−MS: *m*/*z* 430.

4-{[6-(6-Fluoropyridin-3-yl)quinazolin-2-yl]amino}-*N*-(2-methoxyethyl)benzamide (32). The title compound was synthesized from 4-bromo-*N*-(2-methoxyethyl)benzamide (**17**) and 6-(6-fluoropyridin-3-yl)quinazolin-2-amine (**15**) following a similar procedure to that of **3**. ^{1}H NMR: 10.27 (s, 1H), 9.40 (s, 1H), 8.69 (bs, 1H), 8.38 (m, 3H), 8.21 (m, 1H), 8.06 (d, 2H), 7.84 (m, 3H), 7.35 (m, 1H), 3.45 (m, 4H), 3.27 (s, 3H). LC−MS: *m*/*z* 418.

N-(2-Methoxyethyl)-4-(6-(pyrimidin-5-yl)quinazolin-2-ylamino)benzamide (33). The title compound was synthesized from 4-bromo-*N*-(2-methoxyethyl)benzamide (**17**) and 6-(pyrimidin-5-yl)-quinazolin-2-amine (**16**) following a similar procedure to that of **3**. ^{1}H NMR: 10.33 (s, 1H), 9.42 (s, 1H), 9.29 (s, 2H), 9.23 (s, 1H), 8.47 (m, 1H), 8.33 (m, 1H), 8.07 (m, 2H), 7.87 (m, 3H), 3.46 (m, 4H), 3.28 (s, 3H). LC−MS: *m*/*z* 401.

***N*-(2-Methoxyethyl)-3-[(6-pyridin-4-ylquinazolin-2-yl)-amino]benzamide (34).** The title compound was synthesized from 6-pyridin-4-ylquinazolin-2-amine (**6**) and 3-bromo-*N*-(2-methoxyethyl)-benzamide (**18**) following a similar procedure to that of **3**. ^{1}H NMR: 10.17 (s, 1H), 9.41 (s, 1H), 8.68 (d, 2H), 8.45 (m, 3H), 8.29 (d, 1H), 8.16 (d, 1H), 7.84 (d, 2H), 7.78 (d, 1H), 7.44 (m, 2H), 3.58 (m, 4H), 3.29 (s, 3H). LC−MS: *m*/*z* 400.

***N*-(2-Methoxyethyl)-2-methyl-4-[(6-pyridin-4-ylquinazolin-2-yl)amino]benzamide (35).** The title compound was synthesized from 4-bromo-*N*-(2-methoxyethyl)-2-methylbenzamide (**19**) and 6-pyridin-4-ylquinazolin-2-amine (**6**) following a similar procedure to that of **3**. ^{1}H NMR: 10.12 (s, 1H), 9.41 (s, 1H), 8.68 (d, 2H), 8.44 (m, 1H), 8.28 (d, 1H), 8.16 (m, 1H), 7.92 (d, 1H), 7.83 (m, 4H), 7.33 (d, 1H), 3.45 (m, 4H), 3.28 (s, 3H), 2.38 (s, 3H). LC−MS: *m*/*z* 414.

2-Fluoro-*N*-(2-methoxyethyl)-4-[(6-pyridin-4-ylquinazolin-2-yl)amino]benzamide (36). The title compound was synthesized from 4-bromo-2-fluoro-*N*-(2-methoxyethyl)benzamide (**20**) and 6-pyridin-4-ylquinazolin-2-amine (**6**) following a similar procedure to that of **3**. ^{1}H NMR: 10.52 (s, 1H), 9.47 (s, 1H), 8.69 (d, 2H), 8.48 (s, 1H), 8.33 (d, 1H), 8.16 (d, 1H), 8.02 (m, 1H), 7.86 (m, 3H), 7.71 (m, 2H), 3.44 (m, 4H), 3.27 (s, 3H). LC−MS: *m*/*z* 418.

***N*-[2-(Dimethylamino)ethyl]-4-[(6-pyridin-4-ylquinazolin-2-yl)amino]benzamide (37).** The title compound was synthesized from 4-bromo-*N*-[2-(dimethylamino)ethyl]benzamide (**21**) and 6-pyridin-4-ylquinazolin-2-amine (**6**) following a similar procedure to that of **3**. ^{1}H NMR: 10.31 (s, 1H), 9.43 (s, 1H), 8.68 (d, 2H), 8.46 (m, 1H), 8.28 (m, 2H), 8.07 (m, 2H), 7.84 (m, 5H), 3.36 (m, 2H), 2.39 (m, 2H), 2.17 (s, 6H). LC−MS: *m*/*z* 413.

***N*-[2-(1-Methylpyrrolidin-2-yl)ethyl]-4-[(6-pyridin-4-ylquinazolin-2-yl)amino]benzamide (38).** The title compound was synthesized from 4-bromo-*N*-[2-(1-methylpyrrolidin-2-yl)ethyl]-benzamide (**22**) and 6-pyridin-4-ylquinazolin-2-amine (**6**) following a similar procedure to that of **3**. ^{1}H NMR: 10.30 (s, 1H), 9.43 (s, 1H), 8.69

(d, 2H), 8.46 (s, 1H), 8.30 (m, 2H), 8.07 (d, 2H), 7.85 (m, 5H), 3.27 (m, 2H), 2.92 (m, 1H), 2.20 (s, 3H), 2.00 (m, 4H), 1.62 (m, 2H), 1.44 (m, 2H). LC−MS: *m*/*z* 453.

4-[(6-Pyridin-4-ylquinazolin-2-yl)amino]-*N*-(2-pyrrolidin-1-ylethyl)benzamide (39). The title compound was synthesized from 4-bromo-*N*-(2-pyrrolidin-1-ylethyl)benzamide (**23**) and 6-pyridin-4-ylquinazolin-2-amine (**6**) following a similar procedure to that of **3**. ^{1}H NMR: 10.31 (s, 1H), 9.43 (s, 1H), 8.69 (d, 2H), 8.46 (s, 1H), 8.28 (m, 2H), 8.07 (d, 2H), 7.84 (m, 5H), 3.35 (m, 2H), 2.41−2.53 (m, 4H), 1.67 (m, 6H). LC−MS: *m*/*z* 439.

4-[(6-Pyridin-4-ylquinazolin-2-yl)amino]benzaldehyde (40). 6-Pyridin-4-ylquinazolin-2-amine (**6**, 2 g, 9.0 mmol), 4-bromobenzaldehyde (1.83 g, 9.9 mmol), Cs_2CO_3 (8.8 g, 27 mmol, 3.0 equiv), and BINAP (1.12 g, 1.8 mmol, 0.2 equiv) in dioxane (60 mL) were treated with $Pd_2(dba)_3$ (825 mg, 0.9 mmol). The reaction mixture was heated to 100 °C for 3 h. The reaction was cooled and filtered. The crude mixture was purified on an ISCO system (EtOAc/Et_3N) to yield 1.5 g (51%) of the title compound. ^{1}H NMR: 10.61 (s, 1H), 9.87 (s, 1H), 9.48 (s, 1H), 8.69 (m, 2H), 8.49 (m, 1H), 8.33 (m, 1H), 8.25 (d, 2H), 7.87 (m, 5H). LC−MS: *m*/*z* 327.

***N*-(4-Bromophenyl)-3-methoxy-*N*-methylpropanamide (41).** The title compound was synthesized from 3-methoxypropanoic acid and (4-bromophenyl)methylamine using a method analogous to that of **18**. LC−MS: *m*/*z* 273.

[1-(4-Bromophenyl)ethyl](2-methoxyethyl)amine (42). To a solution of 1-(4-bromophenyl)ethanone (500 mg, 2.51 mmol) and (2-methoxyethyl)amine (188 mg, 2.51 mmol) in toluene (13 mL) were added diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (907 mg, 3.51 mmol), thiourea (19 mg, 0.25 mmol), and 5 Å molecular sieves (∼5 g). The reaction was heated at 50 °C under nitrogen for approximately 40 h. The reaction mixture was filtered, solvent was evaporated under reduced pressure, and the residue was purified by an ISCO system (EtOAc/hexane, TLC with I_2) to give 120 mg of a colorless oil (19% yield). ^{1}H NMR ($CDCl_3$): 7.39 (d, 2H), 7.17 (d, 2H), 3.69 (m, 1H), 3.41 (m, 2H), 3.30 (s, 3H), 2.59 (m, 2H), 1.29 (d, 3H).

***N*-(1-(4-Bromophenyl)ethyl)-3-methoxypropanamide (43).** The title compound was synthesized from 1-(4-bromophenyl)-ethylamine and 3-methoxypropanoyl chloride using a method analogous to that of **17**. LC−MS: *m*/*z* 287.

***N*-[(1*R*)-1-(4-Bromophenyl)ethyl]-3-methoxypropanamide (44).** The title compound was synthesized from [(1*R*)-1-(4-bromophenyl)ethyl]amine and 3-methoxypropanoic acid using a method analogous to that of **18**. LC−MS: *m*/*z* 287.

***N*-[(1*S*)-1-(4-Bromophenyl)ethyl]-3-methoxypropanamide (45).** The title compound was synthesized from [(1*S*)-1-(4-bromophenyl)ethyl]amine and 3-methoxypropanoic acid using a method analogous to that of **18**. LC−MS: *m*/*z* 287.

***N*-(1-(4-Bromophenyl)ethyl)acetamide (46).** The title compound was synthesized from 1-(4-bromophenyl)ethanamine and acetyl chloride using a method analogous to that of **17**. LC−MS: *m*/*z* 243.

***(R)*-*N*-(1-(4-Bromophenyl)ethyl)acetamide (47).** The title compound was synthesized from (*R*)-1-(4-bromophenyl)ethanamine and acetyl chloride using a method analogous to that of **17**. LC−MS: *m*/*z* 243.

***N*-(4-{[(2-Methoxyethyl)amino]methyl}phenyl)-6-pyridin-4-ylquinazolin-2-amine (48).** 4-[(6-Pyridin-4-ylquinazolin-2-yl)-amino]benzaldehyde (**40**, 70 mg, 0.21 mmol) and (2-methoxyethyl)-amine (18 mg, 0.24 mmol) in 5 mL of MeOH (with 3 Å molecular sieves) were stirred at room temperature, whereupon a few drops of acetic acid were added. $NaBH_3CN$ (22 mg, 1.6 equiv) was then added and the reaction mixture was stirred at room temperature overnight followed by quenching with NaOH (1 N, aq, ∼5 mL). The reaction mixture was extracted with EtOAc, and the water layers were then extracted with EtOAc three times. The combined organic layers were washed with water and brine, evaporated, and purified by Gilson HPLC (0.1% 10 mM ammonium acetate in CH_3CN and water) to give 25 mg (95%) of the title compound. ^{1}H NMR: 9.99 (s, 1H), 9.36 (s, 1H), 8.67 (d, 2H), 8.41 (d, 1H), 8.25 (m, 1H), 7.91 (d, 2H), 7.83 (d, 2H), 7.75 (d, 1H), 7.27 (d, 2H), 3.66 (s, 2H), 3.39 (m, 2H), 3.23 (s, 3H), 2.63 (m, 2H). LC−MS: *m*/*z* 384 (M−H).

Compounds **49** and **50** were prepared following a similar procedure to that of **48**.

***N*-(4-{[(2-Methoxyethyl)(methyl)amino]methyl}phenyl)-6-pyridin-4-ylquinazolin-2-amine (49).** The title compound was synthesized from 4-[(6-pyridin-4-ylquinazolin-2-yl)amino]-benzaldehyde (**40**) and (2-methoxyethyl)methylamine. ^{1}H NMR: 10.01 (s, 1H), 9.37 (s, 1H), 8.67 (d, 2H), 8.41 (d, 1H), 8.25 (m, 1H), 8.18 (s, 1H), 7.92 (d, 2H), 7.83 (d, 2H), 7.75 (d, 1H), 7.24 (d, 2H), 3.66 (s, 2H), 3.47 (m, 2H), 3.20 (s, 3H), 2.66 (m, 2H), 2.27 (s, 3H). LC−MS: *m*/*z* 422 (M + Na).

***N*,*N*-Dimethyl-*N*′-{4-[(6-pyridin-4-ylquinazolin-2-yl)amino]-benzyl}ethane-1,2-diamine (50).** The title compound was synthesized from 4-[(6-pyridin-4-ylquinazolin-2-yl)amino]benzaldehyde (**40**) and *N*,*N*-dimethylethane-1,2-diamine. ^{1}H NMR: 10.00 (s, 1H), 9.38 (s, 1H), 8.69 (d, 2H), 8.43 (d, 1H), 8.26 (m, 1H), 7.92 (d, 2H), 7.84 (d, 2H), 7.76 (d, 1H), 7.28 (d, 2H), 3.67 (s, 2H), 2.54 (m, 2H), 2.33 (m, 2H), 2.12 (s, 6H). LC−MS: *m*/*z* 397 (M − H).

6-Pyridin-4-yl-*N*-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-quinazolin-2-amine (51). The title compound was synthesized from 6-pyridin-4-ylquinazolin-2-amine (**6**) and 1-[2-(4-bromophenoxy)-ethyl]pyrrolidine (commercially available) using a method analogous to the preparation of **3**. ^{1}H NMR: 9.86 (s, 1H), 9.33 (s, 1H), 8.67 (d, 2H), 8.39 (s, 1H), 8.21 (m, 1H), 7.83 (m, 4H), 7.70 (d, 1H), 6.95 (d, 2H), 4.04 (m, 2H), 2.79 (m, 2H), 2.53 (m, 4H), 1.68 (m, 4H). LC−MS: *m*/*z* 412. Purity: 90%.

3-Methoxy-*N*-methyl-*N*-(4-(6-(pyridin-4-yl)quinazolin-2-ylamino)phenyl)propanamide (52). The title compound was synthesized from *N*-(4-bromophenyl)-3-methoxy-*N*-methylpropanamide (**41**) and 6-pyridin-4-ylquinazolin-2-amine (**6**) using a method analogous to the preparation of **3**, except with Xantphos and palladium(II) acetate and by heating in a microwave at 160 °C for 1 h. ^{1}H NMR: 10.2 (s, 1H), 9.41 (s, 1H), 8.68 (d, 2H), 8.44 (s, 1H), 8.28 (d, 1H), 8.06 (d, 2H), 7.83 (m, 3H), 7.28 (d, 2H), 3.48 (t, 2H), 3.14 (m, 6H), 2.27 (t, 2H). LC−MS: *m*/*z* 414.

***N*-(4-{1-[(2-Methoxyethyl)amino]ethyl}phenyl)-6-pyridin-4-ylquinazolin-2-amine (53).** The title compound was synthesized from [1-(4-bromophenyl)ethyl](2-methoxyethyl)amine (**42**) and 6-pyridin-4-ylquinazolin-2-amine (**6**) using a method analogous to the preparation of **3**. ^{1}H NMR: 9.97 (s, 1H), 9.36 (s, 1H), 8.67 (d, 2H), 8.41 (d, 1H), 8.25 (m, 2H), 7.90 (d, 2H), 7.83 (d, 2H), 7.74 (d, 1H), 7.27 (d, 2H), 3.68 (m, 1H), 3.34 (m, 2H), 3.21 (s, 3H), 2.43 (m, 2H), 1.25 (d, 3H). LC−MS: *m*/*z* 422 (M + Na).

3-Methoxy-*N*-(1-{4-[(6-pyridin-4-ylquinazolin-2-yl)amino]-phenyl}ethyl)propanamide (54). The title compound was synthesized from *N*-(1-(4-bromophenyl)ethyl)-3-methoxypropanamide (**43**) and 6-pyridin-4-ylquinazolin-2-amine (**6**) using a method analogous to the preparation of **3**, using Xantphos and palladium(II) acetate and by heating in a microwave at 160 °C for 1 h. ^{1}H NMR: 9.98 (s, 1H), 9.36 (s, 1H), 8.68 (d, 2H), 8.42 (s, 1H), 8.25 (d, 2H), 7.89 (d, 2H), 7.84 (d, 2H), 7.76 (d, 1H), 7.27 (d, 2H), 4.9 (m, 1H), 3.52 (t, 2H), 3.21 (s, 3H), 2.35 (t, 2H), 1.34 (s, 3H). LC−MS: *m*/*z* 428. Purity: 93%.

The following compounds **55**−**58** were prepared in a similar fashion as **54**.

3-Methoxy-*N*-((1*R*)-1-{4-[(6-pyridin-4-ylquinazolin-2-yl)-amino]phenyl}ethyl)propanamide (55). The title compound was synthesized from *N*-[(1*R*)-1-(4-bromophenyl)ethyl]-3-methoxypropanamide (**44**) and 6-pyridin-4-ylquinazolin-2-amine (**6**). ^{1}H NMR: 9.98 (s, 1H), 9.36 (s, 1H), 8.67 (d, 2H), 8.41 (s, 1H), 8.24 (d, 2H), 7.89 (d, 2H), 7.83 (d, 2H), 7.75 (d, 1H), 7.27 (d, 2H), 4.90 (m, 1H), 3.52 (t, 2H), 3.21 (s, 3H), 2.35 (t, 2H), 1.34 (d, 3H). LC−MS: *m*/*z* 428.

3-Methoxy-*N*-((1*S*)-1-{4-[(6-pyridin-4-ylquinazolin-2-yl)-amino]phenyl}ethyl)propanamide (56). The title compound was synthesized from *N*-[(1*S*)-1-(4-bromophenyl)ethyl]-3-methoxypropanamide (**45**) and 6-pyridin-4-ylquinazolin-2-amine (**6**). ^{1}H NMR: 9.98 (s, 1H), 9.36 (s, 1H), 8.67 (d, 2H), 8.41 (s, 1H), 8.25 (d, 2H), 7.89 (d, 2H), 7.83 (d, 2H), 7.74 (d, 1H), 7.27 (d, 2H), 4.9 (m, 1H), 3.52 (t, 2H), 3.21 (s, 3H), 2.35 (t, 2H), 1.3 (d, 3H). LC−MS: *m*/*z* 428.

***N*-(1-(4-(6-(Pyridin-4-yl)quinazolin-2-ylamino)phenyl)ethyl)-acetamide (57).** The title compound was synthesized from *N*-(1-(4-bromophenyl)ethyl)acetamide (**46**) and 6-pyridin-4-ylquinazolin-2-amine (**6**). ^{1}H NMR: 9.98 (s, 1H), 9.36 (s, 1H), 8.67 (d, 2H), 8.41

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(s, 1H), 8.25 (m, 2H), 7.90 (d, 2H), 7.83 (d, 2H), 7.75 (d, 1H), 7.27 (d, 2H), 4.88 (m, 1H), 1.83 (s, 3H), 1.33 (d, 3H). LC−MS: *m*/*z* 384. Purity: 90%.

(*R*)-*N*-(1-(4-(6-(Pyridin-4-yl)quinazolin-2-ylamino)phenyl)-ethyl)acetamide (58). The title compound was synthesized from (*R*)-*N*-(1-(4-bromophenyl)ethyl)acetamide (**47**) and 6-pyridin-4-ylquinazolin-2-amine (**6**). ^{1}H NMR: 9.98 (s, 1H), 9.36 (s, 1H), 8.67 (d, 2H), 8.41 (s, 1H), 8.25 (m, 2H), 7.90 (d, 2H), 7.83 (d, 2H), 7.76 (d, 1H), 7.27 (d, 2H), 4.88 (m, 1H), 1.83 (s, 3H), 1.33 (d, 3H). LC−MS: *m*/*z* 384.

[4-(2-Methoxyethoxy)phenyl]amine (59). 4-Aminophenol (2.2 g, 19.8 mmol) and potassium carbonate (5.5 g, 39.6 mmol) were dissolved in DMF. To the reaction mixture was added 1-chloro-2-methoxyethane (2 mL, 21.8 mmol) and the mixture was stirred overnight at 80 °C. The resulting solids were filtered, and the filtrate was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by an ISCO system (50−100% EtOAc in hexanes) to afford 538 mg of the title compound (16% yield). LC−MS: *m*/*z* 168.

***N*-(4-Aminophenyl)-3-methoxypropanamide (60).** The title compound was synthesized from deprotection of *tert*-butyl {4-[3-methoxypropanoyl)amino]phenyl}carbamate intermediate, which was synthesized in analogy to **18** from *tert*-butyl (4-aminophenyl)carbamate and 3-methoxypropanoic acid and was carried forward crude into the BOC group deprotection using standard acid mediated conditions. LC−MS: *m*/*z* 403.

***N*-(2-Methoxyethyl)-*N*-methylbenzene-1,4-diamine (61).** To a solution of *N*-(2-methoxyethyl)-*N*-methyl-4-nitroaniline (prepared from 1-bromo-4-nitrobenzene and 2-methoxyethylamine using a method analogous to the preparation of **3**, 700 mg, 3.3 mmol) in ethanol (8 mL) was added $SnCl_2 \cdot H_2O$ (1.8 g, 8.3 mmol), and the reaction was stirred overnight at 70 °C. To the reaction mixture was then added 4.0 M NaOH. The mixture was extracted (2×) with EtOAc, and the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford 505 mg of a green oil, which was taken on crude immediately to the next reaction.

6-Bromo-*N*-[4-(2-methoxyethoxy)phenyl]quinazolin-2-amine (62). To [4-(2-methoxyethoxy)phenyl]amine (**59**, 100 mg, 0.598 mmol) in propan-2-ol (3 mL) was added 6-bromo-2-chloroquinazoline (prepared in analogy to ref 16; 131 mg, 0.538 mmol). The reaction mixture was stirred for 2 h at 100 °C and then allowed to cool to room temperature. The title compound was formed as a precipitate from the solution yielding 123 mg (56% yield). LC−MS: *m*/*z* 388.

***N*-(4-(6-Bromoquinazolin-2-ylamino)phenyl)-3-methoxypropanamide (63).** The title compound was synthesized from 6-bromo-2-chloroquinazoline (prepared in analogy to ref 16) and *N*-(4-aminophenyl)-3-methoxypropanamide (**60**) using a method analogous to **62**. LC−MS: *m*/*z* 403.

***N*-{4-[(6-Bromoquinazolin-2-yl)amino]phenyl}-*N*-methylacetamide (64).** 6-Bromo-2-chloroquinazoline (prepared in analogy to ref 16; 100 mg, 0.412 mmol, 1.0 equiv), *N*-(4-aminophenyl)-*N*-methylacetamide (101 mg, 0.617 mmol, 1.5 equiv), and acetonitrile (5.0 mL) were added to a microwave vial which was heated in a microwave at 125 °C for 30 min. The reaction was then concentrated to afford a crude solid that was purified by an ISCO system (100% hexanes to 100% EtOAc) to obtain a yellow solid. LC−MS: *m*/*z* 372.

***N*-{4-[(6-Bromoquinazolin-2-yl)amino]phenyl}acetamide (65).** The title compound was synthesized from 6-bromo-2-chloroquinazoline (prepared in analogy to ref 16) and *N*-(4-aminophenyl)acetamide using a method similar to that of **64**. LC−MS: *m*/*z* 372.

***N*′-(6-Bromoquinazolin-2-yl)-*N*-(2-methoxyethyl)-*N*-methylbenzene-1,4-diamine (66).** The title compound was synthesized from 6-bromo-2-chloroquinazoline (prepared in analogy to ref 16) and *N*-(2-methoxyethyl)- *N*-methylbenzene-1,4-diamine (**61**) prepared by a method similar to that of **62**. LC−MS: *m*/*z* 389.

***N*-[4-(2-Methoxyethoxy)phenyl]-6-pyridin-4-ylquinazolin-2-amine (67).** The title compound was synthesized from 4-pyridinylboronic acid and 6-bromo-*N*-[4-(2-methoxyethoxy)phenyl]quinazolin-2-amine (**62**) using a procedure analogous to that of **6**. ^{1}H NMR: 9.88 (s, 1H), 9.32 (s, 1H), 8.66 (s, 2H), 8.39 (s, 1H), 8.22 (d, 1H), 7.90−7.80 (m, 3H), 7.75−7.64 (m, 2H), 6.94 (d, 2H), 4.10−4.03 (m, 2H), 3.65 (t, 2H), 3.31 (s, 3H). LC−MS: *m*/*z* 373.

3-Methoxy-*N*-(4-(6-(pyridin-4-yl)quinazolin-2-ylamino)-phenyl)propanamide (68). The title compound was synthesized from *N*-(4-(6-bromoquinazolin-2-ylamino)phenyl)-3-methoxypropanamide (**63**) and 4-pyridinylboronic acid using a method similar to that of **6**, except with $PdCl_2(dppf) \cdot CH_2Cl_2$ as catalyst. Purification was performed by Gilson HPLC (0.1% ammonium acetate in CH_3CN and water) to yield a yellow solid (16 mg, 0.04 mmol, 30.6% yield). ^{1}H NMR: 10.17 (s, 1H), 9.98 (s, 1H), 9.39 (s, 1H), 8.99 (d, 2H), 8.72 (s, 1H), 8.50 (d, 2H), 8.43 (d, 1H), 7.90 (d, 2H), 7.81 (d, 1H), 7.62−7.55 (m, 2H), 3.61 (t, 2H), 3.24 (s, 3H), 2.54 (t, 2H). LC−MS: *m*/*z* 400.

***N*-Methyl-*N*-{4-[(6-pyridin-4-ylquinazolin-2-yl)amino]-phenyl}acetamide (69).** The title compound was synthesized from *N*-{4-[(6-bromoquinazolin-2-yl)amino]phenyl}-*N*-methylacetamide (**64**) and 4-pyridinylboronic acid using a similar method to that of **68**, except with cesium carbonate as base, dioxane/water (4:1) as solvent, and with reaction temperature of 80 °C. Purification was performed by Gilson HPLC (0.1% ammonium acetate in CH_3CN and water). ^{1}H NMR: 10.20 (s, 1H), 9.41 (s, 1H), 8.68 (d, 2H), 8.45 (s, 1H), 8.28 (m, 1H), 8.06 (d, 2H), 7.82 (m, 3H), 7.29 (d, 2H), 3.14 (s, 3H), 1.78 (s, 3H). LC−MS: *m*/*z* 370.

***N*-{4-[(6-Pyridin-4-ylquinazolin-2-yl)amino]phenyl}-acetamide (70).** The title compound was synthesized from *N*-{4-[(6-bromoquinazolin-2-yl)amino]phenyl}acetamide (**65**) and 4-pyridinylboronic acid using a similar method to that of **69**. ^{1}H NMR: 9.96 (s, 1H), 9.87 (s, 1H), 9.35 (s, 1H), 8.68 (m, 2H), 8.40 (s, 1H), 8.25 (m, 1H), 7.86 (m, 5H), 7.53 (m, 2H), 2.02 (s, 3H). LC−MS: *m*/*z* 356.

***N*-(2-Methoxyethyl)-*N*-methyl-*N*′-(6-pyridin-4-ylquinazolin-2-yl)benzene-1,4-diamine (71).** The title compound was synthesized from *N*′-(6-bromoquinazolin-2-yl)-*N*-(2-methoxyethyl)-*N*-methylbenzene-1,4-diamine (**66**) and 4-pyridinylboronic acid using a similar method to that of **69**. ^{1}H NMR: 9.86 (s, 1H), 9.30 (s, 1H), 8.78 (d, 2H), 8.49 (s, 1H), 8.28 (d, 1H), 8.08 (d, 2H), 7.80 (s, 2H), 7.69 (d, 1H), 6.83 (s, 2H), 3.48 (bs, 7H), 2.94 (s, 3H). LC−MS: *m*/*z* 386.

(*R*)-*tert*-Butyl 1-(4-Bromophenyl)ethylcarbamate (72). (*R*)-1-(4-Bromophenyl)ethanamine (5 g, 24.99 mmol), BOC anhydride (6.00 g, 27.94 mmol), and THF (50 mL) were stirred at room temperature for 12 h. The resulting reaction mixture was concentrated under reduced pressure to afford a white solid which was used directly in the next step. ^{1}H NMR: 7.50 (m, 2H), 7.24 (m, 2H), 4.48−4.66 (m, 1H), 1.35 (s, 9 H), 1.27 (d, *J* = 7.16 Hz, 3H). LC−MS: *m*/*z* 200 (M + H − BOC).

(*R*)-*N*-(4-(1-Aminoethyl)phenyl)-6-(pyridin-4-yl)quinazolin-2-amine Hydrochloride (73). The title compound was synthesized from (*R*)-*tert*-butyl 1-(4-bromophenyl)ethylcarbamate (**72**) and 6-pyridin-4-ylquinazolin-2-amine (**6**) using a method analogous to the preparation of **3**, with Xantphos and palladium(II) acetate and by heating at 100 °C for 4 h. Purification on an ISCO system (100% hexanes to 100% ethyl acetate) afforded (*R*)-*tert*-butyl 1-(4-(6-(pyridin-4-yl)quinazolin-2-ylamino)phenyl)ethylcarbamate, which was carried forward and treated with 2 N HCl in ether solution followed by concentration under reduced pressure to afford the title compound. ^{1}H NMR: 10.20−10.43 (m, 1H), 9.44 (s, 1H), 8.97 (d, *J* = 5.27 Hz, 2H), 8.65−8.76 (m, 1H), 8.25−8.49 (m, 6H), 8.03 (m, 2H), 7.85 (d, *J* = 8.67 Hz, 1H), 7.49 (m, 2H), 4.39 (m, 1H), 1.52 (d, *J* = 6.59 Hz, 3H). LC−MS: *m*/*z* 342.

Benzyl 3-Hydroxy-5-oxo-5,6-dihydropyridine-1(2*H*)-carboxylate (74). To a 50 mL round-bottomed flask was added 3,5-dimethoxypyridine (0.983 g, 7.06 mmol) and $NaBH_4$ (0.481 g, 12.72 mmol) in acetonitrile (20.54 mL) to give a colorless suspension. Benzyl carbonochloridate (1.256 mL, 8.48 mmol) was added, dropwise, at 0 °C over 20 min to produce a milky mixture. The reaction mixture was stirred for an additional 30 min at 0 °C (whereby LC−MS indicated the consumption of starting material) and then poured into 1 M aqueous NaOH (20 mL). The reaction was extracted with EtOAc (3 × 20 mL), the organic fractions were combined and rinsed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield an oily mixture. Exposure of the mixture to MeOH produced small crystals, which were isolated via vacuum filtration. The resulting filtrate was concentrated under reduced pressure, exposed to MeOH (5 mL), cooled at 0 °C for 30 min, and the resulting solid was isolated via

vacuum-filtration. The filtrate was concentrated via reduced pressure to yield the dimethyl enol ether intermediate, which was subsequently dissolved in 1,4-dioxane (20 mL). Then 4 M aqueous HCl was added (10 mL) and reaction mixture was stirred at 23 °C for 3 h. The reaction was then extracted with EtOAc (3 × 20 mL), and the organic extracts were combined, rinsed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the title compound (75% purity by LC−MS), which was taken forward as the crude material to the next step. LC−MS: *m*/*z* 248.

(*R*)-*N*-((*R*)-1-(4-(6-(Pyridin-4-yl)quinazolin-2-ylamino)-phenyl)ethyl)piperidine-2-carboxamide Hydrochloride (75). In a 10 mL vial, (*R*)-*N*-(4-(1-aminoethyl)phenyl)-6-(pyridin-4-yl)-quinazolin-2-amine hydrochloride (**73**, 5.567 g, 12.35 mmol), (*R*)-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid hydrochloride (3.94 g, 14.82 mmol), DIPEA (9.71 mL, 55.57 mmol), and HATU (9.39 g, 24.70 mmol) were combined in DMF (61.7 mL) to give a yellow solution. The reaction was stirred for 18 h at 60 °C, poured into 10% aqueous K_2HPO_4 (60 mL), and extracted with EtOAc (3 × 40 mL). The organic extracts were combined and rinsed with saturated NH_4Cl (3 × 30 mL) and brine (40 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield a yellow foam. HCl (4 M) in dioxane (31.2 mL, 125 mmol) and MeOH (6.24 mL) were added to afford a yellow solution. The reaction was stirred for 4 h at 23 °C and then evaporated to dryness, followed by addition of toluene, concentration under reduced pressure, and then drying under high vacuum to yield the title compound. ^{1}H NMR: 9.99 (s, 1H), 9.37 (s, 1H), 8.68 (d, *J* = 5.09 Hz, 2H), 8.42 (s, 1H), 8.26 (d, *J* = 7.35 Hz, 1 H), 7.67−8.01 (m, 6H), 7.28 (d, *J* = 8.29 Hz, 2H), 4.90 (m, 1H), 3.06 (d, *J* = 8.85 Hz, 1H), 2.92 (d, *J* = 12.43 Hz, 1H), 2.10−2.24 (m, 1H), 1.73 (d, *J* = 9.42 Hz, 2H), 1.17−1.53 (m, 7H). LC−MS: *m*/*z* 453.

1-Methyl-*N*-((*R*)-1-(4-(6-(pyridin-4-yl)quinazolin-2-ylamino)-phenyl)ethyl)piperidine-2-carboxamide Hydrochloride (76). The title compound was synthesized from 1-methylpiperidine-2-carboxylic acid and (*R*)-*N*-(4-(1-aminoethyl)phenyl)-6-(pyridin-4-yl)-quinazolin-2-amine hydrochloride (**73**) using a method analogous to the preparation of **75**. ^{1}H NMR (MeOH-d_4), reported as a mixture of diastereomers: 9.23 (s, 1H), 8.49−8.64 (m, 2H), 8.24 (m, 1H), 8.15 (m, 1H), 7.67−7.91 (m, 5 H), 7.22−7.40 (m, 2H), 4.96−5.10 (m, 1H), 3.13−3.18 (m, 2H), 2.74−3.03 (m, 1H), 2.58−2.72 (m, 1H), 2.46−2.54 (m, 3H), 1.97−2.07 (m, 1H), 1.80 (m, 2H), 1.57−1.74 (m, 2H), 1.41−1.55 (m, 3H). LC−MS: *m*/*z* 467.

(*R*)-1-(2-Hydroxyethyl)-*N*-((R)-1-(4-(6-(pyridin-4-yl)-quinazolin-2 ylamino)phenyl)ethyl)piperidine-2-carboxamide (77). In a 10 mL vial, (*R*)-*N*-((*R*)-1-(4-(6-(pyridin-4-yl)quinazolin-2-ylamino)phenyl)ethyl)piperidine-2-carboxamide hydrochloride (**75**, 0.463 g, 0.82 mmol), 2-(*tert*-butyldimethylsilyloxy)acetaldehyde (0.158 g, 0.91 mmol), acetic acid (0.047 mL, 0.82 mmol), and DIPEA (0.460 mL, 2.64 mmol) were combined in MeOH (4.12 mL) to afford a yellow solution. Sodium cyanoborohydride (0.078 g, 1.24 mmol) was added and the reaction was stirred for 4 h at 23 °C. LC−MS indicated that the TBDMS group was cleaved under the reaction conditions, and all of the starting material was consumed. The reaction was poured into 1 M aq NaOH (30 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were combined and rinsed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield a pale yellow solid which was purified via an ISCO system (10% MeOH/DCM) to yield the title compound. ^{1}H NMR (DMSO-d_6 with a drop of MeOH added for dissolution): 9.32 (s, 1H), 8.58−8.70 (m, 2H), 8.34 (br s, 1H), 8.20 (dd, *J* = 8.85, 2.07 Hz, 1H), 7.89 (m, *J* = 8.48 Hz, 2H), 7.71−7.83 (m, 3H), 7.30 (m, *J* = 8.48 Hz, 2H), 4.88 (q, *J* = 6.91 Hz, 1H), 3.37−3.64 (m, 2H), 2.69−2.82 (m, 1H), 2.56−2.65 (m, 1H), 2.13−2.31 (m, 1H), 1.96−2.13 (m, 1H), 1.59−1.81 (m, 2H), 1.42−1.59 (m, 3H), 1.37 (d, *J* = 6.97 Hz, 3H), 1.12−1.33 (m, 2H). LC−MS: *m*/*z* 497.

(*S*)-*N*-((*R*)-1-(4-(6-(Pyridin-4-yl)quinazolin-2-ylamino)-phenyl)ethyl)piperidine-3-carboxamide Hydrochloride (78). The title compound was synthesized from (*S*)-1-(*tert*-butoxycarbonyl)-piperidine-3-carboxylic acid and (*R*)-*N*-(4-(1-aminoethyl)phenyl)-6-(pyridin-4-yl)quinazolin-2-amine hydrochloride (**73**) using a method similar to that of **75** except using 2 N HCl in ether for BOC group deprotection. ^{1}H NMR: 10.17 (s, 1H), 9.40 (m, 2H), 8.98 (m, 2H), 8.70 (m, 1H), 8.46 (m, 2H), 7.91 (m, 5H), 7.28 (m, 2H), 4.88 (m, 1H), 3.67 (m, 2H), 2.94 (m, 2H), 1.95 (m, 1H), 1.73 (m, 2H), 1.58 (m, 2H), 1.37 (m, 3H). LC−MS: *m*/*z* 453.

(*R*)-*N*-(1-(4-(6-(Pyridin-4-yl)quinazolin-2-ylamino)phenyl)-ethyl)piperidine-4-carboxamide Hydrochloride (79). The title compound was synthesized from 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid and (*R*)-*N*-(4-(1-aminoethyl)phenyl)-6-(pyridin-4-yl)-quinazolin-2-amine hydrochloride (**73**) using a method similar to that of **75**. ^{1}H NMR: 10.21 (s, 1H), 9.41 (s, 1H), 9.24 (d, *J* = 9.80 Hz, 1H), 9.00 (d, *J* = 6.97 Hz, 2H), 8.69−8.86 (m, 2H), 8.52 (d, *J* = 6.97 Hz, 2H), 8.45 (dt, *J* = 8.76, 2.03 Hz, 2H), 7.89 (m, 2H), 7.80 (d, *J* = 9.04 Hz, 1H), 7.29 (m, 2H), 4.89 (m, 1H), 3.59−3.75 (m, 1H), 3.39−3.54 (m, 1H), 3.17−3.31 (m, 2H), 2.73−2.94 (m, 2H), 1.63−1.94 (m, 3H), 1.36 (d, *J* = 6.97 Hz, 3 H). LC−MS: *m*/*z* 453.

(*R*)-*N*-((*R*)-1-(4-(6-(Pyridin-4-yl)quinazolin-2-ylamino)-phenyl)ethyl)pyrrolidine-2-carboxamide Hydrochloride (80). The title compound was synthesized from BOC-D-proline and (*R*)-*N*-(4-(1-aminoethyl)phenyl)-6-(pyridin-4-yl)quinazolin-2-amine hydrochloride (**73**) using a method similar to that of **75**. ^{1}H NMR: 10.21 (br s, 1H), 10.07 (s, 1H), 9.34−9.42 (m, 1H), 9.10−9.23 (m, 1H), 8.80 (d, *J* = 5.27 Hz, 2H), 8.41−8.58 (m, 2H), 8.32 (dd, *J* = 9.04, 2.07 Hz, 1H), 8.05−8.13 (m, 2H), 7.95 (s, 1H), 7.77 (d, *J* = 8.85 Hz, 1H), 7.31 (d, *J* = 8.67 Hz, 2H), 4.95 (quin, 1H), 4.15−4.32 (m, 1H), 3.63−3.76 (m, 1H), 3.41−3.54 (m, 1H), 2.30−2.43 (m, 1H), 1.69−1.96 (m, 3H), 1.43 (d, *J* = 6.97 Hz, 3 H). LC−MS: *m*/*z* 439.

(*R*)-3-(1-(4-(6-(Pyridin-4-yl)quinazolin-2-ylamino)phenyl)-ethylamino)cyclohex-2-enone (81). To (*R*)-*N*-(4-(1-aminoethyl)-phenyl)-6-(pyridin-4-yl)quinazolin-2-amine hydrochloride (**73**, 0.298 g, 0.66 mmol) and cyclohexane-1,3-dione (0.222 g, 1.98 mmol), acetic acid (0.038 mL, 0.66 mmol), and DIPEA (0.358 mL, 2.05 mmol) was added MeOH (3.31 mL) to give a yellow solution. The reaction was stirred for 12 h at 60 °C. The reaction was quenched with 1 M aqueous NaOH (30 mL). The resulting thick oil was triturated with a mixture of MTBE (10 mL) and EtOAc (6 mL). The resultant yellow solid was isolated via vacuum filtration, rinsed with MTBE (2 × 5 mL), and dried under high-vacuum to yield the title compound. ^{1}H NMR: 10.01 (s, 1H), 9.31−9.40 (m, 1H), 8.63−8.75 (m, 2H), 8.42 (d, *J* = 2.07 Hz, 1H), 8.26 (dd, *J* = 8.85, 2.26 Hz, 1H), 7.92 (m, 2H), 7.81−7.87 (m, 2H), 7.77 (d, *J* = 8.85 Hz, 1H), 7.40 (d, *J* = 6.78 Hz, 1H), 7.27 (m, 2H), 4.67 (s, 1H), 4.42 (quin, 1H), 2.39 (m, 2H), 2.01 (m, 2H), 1.73−1.86 (m, 2H), 1.41 (d, *J* = 6.78 Hz, 3H). LC−MS: *m*/*z* 436.

(*R*)-3-(1-(4-(6-(Pyridin-4-yl)quinazolin-2-ylamino)phenyl)-ethylamino)cyclopent-2-enone (82). The title compound was synthesized from (*R*)-*N*-(4-(1-aminoethyl)phenyl)-6-(pyridin-4-yl)-quinazolin-2-amine hydrochloride (**73**) and cyclopentane-1,3-dione using a method analogous to the preparation of **81**. ^{1}H NMR: 10.02 (s, 1H), 9.38 (s, 1H), 8.65−8.72 (m, 2H), 8.42 (d, *J* = 2.07 Hz, 1H), 8.26 (dd, *J* = 8.76, 2.17 Hz, 1H), 8.01 (d, *J* = 6.97 Hz, 1H), 7.93 (m, 2H), 7.81−7.86 (m, 2H), 7.77 (d, *J* = 8.85 Hz, 1H), 7.30 (m, 2H), 4.67 (s, 1H), 4.41 (quin, 1H), 2.52−2.58 (m, 2H), 2.04−2.15 (m, 2H), 1.44 (d, *J* = 6.78 Hz, 3H). LC−MS: *m*/*z* 422.

(*R*)-4-(1-(4-(6-(Pyridin-4-yl)quinazolin-2-ylamino)phenyl)-ethylamino)-5,6-dihydropyridin-2(1*H*)-one (83). The title compound was synthesized from (*R*)-*N*-(4-(1-aminoethyl)phenyl)-6-(pyridin-4-yl)quinazolin-2-amine (**73**-free base) and piperidine-2,4-dione using a method analogous to the preparation of **81**, except using DMF as solvent and heating in a microwave at 150 °C for 30 min. Compound was purified by an ISCO system (0−40% methanol/ethyl acetate gradient). ^{1}H NMR (MeOH-d_4): 7.48 (s, 1H), 6.89−6.95 (m, 2H), 6.46 (d, *J* = 2.02 Hz, 1H), 6.40 (dd, *J* = 8.84, 2.27 Hz, 1H), 6.19 (d, *J* = 8.59 Hz, 2H), 6.06−6.11 (m, 2H), 6.02 (d, *J* = 8.84 Hz, 1H), 5.65 (d, *J* = 8.59 Hz, 2H), 2.88 (s, 1H), 2.82 (q, *J* = 6.65 Hz, 1H), 1.72−1.75 (m, 2H), 0.89 (t, *J* = 6.95 Hz, 2H), −0.13 (d, *J* = 6.82 Hz, 3H). LC−MS: *m*/*z* 437. Purity: 90%.

(*R*)-5-(1-(4-(6-(Pyridin-4-yl)quinazolin-2-ylamino)phenyl)-ethylamino)-1,2-dihydropyridin-3(6*H*)-one (84). (i) (*R*)-*N*-(4-(1-Aminoethyl)phenyl)-6-(pyridin-4-yl)quinazolin-2-amine (**73**-free base, 1.016 g, 2.98 mmol), benzyl 3-hydroxy-5-oxo-5,6-dihydropyridine-1(2*H*)-carboxylate (**74**, 0.883 g, 3.57 mmol), and acetic acid (0.170 mL, 2.98 mmol) were combined in NMP (6.97 mL) to give a yellow solution.

The reaction was heated at 105 °C for 6 h, cooled to ambient temperature, and poured into saturated aq NH_4Cl (40 mL). The mixture was extracted with EtOAc (3 × 30 mL), and the organic fractions were combined, rinsed with 1 M aqueous NaOH (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield a dark orange oil which was purified via column chromatography (SiO_2, 10% MeOH/DCM) to yield (*R*)-benzyl-5-oxo-3-(1-(4-(6-(pyridin-4-yl)quinazolin-2-ylamino)phenyl)-ethylamino)-5,6-dihydropyridine-1(2*H*)-carboxylate which was carried forward crude into the next step. LC−MS: *m*/*z* 570. (ii) In a 20 mL round-bottomed flask, (*R*)-benzyl 5-oxo-3-(1-(4-(6-(pyridin-4-yl)-quinazolin-2-ylamino)phenyl)ethylamino)-5,6-dihydropyridine-1(2*H*)-carboxylate (0.380 g, 0.53 mmol) and Pearlman's catalyst (0.056 g, 0.08 mmol) were combined in MeOH (2.66 mL) to give a yellow suspension. The reaction was stirred for 18 h at 23 °C under a hydrogen balloon (1 atm). The reaction was filtered, and the filtrate was concentrated over Celite and subjected to column chromatography (SiO_2, 18% MeOH/DCM) to yield the title compound as a yellow solid. ^{1}H NMR (MeOH-d_4): 8.94−9.12 (m, 1H), 8.40−8.59 (m, 2H), 8.08 (m, 2H), 7.48−7.86 (m, 5H), 7.26 (m, 2H), 5.06 (s, 1H), 4.30−4.59 (m, 1H), 3.42−3.62 (m, 2H), 3.14−3.25 (m, 2H), 1.50 (m, 3H). LC−MS: *m*/*z* 437.

(*R*)-*N*-(1-(4-Aminophenyl)ethyl)acetamide (85). (i) (*R*)-1-(4-Bromophenyl)ethanamine (25 g, 0.125 mol) was treated with acetic anhydride (100 mL). The reaction mixture was heated to 50 °C for 4 h. The organics were removed under reduced pressure to afford (*R*)-*N*-(1-(4-bromophenyl)ethyl)acetamide (30 g, 99% yield), which was used directly in the next step. (ii) A solution of (*R*)-*N*-(1-(4-bromophenyl)-ethyl)acetamide (30 g, 120 mmol), diphenylmethanimine (27.2 g, 150 mmol, 1.3 equiv), $Pd_2(dba)_3$-CH_2Cl_2 (6.5 g, 6.3 mmol, 0.53 equiv), 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropyl-1,1′-biphenyl (X-Phos, 6.1 g, 8.2 mmol, 0.068 equiv), and Cs_2CO_3 (122 g, 375 mmol, 3 equiv) in 1,4-dioxane (1.5 L) was heated to 100 °C for 12 h. The reaction mixture was cooled to 25 °C and poured into water, followed by extraction with EtOAc. The organics were dried over Na_2SO_4 (s) and removed under reduced pressure. The resulting product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 1:1) to afford (*R*)-*N*-(1-(4-(Diphenylmethyleneamino)phenyl)ethyl)acetamide (33.6 g, 78% yield). LC−MS: *m*/*z* 343. (iii) (*R*)-*N*-(1-(4-(diphenylmethyleneamino)phenyl)ethyl)acetamide (33.5 g, 97.8 mmol) in Et_2O (300 mL) was treated with 1 N HCl (300 mL). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was triturated with Et_2O. The resulting solid was dissolved in a mixture of 10% w/v aq K_2HPO_4 and EtOAc. The organics were washed with NaCl (satd) and then dried with Na_2SO_4 (s). The organics were removed under reduced pressure to afford the title compound (17.2 g, 98% yield). LC−MS: *m*/*z* 179.

(*R*)-*N*-(1-(4-(6-Bromo-8-methoxyquinazolin-2-ylamino)-phenyl)ethyl)acetamide (86). 6-Bromo-2-chloro-8-methoxyquinazoline (prepared as described in ref 17; 100 mg, 0.366 mmol) and (*R*)-*N*-(1-(4-aminophenyl)ethyl)acetamide (**85**, 98 mg, 0.549 mmol, 1.5 equiv) were dissolved in 2-propanol (20 mL), and the mixture was heated to reflux for 3 h. DIPEA (0.140 mL, 0.805 mmol, 2.2 equiv) was then added and the mixture was heated at reflux for 12 h. The crude mixture was then concentrated under reduced pressure. The resulting suspension was washed with methanol, and the solid was collected by filtration and then dried under high vacuum to afford the title compound (110 mg, 73% yield), which was carried forward crude into the next step.

(*R*)-*N*-(1-(4-(8-Methoxy-6-(pyridin-4-yl)quinazolin-2-ylamino)phenyl)ethyl)acetamide (87). The title compound was synthesized from (*R*)-*N*-(1-(4-(6-bromo-8-methoxyquinazolin-2-ylamino)phenyl)ethyl)acetamide (**86**) and 4-pyridinylboronic acid using a method analogous to the preparation of **6**, except using Cs_2CO_3 as base and 1,4-dioxane/water (2:1) as solvent. The crude product was purified by column chromatography (DCM/MeOH) to afford 80 mg (80%) of the title compound. ^{1}H NMR: 10.01 (s, 1H), 9.32 (s, 1H), 8.68 (s, 2H), 8.23 (d, 1H), 7.97 (m, 5H), 7.64 (s, 1H), 7.23 (m, 2H), 4.90 (m, 1H), 4.08 (s, 3H), 1.83 (s, 3H), 1.33 (d, 3H). LC−MS: *m*/*z* 414.

6-Bromo-7-methoxyquinazolin-2-amine (88). 2-Amino-5-bromo-4-methoxybenzaldehyde (prepared as described in ref 17; 180 mg, 0.78 mmol) was dissolved in decalin (5 mL). Guanidine carbonate (0.4 g, 2.2 mmol) was added, and the mixture was heated at 210 °C for 3 h. The mixture was allowed to cool and was purified by silica gel chromatography to give the product as a yellow solid (110 mg, 55%). ^{1}H NMR: 8.90 (s, 1H), 8.05 (s, 1H) 3.92 (s, 3H), 6.87 (s, 1H). LC−MS: *m*/*z* 254.

6-Bromo-7-chloroquinazolin-2-amine (89). To 2-amino-5-bromo-4-chlorobenzaldehyde (prepared as described in ref 17; 6.44 g, 27.5 mmol) and guanidine carbonate (7.45 g, 41.35 mmol) was added DMA (55 mL), and the resulting mixture was placed in a 140 °C oil bath. After 4 h, the reaction was allowed to cool and was then diluted with H_2O (200 mL), precipitating an orange-colored amorphous solid that was isolated by suction-filtration. The filter cake was washed with H_2O and dried in air to give a yellow solid (6.54 g) which was suspended in refluxing MeOH (100 mL) for 16 h. The resulting mixture was allowed to cool and was suction-filtered, washed with MeOH, and dried in air to give the product as a yellow solid (4.73 g, 67%). ^{1}H NMR: 9.11 (s, 1H), 8.27 (s, 1H), 7.63 (s, 1H), 7.20 (s, 2H). LC−MS: *m*/*z* 259.

6-Bromo-8-chloroquinazolin-2-amine (90). The title compound was synthesized from 2-amino-5-bromo-3-chlorobenzaldehyde (prepared as described in ref 17) using a method analogous to the preparation of **89**, to afford a yellow solid (7.38 g, 84% yield). ^{1}H NMR: 9.13 (s, 1H), 7.99−8.11 (m, 2H), 7.38 (br. s., 2H); *m*/*z* 259.

7-Methoxy-6-(pyridin-4-yl)quinazolin-2-amine (91). The title compound was synthesized from 6-bromo-7-methoxyquinazolin-2-amine (**88**) and 4-pyridinylboronic acid using a method analogous to the preparation of **87**, but with Cs_2CO_3 and dioxane/water (2/1) as solvent (94% yield). LC−MS: *m*/*z* 253.

7-Chloro-6-(pyridin-4-yl)quinazolin-2-amine (92). The title compound was synthesized from 6-bromo-7-chloroquinazolin-2-amine (**89**) using a method analogous to the preparation of **6**, except with $(PPh_3)_2PdCl_2$ (4.0 mol %) as catalyst and dioxane/water (2/1) as solvent (3.42 g, 77%). ^{1}H NMR: 9.18 (s, 1H), 8.64−8.75 (m, 2H), 7.94 (s, 1H), 7.60 (s, 1H), 7.48−7.58 (m, 2H), 7.21 (s, 2H). LC−MS: *m*/*z* 257.

8-Chloro-6-(pyridin-4-yl)quinazolin-2-amine (93). The title compound was synthesized from 6-bromo-8-chloroquinazolin-2-amine (**90**) following the procedure described for the preparation of **92**, to afford the title compound as a yellow solid (3.41 g, 99%) that was contaminated with a minor amount of the bis-4-pyridyl product derived from coupling at both the bromo and chloro positions, which was used without further purification. LC−MS: *m*/*z* 257.

(*R*)-*tert*-Butyl 1-(4-(7-Methoxy-6-(pyridin-4-yl)quinazolin-2-ylamino)phenyl)ethylcarbamate (94). The title compound was synthesized from (*R*)-*tert*-butyl 1-(4-bromophenyl)ethylcarbamate (**72**) and 7-methoxy-6-(pyridin-4-yl)quinazolin-2-amine (**91**) using a method analogous to the preparation of **3**, with Xantphos and palladium(II) acetate followed by purification on an ISCO system (CH_2Cl_2:MeOH = 30:1) to afford the title compound (0.41 g, 73%). ^{1}H NMR: 10.07 (s, 1H), 9.14 (s, 1H), 8.60−8.62 (m, 2H), 7.93 (s, 1H), 7.85−7.88 (m, 2H), 7.56−7.58 (m, 2H), 7.22−7.25 (m, 2H), 7.15 (s, 1H), 4.52−4.61 (m, 1H), 3.96 (s, 3H), 1.35 (s, 9H), 1.29 (d, *J* = 7.1 Hz, 3H).

(*R*)-*tert*-Butyl 1-(4-(7-Chloro-6-(pyridin-4-yl)quinazolin-2-ylamino)phenyl)ethylcarbamate (95). The title compound was synthesized from 7-chloro-6-(pyridin-4-yl)quinazolin-2-amine (**92**) using a method analogous to the preparation of **3**, with Xantphos and heating at 90 °C followed by purification on an ISCO system (CH_2Cl_2:MeOH = 30:1) to afford the product (2.73 g, 49%). ^{1}H NMR: 10.07 (s, 1 H), 9.35 (s, 1H), 8.67−8.76 (m, 2H), 8.05 (s, 1H), 7.82−7.94 (m, 3H), 7.52−7.61 (m, 2H), 7.31−7.38 (m, 1H), 7.23−7.30 (m, 2H), 4.54−4.65 (m, 1H), 1.38 (s, 9H), 1.31 (d, *J* = 7.1 Hz, 3H). LC−MS: *m*/*z* 476.

(*R*)-*tert*-Butyl 1-(4-(8-Chloro-6-(pyridin-4-yl)quinazolin-2-ylamino)phenyl)ethylcarbamate (96). The title compound was synthesized from 8-chloro-6-(pyridin-4-yl)quinazolin-2-amine (**93**) using a method analogous to the preparation of **95** (2.92 g, 51%). ^{1}H NMR: 10.29 (s, 1H), 9.41 (s, 1H), 8.66−8.72 (m, 2H), 8.46−8.49 (m,

1H), 8.41−8.45 (m, 1H), 8.02−8.12 (m, 2H), 7.84−7.90 (m, 2H), 7.25−7.40 (m, 3H), 4.55−4.67 (m, 1H), 1.37 (s, 9H), 1.32 (d, J = 7.07 Hz, 3H). LC−MS: m/z 476.

(*R*)-*N*-(1-(4-(7-Methoxy-6-(pyridin-4-yl)quinazolin-2-ylamino)phenyl)ethyl)acetamide (97). (i) (*R*)-*tert*-Butyl 1-(4-(7-methoxy-6-(pyridin-4-yl)quinazolin-2-ylamino)phenyl)ethylcarbamate (**94**, 0.40 g, 0.8 mmol) was added to HCl/THF (50 mL) and the mixture was allowed to stir at room temperature overnight. The mixture was concentrated, and the solid residue was washed with hexanes to afford (*R*)-*N*-(4-(1-aminoethyl)phenyl)-7-methoxy-6-(pyridin-4-yl)-quinazolin-2-amine dihydrochloride (0.34 g, 98%, m/z 373), which was carried forward into the next step. (ii) (*R*)-*N*-(4-(1-Aminoethyl)-phenyl)-7-methoxy-6-(pyridin-4-yl)quinazolin-2-amine dihydrochloride (102 mg, 0.23 mmol) was added to EtOAc (5 mL) and triethylamine (300 μL, 2.2 mmol) followed by acetic anhydride (100 μL, 1.1 mmol). The resulting mixture was allowed to stir at room temperature. After 1 h, MeOH (1 mL) was added to the heterogeneous mixture to improve overall solubility. After stirring at room temperature overnight, the mixture was diluted with H_2O (10 mL). The biphasic, heterogeneous mixture was suction-filtered, and the filter cake was washed with EtOAc and H_2O to afford the title compound (40 mg, 42%). ^{1}H NMR: 9.82 (s, 1H), 9.16 (s, 1H), 8.61−8.68 (m, 2H), 8.21−8.27 (m, 1H), 7.95 (s, 1H), 7.87−7.93 (m, 2H), 7.56−7.62 (m, 2H), 7.23−7.30 (m, 2H), 7.16 (s, 1H), 4.84−4.93 (m, 1H), 3.97 (s, 3H), 1.84 (s, 3H), 1.35 (d, J = 6.8 Hz, 3H). LC−MS: m/z 414.

(*R*)-*N*-(1-(4-(7-Chloro-6-(pyridin-4-yl)quinazolin-2-ylamino)-phenyl)ethyl)acetamide (98). The title compound was synthesized from (*R*)-*tert*-butyl 1-(4-(7-chloro-6-(pyridin-4-yl)quinazolin-2-ylamino)phenyl)ethylcarbamate (**95**) using a method similar to that for the preparation of **97**, except with 4 N HCl/dioxane for BOC group deprotection, followed by treatment with acetic anhydride as described for the preparation of **97**. ^{1}H NMR: 10.09 (s, 1H), 9.35 (s, 1H), 8.68−8.74 (m, 2H), 8.21−8.28 (m, 1 H), 8.06 (s, 1H), 7.85−7.94 (m, 3H), 7.55−7.58 (m, 2H), 7.25−7.30 (m, 2H), 4.84−4.94 (m, 1 H), 1.84 (s, 3H), 1.34 (d, J = 7.1 Hz, 3H). LC−MS: m/z 418.

(*R*)-*N*-(1-(4-(8-Chloro-6-(pyridin-4-yl)quinazolin-2-ylamino)-phenyl)ethyl)acetamide (99). The title compound was synthesized from (*R*)-*tert*-butyl 1-(4-(8-chloro-6-(pyridin-4-yl)quinazolin-2-ylamino)phenyl)ethylcarbamate (**96**) using a method similar to that for the preparation of **98**. ^{1}H NMR: 10.29 (s, 1 H), 9.41 (s, 1 H), 8.65−8.73 (m, 2H), 8.45−8.49 (m, 1H), 8.41−8.44 (m, 1H), 8.20−8.26 (m, 1H), 8.03−8.13 (m, 2H), 7.84−7.90 (m, 2H), 7.27−7.33 (m, 2H), 4.85−4.95 (m, 1H), 1.85 (s, 3H), 1.35 (d, J = 6.8 Hz, 3H). LC−MS: m/z 418.

(*R*)-*N*-(1-(4-(7-Methyl-6-(pyridin-4-yl)quinazolin-2-ylamino)-phenyl)ethyl)acetamide (100). (i) A test tube equipped with a stir bar was charged with (*R*)-*tert*-butyl 1-(4-(7-chloro-6-(pyridin-4-yl)-quinazolin-2-ylamino)phenyl)ethylcarbamate (**95**, 238 mg, 0.50 mmol), methylboronic acid (63 mg, 1.05 mmol), $Pd(OAc)_2$ (4.4 mg, 3.9 mol %), $PCy_3{\cdot}HBF_4$(19.3 mg, 10.5 mol %), and potassium carbonate (281 mg, 2.03 mmol). The tube was evacuated and back-filled with N_2, and then dioxane (1.5 mL) and water (0.5 mL) were added. The mixture was allowed to stir at room temperature for a few minutes and was then placed in a 100 °C oil bath. After heating for 12 h, the reaction was allowed to cool, and the mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc, and the combined organics were concentrated under reduced pressure. The resulting solid residue was used without further purification in the next step. LC−MS: m/z 456. (ii and iii) BOC-deprotection and acylation were accomplished using a method analogous to the preparation of **97**. ^{1}H NMR: 9.87 (s, 1H), 9.27 (s, 1H), 8.65−8.71 (m, 2H), 8.21−8.27 (m, 1H), 7.87−7.93 (m, 2H), 7.81 (s, 1H), 7.62 (s, 1H), 7.46−7.53 (m, 2H), 7.23−7.29 (m, 2H), 4.83−4.93 (m, 1H), 2.41 (s, 3H), 1.84 (s, 3H), 1.34 (d, J = 7.1 Hz, 3H). LC−MS: m/z 398.

(*R*)-*N*-(1-(4-(8-Methyl-6-(pyridin-4-yl)quinazolin-2-ylamino)-phenyl)ethyl)acetamide (101). The title compound was synthesized from (*R*)-*tert*-butyl 1-(4-(8-chloro-6-(pyridin-4-yl)quinazolin-2-ylamino)phenyl)ethylcarbamate (**96**) using a method analogous to the preparation of **100**. ^{1}H NMR: 10.01 (s, 1H), 9.34 (s, 1H), 8.64−8.71 (m, 2H), 8.19−8.29 (m, 2H), 8.17 (s, 1H), 7.96−8.04 (m, 2H), 7.79−7.86 (m, 2H), 7.24−7.33 (m, 2H), 4.85−4.95 (m, 1H), 2.69 (s, 3H), 1.84 (s, 3H), 1.35 (d, J = 7.1 Hz, 3H). LC−MS: m/z 398.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables SI1−SI4, Figure SI1, protein expression, purification, crystallization, and structure determination for **3** and **48**, biological and DMPK assay details, pharmacodynamic protocol, and A375 mouse xenograft assay protocol details. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

PDB ID for **3**−EphB4 complex, 4bb4; PDB ID for the **48**−B-Raf complex, 4H58.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; CL_{int}, in vitro intrinsic clearance; CL_{obs}, measured in vivo clearance; DFG, sequence of the three amino acids aspartic acid-phenylalanine-glycine; DIPEA, diisopropylethylamine; DME, ethylene glycol dimethyl ether; EtOAc, ethyl acetate; Fu, fraction unbound; HATU, (Dimethylamino)-*N*,*N*-dimethyl(3*H*-[1,2,3]triazolo-[4,5-*b*]pyridin-3-yloxy)methaniminium hexafluorophosphate; Hep, hepatocytes; HOAc, acetic acid; HPMC, hydroxypropyl methylcellulose; Hu, human; LC−MS, liquid chromatography−mass spectrometry; Mic, microsomes; MS, molecular sieves; MPLC, medium-pressure liquid chromatography; mut, mutant; $Pd_2(dba)_3$, tris(dibenzylideneacetone)dipalladium; $Pd(OAc)_2$, palladium(II) acetate; $PdCl_2(dppf)$-CH_2Cl_2, 1,1′-bis-(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex; $PCy_3{\cdot}HBF_4$, tricyclopentyl phosphine tetrafluoroborate; satd, saturated; TBDMS, *tert*-butyldimethylsiloxy; TEG, triethylene glycol; TGI, tumor growth inhibition; V_{dss}, volume of distribution; Xantphos, 4,5-bis-(diphenylphosphino)-9,9-dimethylxanthene.

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(23) The (*S*)-enantiomer of **57** (not shown) had an IC_{50} = 190 nM in the A375 pERK cell assay.

(24) We chose to switch to screening at 5 mM ATP concentration in the B-Raf^{V600E} enzyme assay as we continued our lead optimization of the aminoquinazoline series and discontinued screening at K_m ATP concentrations (as reported by enzyme potencies shown in Tables 1−3). We believed the higher ATP concentration was more representative of cellular ATP levels and provided a more robust enzyme-cell correlation. For additional details around the advantages of screening kinase inhibitors at various ATP concentrations, see the following paper and references therein: Knight, Z. A.; Shokat, K. M. Features of selective kinase inhibitors. *Chem. Biol.* **2005**, *12*, 621−637.

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(26) Work was done to identify the stereochemical preference at the carboxamide stereogenic center and in each instance the more potent diastereomer is represented in Table 4. We were unable to separate the diastereomers of compound **76** and data shown is for the mixture of diastereomers.

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(29) Wang, X.; Kim, J. Conformation-specific effects on Raf kinase inhibitors. *J. Med. Chem.* **2012**, *55*, 7332−7341.

(30) The kinase selectivity profile of **58** was similar to that of **3** with S(10) selectivity score of 0.01. For a full listing of the kinase panel data, see the Supporting Information.

(31) Additional details around compound **2** will be reported in a future manuscript.