Discovery of Aminoquinazolines as Potent, Orally Bioavailable Inhibitors of Lck: Synthesis, SAR, and in Vivo Anti-Inflammatory Activity

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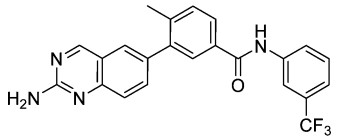
The lymphocyte-specific kinase (Lck) is a cytoplasmic tyrosine kinase of the Src family expressed in T cells and natural killer (NK) cells. Genetic evidence in both mice and humans demonstrates that Lck kinase activity is critical for signaling mediated by the T cell receptor (TCR), which leads to normal T cell development and activation. Selective inhibition of Lck is expected to offer a new therapy for the treatment of T-cell-mediated autoimmune and inflammatory disease. Screening of our kinase-preferred collection identified aminoquinazoline **1** as a potent, nonselective inhibitor of Lck and T cell proliferation. In this report, we describe the synthesis and structure−activity relationships of a series of novel aminoquinazolines possessing in vitro mechanism-based potency. Optimized, orally bioavailable compounds **32** and **47** exhibit anti-inflammatory activity (ED_{50} of 22 and 11 mg/kg, respectively) in the anti-CD3-induced production of interleukin-2 (IL-2) in mice.

Introduction

Different populations of T cells serve pivotal roles in the adaptive immune response by acting as potentiators (CD4+ T helper cells) or effectors (CD8+ cytolytic T effector cells) of immune reactions. The immune specificity of a particular T cell is imparted by the specificity of the T cell receptor (TCR[a]) for antigen, or CD3 complex.[1] Signal transduction pathways used by the TCR have been extensively researched. Novel immunosuppressive agents that target components of these pathways might serve as improved therapies for graft rejection and/or T-cell-mediated autoimmune disease.

Protein kinases have been shown to play important roles in TCR signal transduction. The Src family of cytoplamic tyrosine kinases is made up of eight members: Src, Lck, Fyn, Lyn, Hck, Fgr, Blk, and Yes.[2] Lck and Fyn have been shown to have important roles in TCR signal transduction.[3] TCR signals potentiated by Lck ultimately lead to gene regulation events triggering cytokine release, proliferation, and survival of antigen specific T cells, thereby amplifying specific immune responses.



1

IC_{50} (Lck) = 0.2 nM

IC_{50} (MLR) = 9 nM

IC_{50} (IL-2) = 88 nM

Figure 1. Activity of 2-aminoquinazoline lead **1**.

Genetically modified mice lacking Lck expression and patients with Lck mutations affecting expression and/or catalytic activity show defects in T cell maturation and signaling.[4] These findings suggest that a small-molecule inhibitor of Lck kinase activity could prove to be useful in the treatment of graft rejection and/or T-cell-mediated autoimmune diseases.

The synthesis and characterization of several classes of small molecule Lck inhibitors has been described.[5] In addition, potent and bioavailable Lck antagonists have been shown to have inhibitory activities in vivo in models of T-cell-dependent immune responses.[5j,6] Herein, we describe the synthesis, structure−activity relationships, and pharmacological characterization of aminoquinazolines with potent and selective inhibition of Lck. This activity translates into inhibition of in vitro and in vivo assays of T cell activation.

As a result of our screening efforts in a homogeneous time-resolved fluorescent (HTRF) kinase assay, we identified aminoquinazoline **1** as a potent inhibitor of Lck (Figure 1). Compound **1** also exhibited potent inhibitory activity in two

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[a] Abbreviations: Lck, lymphocyte-specific kinase; TCR, T cell receptor; IL-2, interleukin 2; PTK, protein tyrosine kinase; MLR, human mixed lymphocyte reaction; DFG, aspartic acid−phenylalanine−glycine; MAPK, mitogen activated protein kinase; VEGF, vascular endothelial growth factor.

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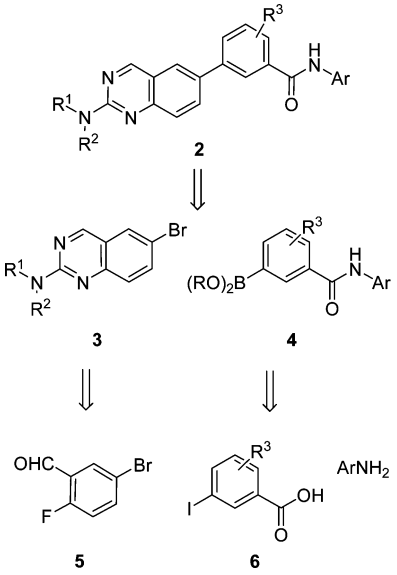
Scheme 1. Retrosynthetic Analysis of 2,6-Quinazolines



cellular assays: the human mixed lymphocyte reaction (MLR) and the T cell receptor/anti-CD3-induced production of interleukin-2 (IL-2). This lead compound suffered from poor selectivity, low solubility (26 μg/mL in fasted state simulated intestinal fluid at pH 6.8 (SIF)), and marginal bioavailability in rats (2%). We therefore initiated the development of chemistry toward this class of compounds to investigate the SAR and to improve the physicochemical and pharmacokinetic (PK) properties. Toward this end, we have identified orally bioavailable Lck inhibitors (**32** and **47**) with good efficacy in a mouse model of inflammation.

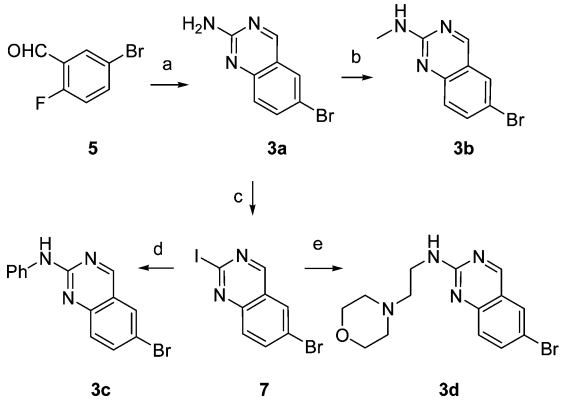
Chemistry

Retrosynthetic analysis of the 2,6-disubstituted quinazoline target compounds **2** is depicted in Scheme 1. We envisioned a convergent synthetic route with final step Suzuki coupling of functionalized quinazoline bromides **3** and boronic esters **4** that would allow for the preparation of a diverse set of compounds. 2-Substituted quinazoline bromides **3** could arise from 5-bromo-2-fluorobenzaldehyde (**5**). Boronic ester benzamides **4** could originate from the coupling of iodobenzoic acids **6** and anilines. In the forward sense, this modular synthetic route was typically employed.

The synthesis of 6-bromoquinazolin-2-amine (**3a**) was accomplished using modifications to the established method of Hynes and Campbell.[7] Acid-promoted condensation with methylamine gas in a high-pressure reactor afforded 6-bromo-*N*-methylquinazolin-2-amine (**3b**). A Sandmeyer reaction[8] was used to prepare 6-bromo-2-iodoquinazoline (**7**) from **3a**. An S_NAr reaction of iodide **7** with anilines was accomplished under thermal, acidic conditions to afford 2-anilino-6-bromoquinazolines such as **3c** and with amines under thermal, basic conditions to afford 2-amino-6-bromoquinazolines such as **3d** (Scheme 2).

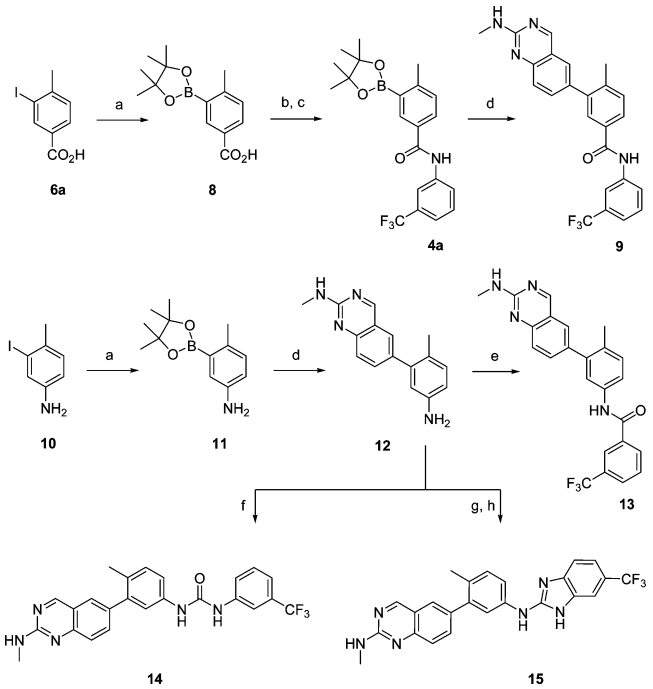
A variety of 2-amino-6-arylquinazolines were synthesized according to the methods outlined in Scheme 3. Synthesis of 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (**8**) was accomplished using modifications to the established method of Miyaura et al.[9] Preparation of boronic ester amides, such as **4a**, was accomplished by initial heating of **8** in thionyl chloride, followed by reaction of the crude acid chloride with the aniline in the presence of triethylamine. Suzuki coupling of boronate **4a** and **3b** afforded 2-amino-6-aryl-quinazoline (**9**). These Suzuki conditions proved to be quite general

Scheme 2. Preparation of 2-Amino-6-bromoquinazolines[a]



[a] (a) Guanidine carbonate, DIEA, NMP, 155 °C; (b) $MeNH_2$(g), *p*-TSA, 820 psi, 160 °C; (c) isoamyl nitrite, CuI, CH_2I_2, THF, reflux; (d) aniline, TFA, IPA, 80 °C; (e) 2-morpholinoethanamine, DIEA, IPA, 70 °C.

Scheme 3. Preparation of 2-Amino-6-arylquinazolines[a]



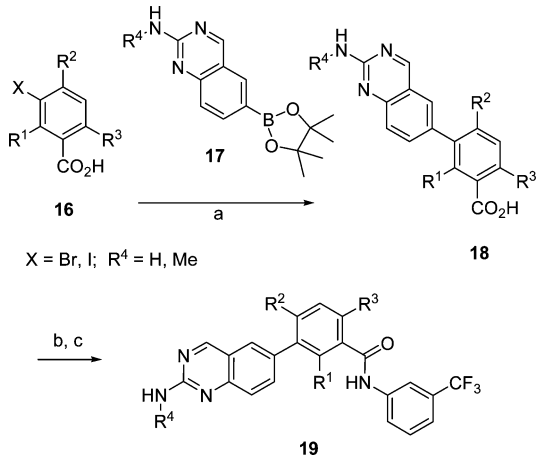
[a] (a) Bis(pinacolato)diboron, 10% Pd(dppf)Cl_2, KOAc, DMF, 70 °C; (b) $SOCl_2$, 80 °C; (c) 3-(trifluoromethyl)benzenamine, NEt_3, CH_2Cl_2, 60 °C; (d) 6-bromo-*N*-methylquinazolin-2-amine (**3b**), 10% Pd(dppf)Cl_2, K_2CO_3, CH_3CN/H_2O, 60 °C; (e) 3-(trifluoromethyl)benzoyl chloride; (f) 1-isocyanato-3-(trifluoromethyl)benzene; (g) *O*,*O*-dipyridin-2-yl carbonothioate, CH_2Cl_2; (h) 4-(trifluoromethyl)benzene-1,2-diamine, PS-DCC, THF, 70 °C.

such that a variety of quinazoline bromides **3** and boronic esters **4** could be coupled in moderate to good yields. Iodide **10** was converted to the boronic ester **11** using the Miyaura protocol.[9] Suzuki coupling to **3b** afforded 6-(5-amino-2-methylphenyl)-*N*-methylquinazolin-2-amine (**12**). This versatile intermediate was used in the preparation of reversed amides **13**, ureas **14**, and aminobenzimidazoles **15** as shown in Scheme 3.

For rapid SAR at the aniline amide or for variation on the central ring, an alternative synthetic route, proceeding through acid intermediates **18**, was occasionally employed (Scheme 4). The halides **16** were either commercially available or prepared according to established methods.

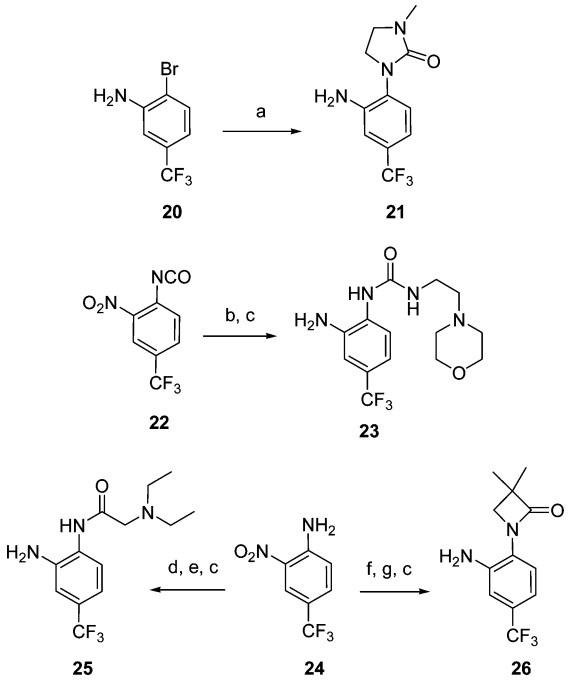
Most of the anilines used in the preparation of boronic esters **4** were commercially available. Others were prepared either by established methods[10] or by short reaction sequences, some of which are illustrated in Scheme 5.

Scheme 4. Alternative Route to Quinazolines[a]



[a] (a) 10% Pd(dppf)Cl_2, K_2CO_3, CH_3CN/H_2O, 60 °C; (b) $SOCl_2$, 80 °C; (c) 3-(trifluoromethyl)benzenamine, NEt_3, CH_2Cl_2, 60 °C.

Scheme 5. Preparation of Anilines[a]



[a] (a)1-Methylimidazolidin-2-one, N^1,N^2-dimethylethane-1,2-diamine, CuI, K_2CO_3, toluene, 110 °C; (b) 2-morpholinoethanamine, benzene, 40 °C; (c) 10% Pd/C, H_2, CH_3OH, EtOAc; (d) chloroacetyl chloride, NEt_3, CH_2Cl_2, reflux; (e) diethylamine, K_2CO_3, THF, 50 °C; (f) 3-chloropivaloyl chloride, NEt_3, CH_2Cl_2, 35 °C; (g) K_2CO_3, acetone, 50 °C.

Results and Discussion

Structure−Activity Relationships (SAR). The cocrystal structure of Lck and **1** was solved at 2.0 Å resolution (Figure 2). The inhibitor occupies the ATP binding site and forces the protein to assume an extended "DFG-out" conformation.[11] The quinazoline ring makes hydrogen bond contacts to the linker region of the enzyme at Met319. The amide moiety makes hydrogen bond contacts with the backbone NH of Asp382 from the DFG sequence and Glu288 from the C-helix. The aryl ring of the amide thus sits deep within the extended hydrophobic pocket, making several van der Waals contacts to lipophilic residues. This DFG-out binding mode is not observed for most reported Src-family kinase inhibitors such as PP1 and PP2.[12]

We initially sought to improve the selectivity of our lead compound by taking advantage of the sequence differences within the extended hydrophobic pocket among structurally related kinases (Table 1). Thus, all compounds were counterscreened for inhibitory activity against a panel of kinases that included the proteins Zap70, Jak3, and p38α, all of which are involved in immune cell signaling pathways. Zap70 is a nonreceptor tyrosine kinase of the Syk family that functions immediately downstream of Lck in the T cell signaling pathway. Like Lck, its expression is restricted to T cells and NK cells.[13] All compounds presented herein were >25 μM vs Zap70. Further downstream is Janus kinase 3 (Jak3), which mediates signal transduction via the γ chain of lymphokine surface receptors.[14] Jak3 is under investigation as the target of the small-molecule immunosuppressive agent 3-[4-methyl-3-[*N*-methyl-*N*-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropionitrile (CP-690550).[15] Mitogen-activated protein kinase (MAPK) p38α is a key signaling protein in the stress-activated signal transduction cascade that results in the production of proinflammatory cytokines such as TNFα and IL-1β.[16] A number of small-molecule p38 inhibitors have advanced into clinical trials in the past few years.[16] We also counterscreened against the structurally related VEGF receptor-2 (KDR), a receptor tyrosine kinase that is responsible for regulating the growth and differentiation of the vascular system and its components.[17] Selectivity over KDR is important with respect to establishing a practical therapeutic window.

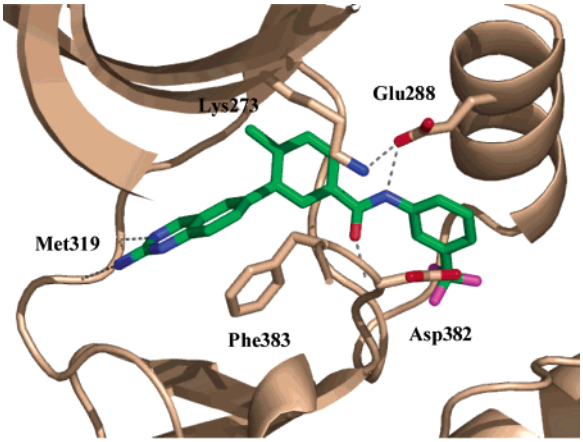


Figure 2. Cocrystal structure of Lck and **1**.

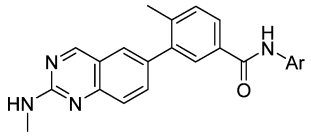
Table 1. Sequence Comparison in Extended Hydrophobic Pocket

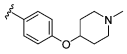
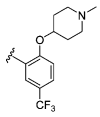
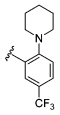
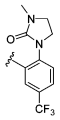
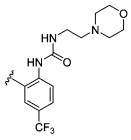
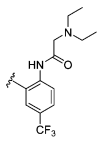
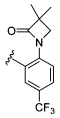
Lck	Thr316[a]	Met292	Leu295	Leu300	Ile355	Tyr360
Zap70	Met	Met	Leu	Ile	Lue	Phe
Jak3	Met	Leu	Leu	Ile	Leu	Cys
p38α	Thr	Leu	Met	Val	Ile	Ile
KDR	Val	Leu	Ile	Val	Leu	Cys

[a] Gatekeeper residue.

Select SAR from variations on the aryl ring of the amide is summarized in Table 2. During the course of our investigations, we observed a general trend toward improved metabolic stability,[18] solubility, and oral bioavailability with 2-NHMe-quinazolines compared to 2-NH_2-quinazolines (i.e., **9** vs **1**). Furthermore, 2-NHMe-quinazolines generally possessed in vitro profiles similar to those of their corresponding 2-NH_2-quinazolines. Therefore, most synthetic efforts were focused on structural modifications to **9**. A study of aryl ring substitution revealed a slight improvement in selectivity with 2,3-disubstituted amides such as **27** and **28**. According to X-ray analysis of compounds similar to **27** and **28**, a substituent on C2 forces the aryl ring to twist out of plane with respect to the amide (dihedral angle was ~20°). Substitution at the amide 4-position (**29** and **30**) had little effect on potency and did not improve

Table 2. SAR: Variations on the Amide Aryl



Cmpd.	Ar	IC$_{50}$ (nM) Lck	KDR	p38α	Jak3	MLR	IL-2
9		0.3	1	2	16	3	33
27		0.01	8	50	133	176	160
28		0.3	48	21	1339	1664	—
29		1	8	93	>8333	230	223
30		0.5	3	14	16	133	86
31		3	21	139	106	1695	—
32		0.5	17	9	868	243	36
33		48	1415	168	253	639	—
34		2	461	4	987	499	—
35		0.4	47	31	722	52	—
36		0.5	306	76	>8333	427	—
37		2	360	172	193	17	89

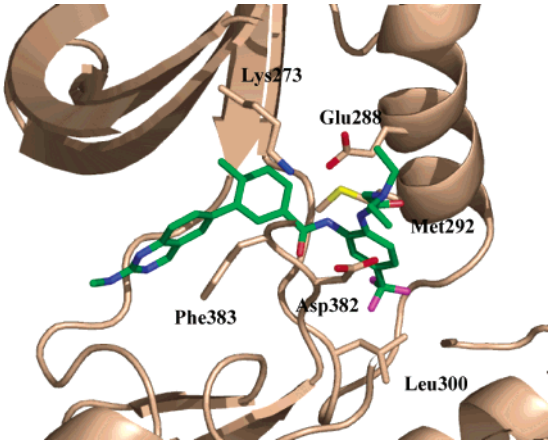


Figure 3. Cocrystal structure of Lck and **36**.

selectivity. 2,3,4-Trisubstituted amides such as **31** were typically less potent. The 2,5-disubstitution pattern (**32**−**37**) was generally well tolerated with a few exceptions (i.e., **33**). X-ray analysis of compounds in this series bound to Lck, revealed that the CF_3 substituent at C5 was buried in a highly lipophilic pocket, allowing the substituent at C2 to project toward solvent. Therefore, we prepared several compounds with tertiary-amine-containing groups at this position (i.e., **32**, **35**, and **36**) in an effort to improve solubility. The incorporation of a urea or amide functionality at C2 afforded compounds with improved selectivity over KDR and Jak3 (**34**−**37**) relative to **9**.

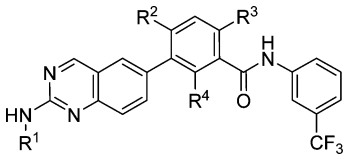
X-Ray analysis of compound **36** bound to Lck (Figure 3) brought to light a plausible reason for the observed selectivity over KDR (566-fold). The substituent on C2 forces the aryl ring to twist significantly out of plane with respect to the amide in order to prevent clashing of the 2-substituent with Glu288 of the C-helix. When these compounds bind to KDR, two potential van der Waals clashes may occur: (1) between the aryl ring and a Leu methyl group (equivalent of Met292 in Lck) and (2) between the CF_3 and a Val methyl group (equivalent of Leu300 in Lck). Both of these apparent clashes result from the aniline ring rotation upon binding to Lck.

A brief examination of modifications to the central aryl ring revealed narrow SAR in this portion of the scaffold (Table 3). A small lipophilic substituent such as methyl or chloro para to the amide (R^2) is important for cell potency. Small substituents at R^3, such as fluoro, were well tolerated but generally did not improve cellular potency or physicochemical properties. The narrow SAR was consistent with expectations, given the lack of space in this region of the binding site (see X-ray structures, Figures 2 and 3).[11,19]

We next examined a number of variations to the amide functionality such as reversed amides, ureas, and aminobenzimidazoles exemplified by **13**−**15** (Table 4). Analogues from these series generally offered no improvement in potency or selectivity over the lead series (i.e., **9**). Truncated analogues such as **45**, lacking the H-bond donor/acceptor moiety and aryl ring to occupy the extended hydrophobic pocket, were less potent.

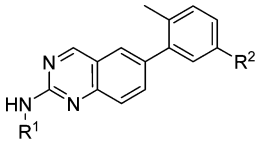
The effect of substitution on the linker-binding portion of the quinazoline is summarized in Table 5. X-Ray crystallographic studies revealed that the quinazolines bind Lck in such an orientation that a substituent off the 2-amino position would presumably be exposed to solvent (Figure 3).[20] As expected, substantial variation at this position was tolerated with little effect on potency. Compounds with a lipophilic substituent such as methyl, phenyl, or cyclopropyl on the amine were highly potent (**9**, **54**, **55**). The introduction of a tertiary-amine-

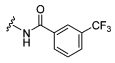
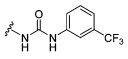
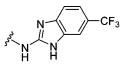
Table 3. SAR: Variations on the Central Aryl Ring



							IC$_{50}$ (nM)	
Cmpd.	R^1	R^2	R^3	R^4	PSA	cLogP	Lck	MLR
9	Me	Me	H	H	67	4.9	0.3	3
38	Me	H	H	H	67	4.5	10	550
39	H	H	H	H	81	4.2	35	2480
40	H	H	F	H	81	3.8	150	>20000
41	H	Cl	H	H	81	4.9	0.4	22
42	Me	Me	F	H	67	4.5	0.5	254
43	H	Me	F	H	81	4.3	0.9	261
44	H	H	H	Me	81	4.7	200	—

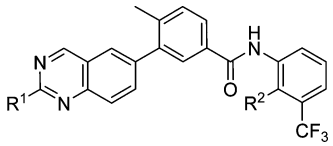
Table 4. SAR: Variations on the H-Bonding Moiety

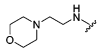
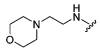


			IC$_{50}$ (nM)				
Cmpd.	R^1	R^2	Lck	KDR	p38α	Jak3	MLR
13	Me		0.3	5	0.9	154	167
14	Me		8	52	5	1141	280
15	Me		297	1438	277	>25000	—
45	H	H	94	4966	3903	9819	—

containing solubilizing group at this position led to a marked improvement in solubility (10- to 15-fold increase). The H-bond donor to the linker is important for cellular potency as demonstrated by a comparison of the data for **49** and **50**. Although compounds **27** and **48**, containing 2-Me, 3-CF$_3$ amides, offered improved selectivity relative to their monosubstituted analogues **9** and **47**, their cellular activity was significantly lower. We were delighted to observe improved selectivity over KDR with some compounds from this series (**51**−**53**). We are presently unable to offer a structural explanation for this apparent selectivity, but it may be due to differences in electropotential surfaces in this region of the kinases (Figure 4). Thus, a positively charged tertiary amine salt is expected to interact favorably with polar surfaces (red = oxygen) and unfavorably with highly lipophilic surfaces (gray = carbon).

Table 5. SAR: Variations on the Quinazoline



			IC$_{50}$ (nM)						
Cmpd.	R^1	R^2	Lck	KDR	p38α	Jak3	MLR	IL-2	SIF sol. (μg/mL)
1	NH$_2$	H	0.2	2	6	20	87	88	27
46	NH$_2$	Me	0.6	15	109	557	102	152	16
9	NHMe	H	0.3	1	2.4	16	3	33	14
27	NHMe	Me	0.01	8	50	133	176	160	19
47		H	0.2	1	3	72	30	21	159
48		Me	3	15	40	626	357	—	175
49		Me	0.4	7	25	2189	5	66	182
50		Me	14	292	65	>25000	844	—	>200
51		Me	6	173	9	>25000	667	—	>200
52		Me	6	246	7	>8333	246	461	172
53		Me	0.6	103	2	>8333	152	745	171
54		Me	1	4	57	46	44	—	—
55		Me	0.07	6	2	331	73	180	13

A few of the most potent and/or selective compounds were advanced into our secondary cellular screening assay, which measures the compound's inhibitory effect on the anti-CD3

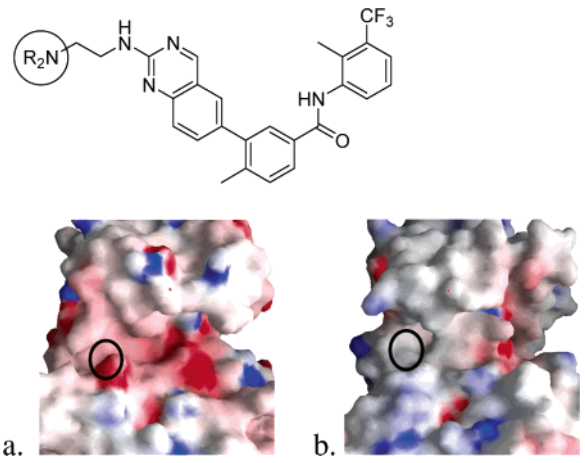


Figure 4. Electrostatic potential surfaces of Lck (a) and KDR (b).

Table 6. Cellular Assay (WB IL-2) and Countersceen (WB TNFα) in Human Whole Blood and Protein Binding

cmpd	WB IL-2 (μM)	WB TNFα (μM)	human protein binding (%)	mouse protein binding (%)	rat protein binding (%)
1	0.216	>10.0	98.7	99.4	97.6
9	0.250	>2.5	96.2	97.0	97.8
32	0.113	>2.5	—	—	—
37	2.31	—	—	—	—
46	1.16	>2.5	99.5	97.9	95.8
47	0.272	>2.5	95.0	97.1	95.3
52	8.4	—	—	—	—
53	7.3	—	—	—	—

Table 7. Mean PK Parameters Following Intravenous Dose (iv) or Oral Dose (po) in Male Sprague-Dawley Rats[a]

	iv			po			
cmpd	CL (mL h^{-1} kg^{-1})	V_{ss} (mL kg^{-1})	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng h mL^{-1})	C_{max} (ng mL^{-1})	t_{max} (h)	F (%)
1	1105[b]	1546	2.7	91[e]	19	4	2
9	1641[c]	3582	2.3	819[e]	75	4	24
32	837[d]	7626	6.5	1369[f]	121	6	55
46	1337[c]	3005	2.0	305[e]	67	4	11
47	2881[c]	5041	1.8	668[e]	128	3	38

[a] $n = 3$ animals per study. [b] Dosed iv at 2 mg/kg as a solution in DMSO. [c] Dosed iv at 1 mg/kg as a solution in DMSO. [d] Dosed iv at 5 mg/kg as a solution in DMSO. [e] Dosed po at 5 mg/kg as a suspension in 1% Tween-80, 2% HPMC, 97% water. [f] Dosed po at 2 mg/kg as a suspension in 1% Tween-80, 2% HPMC, 97% water.

Table 8. Kinase Selectivity Profiles of **32** and **47**

	IC_{50} (μM)			IC_{50} (μM)	
kinase	**32**	**47**	kinase	**32**	**47**
Lck	0.0005	0.0002	JNK2	>25	0.173
Src	0.017	0.002	JNK3	>5	0.145
Syk	1.11	0.292	Jak3	0.868	0.072
Tyk2	2.73	1.83	KDR	0.017	0.001
Itk	>5	>25	p38α	0.009	0.003
Btk	3.33	0.545	Aurora1	>5	>5
CDK5	>25	>25	Aurora2	>25	>25
MSK1	>25	>25	PKBα	>25	>25
Pak2	>25	>25	PKAβ	>25	>25
JNK1	>10	0.389	Zap-70	>25	>25

induced production of IL-2 in 50% human whole blood (WB IL-2). In this assay, compounds **9**, **32**, and **47** were submicromolar inhibitors of IL-2 production (Table 6). Other promising compounds such as **37**, **52**, and **53** were less potent inhibitors of IL-2 production in human whole blood. On the basis of their inhibitory activity in the p38α kinase assay (<10 nM), potent compounds **9**, **32**, and **47** were further counterscreened for inhibitory activity in the lipopolysaccharide-induced production of tumor necrosis factor α in human whole-blood (WB TNFα). Gratifyingly, potency was marginal in this assay (>2.5 μM).

Pharmacokinetic Profiles. On account of their in vitro potencies, several aminoquinazolines were selected for pharmacokinetic (PK) profiling. PK data for discrete intravenous (iv) and oral (po) dosing in male Sprague-Dawley rats are shown in Table 7. Compound **32** exhibited a low rate of clearance and a high volume of distribution, while both parameters were relatively high for compound **47**. However, both **32** and **47** exhibited improved oral exposures and bioavailabilities relative to structurally related compounds from this series (i.e., **1**, **9**, and **46**).

Selectivity Profile. Prior to in vivo testing, compounds **32** and **47** were screened for inhibitory activity against an extensive panel of kinases (Table 8).[21] Excellent selectivity (>1000-fold)

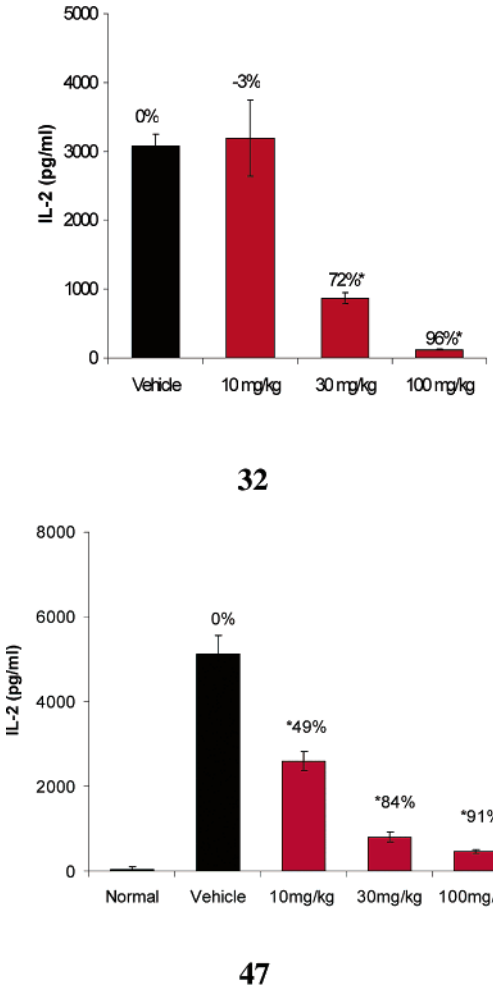


Figure 5. Effect of **32** and **47** on anti-CD3 induced IL-2 production in BALB/c mice. The 12 week old female BALB/c mice were pretreated (po) with **32** or **47** at 10, 30, or 100 mg/kg. After 1.0 h the mice were challenged (iv) with antimouse CD3 monoclonal antibody (3 mg/mouse). After 90 min of anti-CD3 challenge, blood was collected via cardiac puncture. IL-2 levels were measured in serum using the BioSource ELISA kit. Data points represent the mean ± SE; $n = 5$ animals per group: (*) $p \leq 0.05$ vs vehicle control by Mann−Whitney *U*-test.

was observed over a number of structurally diverse kinases including Syk, Tyk2, Itk, Btk, CDK5, Msk1, Pak2, Jnk1, Aurora1, Aurora2, PKBα, PKAβ, and Zap70. As expected, these compounds are not selective over other members of the Src family, including Src kinase.

Pharmacodynamic Profiles. On the basis of their PK and selectivity profiles, compounds **32** and **47** were further evaluated to ascertain in vivo activity upon oral administration at 10, 30, and 100 mg/kg. Both compounds exhibited statistically significant dose-dependent inhibition of anti-CD3-induced IL-2 production in female BALB/c mice (Figure 5). Terminal plasma levels (at 2.5 h) of compounds **32** and **47** were also determined in these experiments to estimate the levels of exposure at each dose. At the estimated ED_{50} values for **32** (22 mg/kg) and **47** (11 mg/kg) the mean terminal plasma concentrations (EC_{50}) were ~1400 and 630 nM, respectively. These levels are in an adequate range relative to the in vitro potency of both compounds in the whole-blood IL-2 assay ($IC_{50} = 113$ and 272 nM, respectively). When adjusted for free fraction based on mouse protein binding (Table 6), the EC_{50} (fu) for **47** is ~18 nM, which is consistent with the in vitro inhibitory activity in the absence of whole blood (IL-2 $IC_{50} = 21$ nM).

Conclusions

As a result of our screening efforts, aminoquinazoline **1** was identified as a potent inhibitor of Lck and T cell proliferation. X-ray crystallographic studies revealed an unusual DFG-out binding mode, which presumably contributes to the marked potency. Extensive SAR investigations resulted in a diverse collection of novel aminoquinazolines and revealed the structural features that contribute to potency, selectivity, and acceptable pharmacokinetic properties for this series. Optimized, orally bioavailable compounds **32** and **47** exhibit anti-inflammatory activity (ED_{50} = 22 and 11 mg/kg, respectively) in the anti-CD3 induced production of IL-2 in mice. These findings demonstrate the potential of this highly tractable chemical series and have paved the way for the advancement of more selective compounds, which will be reported in due course.

Experimental Section

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Dry organic solvents (CH_2Cl_2, CH_3CN, DMF, etc.) were purchased from Aldrich packaged under nitrogen in Sure/Seal bottles. Reactions were monitored using Agilent 1100 series LCMS with UV detection at 254 nm and a low-resonance electrospray mode (ESI). Medium-pressure liquid chromatography (MPLC) was performed on a CombiFlash Companion (Teledyne Isco) with RediSep normal-phase silica gel (35−60 μm) columns and UV detection at 254 nm. Preparative reversed-phase HPLC was performed on a Gilson (215 liquid handler), YMC-Pack Pro C18, 150 mm × 30 mm i.d. column, eluting with a binary solvent system A and B using a gradient elution (system A consisting of H_2O with 0.1% TFA; system B consisting of CH_3CN with 0.1% TFA) with UV detection at 254 nm. Purity was measured using Agilent 1100 series high-performance liquid chromatography (HPLC) systems with UV detection at 254 nm (system A consisting of Agilent Zorbax Eclipse XDB-C8 4.6 mm × 150 mm, 5 μm, 5−100% CH_3CN in H_2O with 0.1% TFA for 15 min at 1.5 mL/min; system B consisting of Waters Xterra 4.6 mm × 150 mm, 3.5 μm, 5−95% CH_3CN in H_2O with 0.1% TFA for 15 min at 1.0 mL/min). Melting points were obtained using an OptiMelt and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AV-400 (400 MHz) spectrometer at ambient temperature or on a Varian 400 MHz or on a Varian 300 MHz spectrometer. Chemical shifts are reported in ppm from the solvent resonance (DMSO-d_6, 2.49 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Mass spectra were obtained on a high-resonance electrospray time-of-flight mass spectrometer in positive ES ionization mode. Combustion analysis was performed by Galbraith Laboratories, Inc., Knoxville, TN.

3-(2-Aminoquinazolin-6-yl)-4-methyl-*N*-(3-(trifluoromethyl)-phenyl)benzamide (1). The title compound was prepared from acid **18a** and 3-(trifluoromethyl)benzenamine using a method analogous to the preparation of compound **46**, giving an off-white amorphous solid. Yield: 0.526 g, 83%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.51 (s, 1H), 9.18 (s, 1H), 8.24 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 1.6 Hz, 1H), 7.94 (dd, J = 8.0, 1.8 Hz, 1H), 7.87 (d, J = 1.9 Hz, 1H), 7.78 (dd, J = 8.6, 2.0 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 7.5 Hz, 1H), 6.93 (s, 2H), 2.37 (s, 3H). HRMS $(C_{23}H_{18}F_3N_4O)^+$: calcd, 423.14272; found, 423.14320. Anal. ($C_{23}H_{17}F_3N_4O$) C, H, N.

6-Bromoquinazolin-2-amine (3a). A stirred mixture of guanidine carbonate (281 g, 1.56 mol), NEt(*i*-Pr)$_2$ (540 mL, 3.12 mol), and NMP (2 L) was heated to 150−160 °C with a heating mantle. A solution of aldehyde **5** (250 g, 1.20 mol) in NMP (100 mL) was added dropwise via addition funnel over 1 h while maintaining reflux. Upon complete addition, the mixture was maintained at 150−160 °C for an additional 1−2 h until consumption of the aldehyde was complete as determined by LC analysis. Upon completion, the heat source was removed and the mixture was allowed to cool to below 100 °C, then quenched by the addition of ice (2 kg) and water (4 L). The resulting bronze solid was stirred for an additional 30 min, then was isolated by vacuum filtration, washing with water (1 L) and then denatured EtOH (1 L). The solids were then transferred to a 5 L flask and stirred in denatured EtOH (2 L) for 2 h before refiltering. Subsequent washes in EtOH (0.5 L), in a 1:1 mixture of toluene/EtOH (0.5 L), and then in toluene (0.5 L) and drying afforded the title compound (168 g, 48%) as a pale-yellow solid. Analytical data were identical to that previously reported.[7]

6-Bromo-*N*-methylquinazolin-2-amine (3b). A 1 L high-pressure reactor was charged with aminoquinazoline **3a** (20.0 g, 89.3 mmol), *p*-toluenesulfonic acid monohydrate (33.9 g, 179 mmol), and methylamine (∼150 g). The reactor was slowly heated to 150 °C (820 psi, internal pressure). After 24 h, the reactor was cooled to room temperature, and excess methylamine was slowly vented. The crude residue was taken up in CH_2Cl_2 (1.0 L) and washed with saturated aqueous $NaHCO_3$ and brine. The organic fraction was concentrated in vacuo and purified by silica gel chromatography (1−3% CH_3OH in CH_2Cl_2) to afford the title compound (14.6 g, 68%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.07 (s, 1H), 8.05 (d, J = 2.3 Hz, 1H), 7.77 (dd, J = 9.1, 2.3 Hz, 1H), 7.52 (s, 1H), 7.43 (d, J = 8.8 Hz, 1H), 2.89 (d, J = 4.8 Hz, 3H). MS, *m*/*z* ($C_9H_8BrN_3$): calcd, 237.0; found, 238.0 (MH).

6-Bromo-*N*-phenylquinazolin-2-amine (3c). In a resealable Pyrex tube, 6-bromo-2-iodoquinazoline (**7**) (1.4 g, 4.1 mmol) and aniline (0.45 mL, 4.9 mmol) were taken up in IPA. 2,2,2-Trifluoroacetic acid (0.63 mL, 8.2 mmol) was added, and the tube was sealed. The suspension was stirred at 70 °C overnight. Then triethylamine (∼1 mL) was added to neutralize the mixture, and the mixture was concentrated. The residue was purified by silica gel chromatography (3−10% CH_3OH in CH_2Cl_2) to afford the title compound (1.1 g, 88%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.02 (s, 1H), 9.29 (s, 1H), 8.19 (d, J = 2.5 Hz, 1H), 7.97 (d, J = 8.6 Hz, 2H), 7.91 (dd, J = 8.8, 2.3 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.34 (t, J = 7.8 Hz, 2H), 7.01 (t, J = 7.2 Hz, 1H). MS, *m*/*z* ($C_{14}H_{10}BrN_3$): calcd, 300.1; found, 300, 302 (M, M + 2).

6-Bromo-*N*-(2-morpholinoethyl)quinazolin-2-amine (3d). In a resealable Pyrex tube, iodide **7** (0.130 g, 0.388 mmol) was dissolved in IPA (3 mL), and DIEA (0.102 mL, 0.582 mmol) and 2-morpholinoethanamine (0.260 mL, 1.94 mmol) were added. The tube was sealed, and the mixture was heated at 80 °C for 2 h. After cooling to room temperature, the mixture was concentrated to a yellow residue and purified by silica gel chromatography (0−20% CH_3OH in CH_2Cl_2) to afford the title compound (0.125 g, 95%) as a yellow amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (s, 1H), 8.05 (d, J = 2.3 Hz, 1H), 7.78 (dd, J = 8.8, 2.3 Hz, 1H), 7.40 (d, J = 8.6 Hz, 2H), 3.54−3.61 (m, 4H), 3.49 (q, J = 6.3 Hz, 2H), 2.51−2.58 (m, 2H), 2.38−2.47 (m, 4H). MS, *m*/*z* ($C_{14}H_{17}BrN_4O$): calcd, 337; found, 337, 339 (M, M + 2).

6-Bromo-*N*-(3-morpholinopropyl)quinazolin-2-amine (3e). The title compound was prepared from iodoquinazoline **7** and 3-morpholinopropan-1-amine using a method analogous to the preparation of compound **3d**, giving a pale-yellow amorphous solid. Yield: 0.14 g, 89%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 7.94 (d, J = 2.3 Hz, 1H), 7.66 (dd, J = 9.1, 2.3 Hz, 1H), 7.52 (s, 1H), 7.28 (d, J = 9.1 Hz, 1H), 3.45−3.50 (m, 4H), 3.29 (q, J = 6.3 Hz, 2H), 2.23−2.29 (m, 6H), 1.59−1.69 (m, 2H). MS, *m*/*z* ($C_{15}H_{19}BrN_4O$): calcd, 351; found, 351, 353 (M, M + 2).

6-Bromo-*N*-methyl-*N*-(3-morpholinopropyl)quinazolin-2-amine (3f). NaH (0.026 g, 0.640 mmol, 60% dispersion in mineral oil) was added to a solution quinazoline **3e** (0.023 g, 0.640 mmol) in THF (3.5 mL) and DMF (0.3 mL). After the mixture was stirred at room temperature for 10 min, MeI (0.04 mL, 0.640 mmol) was added at once. The mixture was allowed to stir at room temperature for 3 h and then quenched with water. The mixture was then extracted several times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concen-

trated to afford the crude title compound as an orange solid, which was used without further purification. MS, *m*/*z* ($C_{16}H_{21}BrN_4O$): calcd, 365; found, 365 (M).

6-Bromo-*N*-(2-(piperidin-1-yl)ethyl)quinazolin-2-amine (3g). The title compound was prepared from iodide **7** and 2-(piperidin-1-yl)ethanamine using a method analogous to the preparation of compound **3d**. The crude material was used without further purification. MS, *m*/*z* ($C_{15}H_{19}BrN_4$): calcd, 335; found, 335, 337 (M, M + 2).

6-Bromo-*N*-(2-(pyrrolidin-1-yl)ethyl)quinazolin-2-amine (3h). The title compound was prepared from iodide **7** and 2-(pyrrolidin-1-yl)ethanamine using a method analogous to the preparation of compound **3d** and was used without further purification. MS, *m*/*z* ($C_{14}H_{17}BrN_4$): calcd, 321; found, 321 (M).

6-Bromo-*N*-(1-methylpiperidin-4-yl)quinazolin-2-amine (3i). The title compound was prepared from iodide **7** and 1-methylpiperidin-4-amine using a method analogous to the preparation of compound **3d**, giving a pale-yellow amorphous solid. Yield: 0.072 g, 50%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (s, 1H), 8.03 (d, J = 2.3 Hz, 1H), 7.76 (dd, J = 9.1, 2.3 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 8.6 Hz, 1H), 3.72−3.85 (m, 1H), 2.76 (d, J = 11.6 Hz, 2H), 2.17 (s, 3H), 1.98 (t, J = 10.9 Hz, 2H), 1.87 (d, J = 11.4 Hz, 2H), 1.50−1.62 (m, 2H). MS, *m*/*z* ($C_{14}H_{17}BrN_4$): calcd, 321.0; found, 321 (M).

6-Bromo-*N*-cyclopropylquinazolin-2-amine (3j). The title compound was prepared from iodide **7** and cyclopropylamine using a method analogous to the preparation of compound **3d**, giving a yellow amorphous solid. Yield: 0.454 g, 77%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H), 8.07 (d, J = 2.0 Hz, 1H), 7.74−7.82 (m, 2H), 7.45 (d, J = 8.8 Hz, 1H), 2.80−2.89 (m, 1H), 0.68−0.75 (m, 2H), 0.50−0.56 (m, 2H). MS, *m*/*z* ($C_{11}H_{10}BrN_3$): calcd, 264.0; found, 264 (M).

4-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (4a). The title compound was prepared from acid **8** and 3-(trifluoromethyl)benzenamine using a method analogous to the preparation of compound **4f** and was used without purification. MS, *m*/*z* ($C_{21}H_{23}BF_3NO_3$): calcd, 405.2; found, 406.2 (MH).

4-Methyl-*N*-(2-methyl-3-(trifluoromethyl)phenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (4b). The title compound was prepared from acid **8** and 2-methyl-3-(trifluoromethyl)benzenamine using a method analogous to the preparation of compound **4f** and was purified by column chromatography (100% CH_2Cl_2). Mp 155.0−159.0 °C. Yield: 1.53 g, 60%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.16 (s, 1H), 8.25 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 7.8, 1.8 Hz, 1H), 7.62 (t, J = 8.1 Hz, 2H), 7.45 (t, J = 8.1 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 2.55 (s, 3H), 2.30 (s, 3H), 1.34 (s, 12H).

***N*-(2,3-Dihydro-1*H*-inden-4-yl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (4c).** *N*-(2,3-Dihydro-1*H*-inden-4-yl)-3-iodo-4-methylbenzamide was prepared from 3-iodo-4-methylbenzoic acid and 2,3-dihydro-1*H*-inden-4-amine using a method analogous to the preparation of *N*-(3-iodo-4-methylphenyl)-3-(trifluoromethyl)benzamide (step 1 of the procedure for the preparation of **13**). It was isolated by trituration with CH_2Cl_2 and filtration through a Büchner micromembrane apparatus to afford the crude product as a white solid, which was used without further purification. MS, *m*/*z* ($C_{17}H_{16}INO$): calcd, 377.2; found, 378 (MH).

N-(2,3-Dihydro-1*H*-inden-4-yl)-3-iodo-4-methylbenzamide (0.53 g, 1.4 mmol), bis(pinacolato)diboron (0.46 g, 1.8 mmol), KOAc (0.48 g, 4.9 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (0.10 g, 0.14 mmol), and DMF (4.3 mL) were combined in a sealed tube and heated to 80 °C for 8 h. Upon completion (as judged by LCMS), the reaction mixture was cooled to room temperature, and the solvent was evaporated in vacuo. The residue was taken up in CH_2Cl_2, washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a thick, brown residue. This residue was passed through a plug of silica (100% CH_2Cl_2) to afford the title compound as a white amorphous solid, which was used without further purification. MS, *m*/*z* ($C_{23}H_{28}BNO_3$): calcd, 377.2; found, 378 (MH).

4-Methyl-*N*-(4-(1-methylpiperidin-4-yloxy)phenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (4d). The title compound was prepared from acid **8** and 4-(1-methylpiperidin-4-yloxy)benzenamine using a method analogous to the preparation of compound **4f** and was used without further purification. MS, *m*/*z* ($C_{26}H_{35}BN_2O_4$): calcd, 450.4; found, 451.2 (MH).

***N*-(4-Chloro-3-(trifluoromethyl)phenyl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (4e).** The title compound was prepared from acid **8** and 4-chloro-3-(trifluoromethyl)benzenamine using a method analogous to the preparation of compound **4f** and was used without further purification. MS, *m*/*z* ($C_{21}H_{22}BClF_3NO_3$): calcd, 439.7; found, 440 (MH).

***N*-(4-Chloro-2-methyl-3-(trifluoromethyl)phenyl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (4f).** Acid **8** (0.300 g, 1.14 mmol) and $SOCl_2$ (2.34 mL, 32.0 mmol) were combined in a resealable Pyrex tube. The tube was sealed and heated to 60 °C for 1 h. Upon completion (as judged by quenching an aliquot with methanol and analysis by LCMS), the reaction mixture was diluted with toluene and the solvent was removed in vacuo. The crude acid chloride was dissolved in CH_2Cl_2 (5.7 mL) in a 25 mL round-bottom flask, and 4-chloro-2-methyl-3-(trifluoromethyl)benzenamine[10c] (0.286 g, 1.37 mmol) and triethylamine (~0.1 mL) were added. The mixture was stirred under nitrogen atmosphere at room temperature overnight. The solvent was removed in vacuo, and the residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to afford the title compound, which was used in the subsequent reaction without further purification. MS, *m*/*z* ($C_{22}H_{24}BClF_3NO_3$): calcd, 453.7; found, 454.1 (MH).

4-Methyl-*N*-(2-(1-methylpiperidin-4-yloxy)-5-(trifluoromethyl)phenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (4g). The title compound was prepared from acid **8** and 2-(1-methylpiperidin-4-yloxy)-5-(trifluoromethyl)benzenamine using a method analogous to the preparation of compound **4f** and was used without further purification. MS, *m*/*z* ($C_{27}H_{34}BF_3N_2O_4$): calcd, 518.4; found, 519.2 (MH).

4-Methyl-*N*-(2-(piperidin-1-yl)-5-(trifluoromethyl)phenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (4h). The title compound was prepared from acid **8** and 2-(piperidin-1-yl)-5-(trifluoromethyl)benzenamine using a method analogous to the preparation of compound **4f** and was used without further purification. MS, *m*/*z* ($C_{26}H_{33}BF_3N_2O_3$): calcd, 489.4; found, 489.5 (MH).

4-Methyl-*N*-(2-(3-methyl-2-oxoimidazolidin-1-yl)-5-(trifluoromethyl)phenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (4i). The title compound was prepared from acid **8** and aniline **21** using a method analogous to the preparation of compound **4f** and was used without further purification. MS, *m*/*z* ($C_{25}H_{29}BF_3N_3O_4$): calcd, 503.2; found, 504.2 (MH).

1-(2-(4-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)-4-(trifluoromethyl)phenyl)-3-(2-morpholinoethyl)urea (4j). The title compound was prepared from acid **8** and aniline **23**, using a method analogous to the preparation of compound **4f**, and was used without further purification. MS, *m*/*z* ($C_{28}H_{36}BF_3N_4O_5$): calcd, 576.3; found, 577.3 (MH).

***N*-(2-(2-(Diethylamino)acetamido)-5-(trifluoromethyl)phenyl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (4k).** The title compound was prepared from acid **8** and aniline **25**, using a method analogous to the preparation of compound **4f**, and was used without further purification. MS, *m*/*z* ($C_{27}H_{35}BF_3N_3O_4$): calcd, 533.3; found, 534.2 (MH).

***N*-(2-(3,3-Dimethyl-2-oxoazetidin-1-yl)-5-(trifluoromethyl)-phenyl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (4l).** The title compound was prepared from acid **8** and aniline **26**, using a method analogous to the preparation of compound **4f**, and was used without further purification. MS, *m*/*z* ($C_{26}H_{30}BF_3N_2O_4$): calcd, 502.2; found, 503.1 (MH).

2-Fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (4m). 5-Bromo-2-fluoro-4-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide was pre-

pared from 5-bromo-2-fluoro-4-methylbenzoic acid[22] and 3-(trifluoromethyl)benzenamine using a method analogous to the preparation of *N*-(3-iodo-4-methylphenyl)-3-(trifluoromethyl)benzamide (step 1 of the procedure for the preparation of **13**). It was purified by silica gel chromatography (2−30% EtOAc in hexanes). Yield: 0.330 g, 51%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.75 (s, 1H), 8.18 (s, 1H), 7.94 (s, 1H), 7.92 (d, J = 6.7 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.50−7.46 (m, 2H), 2.42 (s, 3H). MS (ES, negative ion), *m*/*z* ($C_{15}H_{10}BrF_4NO$): calcd, 376.2; found, 375 (M − 1).

The title compound was prepared from 5-bromo-2-fluoro-4-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide, using a method analogous to the preparation of compound **4c**, and was used without further purification. MS, *m*/*z* ($C_{21}H_{22}BF_4NO_3$): calcd, 423.2l; found, 424 (MH).

6-Bromo-2-iodoquinazoline (7). Aminoquinazoline **3a** (5.00 g, 22.3 mmol), CuI (4.30 g, 22.3 mmol), and CH_2I_2 (9.0 mL, 114 mmol) were dissolved in THF (100 mL), and isoamyl nitrite (85%) (9.0 mL, 68 mmol) was added. After purging with N_2, the mixture was heated to reflux for 2.5 h. After cooling to room temperature, the crude reaction mixture was partitioned between EtOAc (500 mL) and 1 N HCl (500 mL). After separation, the aqueous portion was extracted three times with EtOAc and the combined organic extracts were washed twice with saturated aqueous NH_4Cl, dried over Na_2SO_4, filtered, and concentrated to a purple oil. The oil was passed through a plug of silica (100% CH_2Cl_2) and concentrated to afford the title compound (2.60 g, 35%) as an off-white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.34 (s, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.18 (dd, J = 9.0, 2.15 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H). MS, *m*/*z* ($C_8H_4BrIN_2$): calcd, 334.9; found, 335 (MH).

4-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic Acid (8). Iodide **6a** (5.00 g, 19.1 mmol), bis(pinacolato)diboron (7.26 g, 28.6 mmol), KOAc (9.36 g, 95.4 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (1.30 g, 1.78 mmol), and DMF (100 mL) were combined in a sealed tube and heated to 80 °C for 6 h. Upon completion (as judged by LCMS), the reaction mixture was cooled to room temperature, and the solvent was evaporated in vacuo. The residue was dissolved in EtOAc (150 mL) and 2 N HCl (150 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, mixed with activated charcoal, and filtered through a pad of silica gel. The solvent was removed in vacuo to provide a brown oil. The oil was dissolved in EtOAc and 2 N NaOH. The organic layer was separated and extracted with 2 N NaOH (2 × 100 mL). The water layer was washed with EtOAc until the extracts were clear (6×). The aqueous layer was acidified to pH 3 with 6 N HCl, and a precipitate formed. The precipitate was filtered and dried to yield the title compound (2.7 g, 54%) as an off-white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.78 (br s, 1H), 8.23 (d, J = 1.8 Hz, 1H), 7.89 (dd, J = 7.9, 1.8 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 2.52 (s, 3H), 1.31 (s, 12H). MS, *m*/*z* ($C_{14}H_{20}BO_4$): calcd, 263.1; found, 263.1 (MH).

4-Methyl-3-(2-(methylamino)quinazolin-6-yl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (9). The title compound was prepared from boronate **4a** and bromide **3b** using a method analogous to the preparation of compound **33**. Yield: 0.044 g, 36%. HPLC purity: 100% (system A); 100% (system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 9.13 (s, 1H), 8.21 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.94 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.77−7.42 (m, 5H), 2.90 (d, J = 4.8 Hz, 3H), 2.34 (s, 3H). HRMS $(C_{24}H_{20}F_3N_4O)^+$: calcd, 437.158 37; found, 437.158 80.

4-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenamine (11). Iodide **10** (3.0 g, 13 mmol), bis(pinacolato)diboron (3.6 g, 14 mmol), KOAc (4.4 g, 45 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (0.94 g, 1.3 mmol), and DMSO (35 mL) were combined in a sealed tube and heated to 80 °C for 10 h. Upon completion (as judged by LCMS), the reaction mixture was cooled to room temperature, and the solvent was evaporated in vacuo. The residue was taken up in EtOAc and filtered to remove a gray solid. The filtrate was washed with water and then three times with saturated NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a thick, brown residue. This material was purified by silica gel chromatography (2−10% CH_3OH in CH_2Cl_2) to afford the title compound (1.3 g, 42%) as an off-white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.92 (d, J = 2.6 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.54 (dd, J = 8.0, 2.6 Hz, 1H), 4.80 (br s, 2H), 2.27 (s, 3H), 1.27 (s, 12 H). MS, *m*/*z* ($C_{13}H_{20}BNO_2$): calcd, 233.1; found, 234.1 (MH).

6-(5-Amino-2-methylphenyl)-*N*-methylquinazolin-2-amine (12). Bromide **3b** (0.14 g, 0.61 mmol), boronate **11** (0.17 g, 0.73 mmol), 2 M Na_2CO_3 (0.9 mL, 1.8 mmol), Pd(PPh_3)$_4$ (0.070 g, 0.060 mmol), toluene (5.0 mL), and EtOH (1.0 mL) were combined in a sealed tube and heated to 80 °C for 4.5 h. Upon completion (as judged by LCMS), the reaction mixture was cooled to room temperature and filtered to remove a gray solid. The filtrate was taken up in CH_2Cl_2 and washed with water, then dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a thick, brown residue. This material was passed through a plug of silica gel (10% CH_3OH in CH_2Cl_2) to afford the title compound as a tan amorphous solid, which was used without further purification. MS, *m*/*z* ($C_{16}H_{16}N_4$): calcd, 264.3; found, 265 (MH).

***N*-(4-Methyl-3-(2-(methylamino)quinazolin-6-yl)phenyl)-3-(trifluoromethyl)benzamide (13).** A solution of 3-iodo-4-methylaniline (0.20 g, 0.86 mmol), 3-(trifluoromethyl)benzoyl chloride (0.19 g, 0.13 mL, 0.90 mmol), and CH_2Cl_2 (8.0 mL) was stirred at room temperature for 30 min to afford an off-white suspension. NEt_3 (0.11 g, 0.16 mL, 1.1 mmol) was added, and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was concentrated, and the resulting solid was partitioned between CH_2Cl_2 and water. The organic phase was separated and washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford *N*-(3-iodo-4-methylphenyl)-3-(trifluoromethyl)benzamide (0.31 g, 89%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.47 (s, 1H), 8.34−8.33 (m, 2H), 8.26 (d, J = 7.8 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.73 (dd, J = 8.3, 1.8 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 2.36 (s, 3H).

A resealable tube was charged with boronate **17b** (0.080 g, 0.26 mmol), *N*-(3-iodo-4-methylphenyl)-3-(trifluoromethyl)benzamide (0.11 g, 0.28 mmol), K_2CO_3 (0.06 g, 0.42 mmol), DMF (2.5 mL), and water (0.5 mL). Pd(dppf)Cl_2·CH_2Cl_2 (0.020 g, 0.030 mmol) was added, and the system was purged with argon. The tube was sealed, and the mixture was stirred at room temperature for 18 h. The reaction mixture was partitioned between CH_2Cl_2 and water. The aqueous phase was separated and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a brown oil. This oil was purified via preparative thin layer silica gel chromatography (eluting with 95:5:0.5 CH_2Cl_2/CH_3OH/NH_4OH) to afford the title compound (0.07 g, 59%) as a tan amorphous solid. HPLC purity: 96% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.53 (s, 1H), 9.21 (s, 1H), 8.36−8.42 (m, 1H), 8.34 (d, J = 7.6 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.76−7.88 (m, 6H), 7.62 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 9.1 Hz, 1H), 2.98 (d, J = 4.7 Hz, 3H), 2.33 (s, 3H). HRMS $(C_{24}H_{20}F_3N_4O)^+$: calcd, 437.158 37; found, 437.158 66. Anal. ($C_{24}H_{19}F_3N_4O$·CH_3OH·H_2O) C, H, N.

1-(4-Methyl-3-(2-(methylamino)quinazolin-6-yl)phenyl)-3-(3-(trifluoromethyl)phenyl)urea (14). 1-Isocyanato-3-(trifluoromethyl)benzene (0.0170 mL, 0.119 mmol) was added to a suspension of aniline **12** (0.030 g, 0.113 mmol) in benzene (2 mL). The mixture was allowed to stir at room temperature overnight and then filtered through a micromembrane Büchner apparatus, washing with benzene to afford the title compound (0.028 g, 56%) as an off-white solid. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 1H), 9.04 (s, 1H), 8.79 (s, 1H), 8.02 (s, 1H), 7.77 (d, J = 4.0 Hz, 1H), 7.70 (dd, J = 8.0, 4.0 Hz, 1H), 7.58−7.49 (m, 4H), 7.41−7.22 (m, 4H), 2.92 (s, J = 4.0 Hz, 3H), 2.22 (s, 3H). HRMS $(C_{24}H_{21}F_3N_5O)^+$: calcd, 452.169 27; found, 452.169 83.

***N*-Methyl-6-(2-methyl-5-(5-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-ylamino)phenyl)quinazolin-2-amine (15).** 6-(5-Amino-2-methylphenyl)-*N*-methylquinazolin-2-amine (0.50 g, 1.9 mmol)

was taken up in CH_2Cl_2 (~12 mL). To the solution was added *O*,*O*-dipyridin-2-yl carbonothioate (0.44 g, 1.9 mmol). The light-brown solution was stirred at room temperature for 3 h. The crude reaction mixture was filtered through a Büchner apparatus with a micromembrane filter, and the filtrate was washed with CH_2Cl_2 and dried to afford 6-(5-isothiocyanato-2-methylphenyl)-*N*-methylquinazolin-2-amine as a pale-yellow powder (crop 1). MS, *m*/*z* ($C_{17}H_{14}N_4S$): calcd, 306.4; found, 307 (MH). The mother liquors were washed with water, then dried over Na_2SO_4, filtered, and concentrated to afford 6-(5-isothiocyanato-2-methylphenyl)-*N*-methylquinazolin-2-amine as a yellow-tan solid (crop 2). Crops 1 and 2 were used without further purification.

In a 16 mm × 120 mm resealable Pyrex tube 6-(5-isothiocyanato-2-methylphenyl)-*N*-methylquinazolin-2-amine (0.080 g, 0.26 mmol), PS-DCC (0.49 g, 0.78 mmol), and 4-(trifluoromethyl)-1,2-phenylenediamine (0.070 g, 0.39 mmol) were taken up in THF (6 mL). The tube was sealed, and the mixture was stirred at 70 °C overnight. After cooling, the crude reaction mixture was filtered through a medium glass frit, and PS-DCC was washed with CH_2Cl_2. Concentration and purification by silica gel chromatography (3−80% 90:10:1 CH_2Cl_2 in CH_2Cl_2) afforded the title compound (0.070 g, 58%) as a pale-yellow solid. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.33 (s, 0.5H) and 11.20 (s, 0.5H) [NH-tautomers], 9.73 (s, 0.5 H) and 9.68 (s, 0.5 H) [NH-tautomers], 9.16 (s, 1H), 7.81 (s, 1H), 7.71 (m, 3H), 7.57 (m, 2H), 7.42 (m, 2H), 7.30 (m, 2H), 2.93 (d, J = 4.2 Hz, 3H), 2.23 (s, 3H). HRMS $(C_{24}H_{20}F_3N_6)^+$: calcd, 449.169 61; found, 449.169 39. Anal. ($C_{24}H_{19}F_3N_6 \cdot H_2O$) H, N. C: calcd, 61.80; found, 62.34.

6-(4,4,5,5-Tetramethyl-1,3,2-dioxaboralan-2-yl)quinazolin-2-amine (17a). A pressure flask was charged with $Pd_2(dba)_3$ (0.082 g, 0.089 mmol), (*o*-biphenyl)PCy_2 (0.094 g, 0.270 mmol), and dioxane (10 mL). The flask was purged with argon, and the mixture was stirred for 10 min at ambient temperature. To this stirred solution was added 6-bromoquinazolin-2-amine (**3a**) (1.0 g, 4.5 mmol), bis(pinacolato)diboron (1.4 g, 5.4 mmol), KOAc (0.70 g, 7.1 mmol), and dioxane (10 mL). The mixture was again purged with argon, and the flask was sealed and heated to 80 °C for a period of 15 h. The reaction mixture was then cooled to ambient temperature and filtered through Celite, and the cake was washed with CH_2Cl_2. The filtrate was concentrated in vacuo, and the crude solid was triturated with hexanes to afford the title compound as an orange solid, which was used without further purification. ^{1}H NMR (400 MHz, DMSO): δ 9.17 (s, 1H), 8.17 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.06 (br s, 2H), 1.31 (s, 12H). MS, *m*/*z* ($C_{14}H_{18}BN_3O_2$): calcd, 271.1; found, 272.1 (MH).

***N*-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-quinazolin-2-amine (17b).** The title compound was prepared from bromide **3b** using a method analogous to the preparation of compound **17a**, giving an orange amorphous solid. Yield: 1.15 g, 96%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.98 (s, 1H), 8.01 (s, 1H), 7.70 (d, J = 8.59 Hz, 1H), 7.39 (s, 1H), 7.28 (s, 1H), 2.74 (d, J = 4.7 Hz, 3H), 1.16 (s, 12H).

3-(2-Amino-6-quinazolinyl)-4-methylbenzoic Acid (18a). A flask was charged with boronate **17a** (0.50 g, 1.8 mmol), 3-iodo-4-methylbenzoic acid (0.39 g, 1.5 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.12 g, 0.14 mmol), and K_2CO_3 (0.32 g, 2.4 mmol). The flask was then charged with DMF (14 mL) and water (4 mL), and the solution was purged with argon for a period of 10 min. The solution was stirred at ambient temperature for a period of 15 h, then filtered through a Büchner funnel, and washed with EtOAc. The filtrate was concentrated in vacuo and then redissolved in EtOAc/H_2O (1:1; 30 mL). The aqueous layer was separated and washed with EtOAc and then acidified to pH ~3 with 1 N HCl. The fine tan precipitate obtained was centrifuged in 250 mL ultracentrifuge vials (at 3000 rpm for 15 min) and then washed with 2 × 25 mL of distilled water. After the aqueous washes were decanted, the resulting light-tan solid was lyophilized for a period of 15 h to yield the title compound as a light-tan solid (0.28 g, 70%). ^{1}H NMR (400 MHz, DMSO): δ 9.18 (s, 1H), 7.82 (m, 3H), 7.73 (dd, J = 1.6, 2.0 Hz, 1H), 7.47 (dd, J = 8.8, 8.0 Hz, 2H), 7.12 (br s, 2H), 2.32 (s, 3H). MS, *m*/*z* ($C_{16}H_{13}N_3O_2$): calcd, 279.1; found, 280.1 (MH).

1-(2-Amino-4-(trifluoromethyl)phenyl)-3-methylimidazolidin-2-one (21). A resealable Pyrex tube was charged with bromide **20** (1.1 g, 4.5 mmol), 1-methylimidazolidin-2-one (0.59 g, 5.8 mmol), K_2CO_3 (1.23 g, 9.0 mmol), and CuI (0.85 g, 0.45 mmol). To the mixture was added toluene (3.0 mL) and N^1,N^2-dimethylethane-1,2-diamine (96 μL, 0.90 mmol). The tube was sealed and heated at 110 °C for 24 h. After cooling to room temperature, the mixture was diluted with EtOAc and washed with water and brine. The organic fraction was dried with Na_2SO_4, concentrated in vacuo, and purified by silica gel chromatography (5−10% CH_3OH in CH_2Cl_2) to afford the title compound (0.70 g, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.15 (d, J = 8.1 Hz, 1H), 7.04 (s, 1H), 6.83 (d, J = 8.1 Hz, 1H), 5.46 (s, 2H), 3.63−3.53 (m, 2H), 3.48−3.41 (m, 2H), 2.75 (s, 3H). MS, *m*/*z* ($C_{11}H_{12}F_3N_3O$): calcd, 259.1; found, 260.2 (MH).

1-(2-Amino-4-(trifluoromethyl)phenyl)-3-(2-morpholinoethyl)urea (23). To a solution of isocyanate **22** (0.735 g, 3.17 mmol) in benzene (10 mL) at room temperature was added 2-morpholinoethanamine (0.433 g, 3.33 mmol). The resulting yellow mixture was heated at 40 °C for 16 h. After the mixture was cooled to room temperature, the yellow precipitate was removed by filtration and rinsed with hexanes. The crude 1-(2-morpholinoethyl)-3-(2-nitro-4-(trifluoromethyl)phenyl)urea was advanced without further purification. MS, *m*/*z* ($C_{14}H_{17}F_3N_4O_4$): calcd, 362.1; found, 363.1 (MH).

To a solution of crude 1-(2-morpholinoethyl)-3-(2-nitro-4-(trifluoromethyl)phenyl)urea (0.970 g, 2.68 mmol) in CH_3OH (30 mL) and EtOAc (10 mL) was added 10% Pd/C (0.400 g). The mixture was exposed to an atmosphere of H_2 (balloon). After 24 h, the mixture was filtered, concentrated, and purified by silica gel chromatography (5−10% CH_3OH in CH_2Cl_2) to afford the title compound (0.650 g, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1 H), 7.68 (d, J = 8.3 Hz, 1H), 6.99 (s, 1H), 6.83 (d, J = 8.7 Hz, 1H), 6.30 (t, J = 5.2 Hz, 1H), 5.11 (s, 2H), 3.62−3.55 (m, 4H), 3.18−3.25 (m, 2H), 2.42−2.35 (m, 6H). MS, *m*/*z* ($C_{14}H_{19}F_3N_4O_2$): calcd, 332.2; found, 333.1 (MH).

***N*-(2-Amino-4-(trifluoromethyl)phenyl)-2-(diethylamino)-acetamide (25).** To aniline **24** (7.00 g, 34.0 mmol) in CH_2Cl_2 (300 mL) at 0 °C was added chloroacetyl chloride (3.80 mL, 47.6 mmol) followed by NEt_3 (9.50 mL, 68.0 mmol). The solution was heated at reflux for 48 h. After the mixture was cooled to room temperature, water was added, and the organic fraction was washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (70−100% hexanes/CH_2Cl_2) to afford 2-chloro-*N*-(2-nitro-4-(trifluoromethyl)phenyl)-acetamide (9.10 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 8.11−8.17 (m, 1H), 8.03−8.10 (m, 1H), 4.44 (s, 2H). MS, *m*/*z* ($C_9H_6ClF_3N_2O_3$): calcd, 282.0; found, 283.1 (MH).

To a solution of 2-chloro-*N*-(2-nitro-4-(trifluoromethyl)phenyl)-acetamide (0.750 g, 2.65 mmol) in THF (15 mL) was added K_2CO_3 (0.730 g, 5.30 mmol) and diethylamine (0.30 mL, 2.90 mmol). After heating at 50 °C for 16 h, the mixture was partitioned between EtOAc and water. The organic fraction was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was taken up in CH_3OH (10 mL), and a slurry of 10% Pd/C (0.200 g) in EtOAc (2 mL) was added. After exposure to an atmosphere of H_2 (balloon) for 24 h, the mixture was filtered and concentrated to afford the crude title compound, which was advanced without further purification. MS, *m*/*z* ($C_{13}H_{18}F_3N_3O$): calcd, 289.1; found, 290.2 (MH).

1-(2-Amino-4-(trifluoromethyl)phenyl)-3,3-dimethylazetidin-2-one (26). To a solution of aniline **24** (3.00 g, 14.9 mmol) in CH_2Cl_2 (75 mL) was added 3-chloropivaloyl chloride (2.52 g, 19.4 mmol) followed by NEt_3 (4.15 mL, 29.8 mmol). The solution was heated at 35 °C for 24 h before cooling to room temperature and adding water (100 mL). The organic layer was separated, washed with brine, and dried with Na_2SO_4. After concentration in vacuo, the crude 3-chloro-2,2-dimethyl-*N*-(2-nitro-4-(trifluoromethyl)phenyl)propanamide was advanced without further purification. MS, *m*/*z* ($C_{12}H_{12}ClF_3N_2O_3$): calcd, 324.1; found, 325.1 (MH).

A mixture of 3-chloro-2,2-dimethyl-*N*-(2-nitro-4-(trifluoromethyl)phenyl)propanamide (3.89 g, 12.0 mmol) and K_2CO_3 (4.00 g, 29.0 mmol) in acetone (100 mL) was heated to 50 °C. After 72 h, the mixture was filtered and concentrated in vacuo. The residue was taken up in CH_3OH (25 mL), and a slurry of 10% Pd/C (0.200 g) in EtOAc (5 mL) was added. After exposing the mixture to an atmosphere of H_2 (balloon) for 24 h, the mixture was filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (10−20% hexanes/EtOAc) to afford the title compound (1.75 g, 35% over three steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (d, J = 8.2 Hz, 1H), 7.05 (s, 1H), 6.86 (d, J = 7.0 Hz, 1H), 5.93 (s, 2H), 3.58 (s, 2H), 1.31 (s, 6H). MS, *m*/*z* ($C_{12}H_{13}F_3N_2O$): calcd, 258.1; found, 259.1 (MH).

4-Methyl-*N*-(2-methyl-3-(trifluoromethyl)phenyl)-3-(2-(methylamino)quinazolin-6-yl)benzamide (27). The title compound was prepared from boronate **4b** and bromide **3b**, using a method analogous to the preparation of compound **33**. Yield: 0.087 g, 49%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.17 (s, 1H), 9.16 (s, 1H), 7.97 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 1.8 Hz, 1H), 7.78 (dd, J = 8.6, 1.9 Hz, 1H), 7.62 (m, 3H), 7.51 (d, J = 8.0 Hz, 1H), 7.45 (m, 2H), 2.93 (d, J = 4.8 Hz, 3H), 2.37 (s, 3H), 2.32 (s, 3H). HRMS $(C_{25}H_{22}F_3N_4O)^+$: calcd, 451.174 02; found, 451.174 33. Anal. ($C_{25}H_{21}F_3N_4O$) H, N. C: calcd, 66.66; found, 66.16.

***N*-(2,3-Dihydro-1*H*-inden-4-yl)-4-methyl-3-(2-(methylamino)-quinazolin-6-yl)benzamide (28).** The title compound was prepared from boronate **4c** and bromide **3b**, using a method analogous to the preparation of compound **33**. Yield: 0.094 g, 55%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.94 (s, 1H), 9.15 (s, 1H), 7.92−7.86 (m, 3H), 7.77 (d, J = 8.6, 1H), 7.57 (d, J = 8.9 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.42 (br s, 1 H), 7.20 (d, J = 8.0 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 2.92−2.88 (m, 5H), 2.81 (t, J − 7.4 Hz, 2H), 2.36 (s, 3H), 2.00−1.90 (m, 2H). HRMS $(C_{26}H_{25}N_4O)^+$: calcd, 409.202 29; found, 409.202 17. Anal. ($C_{26}H_{24}N_4O\cdot0.5H_2O$) C, H, N.

4-Methyl-3-(2-(methylamino)quinazolin-6-yl)-*N*-(4-(1-methylpiperidin-4-yloxy)phenyl)benzamide (29). The title compound was prepared from boronate **4d** and bromide **3b**, using a method analogous to the preparation of compound **33**. Yield: 0.697 g, 81%. HPLC purity: 100% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.1 (s, 1H), 9.16 (s, 1H), 7.93−7.85 (m, 3H), 7.78 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 9.8 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.41 (s, 1H), 6.93 (d, J = 8.6 Hz, 2H), 4.31 (s, 1H), 2.93 (d, J = 4.8 Hz, 3H), 2.66−2.57 (m, 3H), 2.36 (s, 3H), 2.22−2.15 (m, 4H), 1.88−1.96 (m, 2H), 1.57−1.67 (m, 2H). HRMS $(C_{29}H_{32}N_5O_2)^+$: calcd, 482.255 05; found, 482.256 53. Anal. ($C_{29}H_{31}N_5O_2\cdot2CH_3OH$) H, N. C: calcd, 68.23; found, 68.82.

***N*-(4-Chloro-3-(trifluoromethyl)phenyl)-4-methyl-3-(2-(methylamino)quinazolin-6-yl)benzamide (30).** The title compound was prepared from boronate **4e** and bromide **3b**, using a method analogous to the preparation of compound **33**. Yield: 0.061 g, 33%. HPLC purity: 99% (system A). ^{1}HNMR (400 MHz, DMSO-d_6): δ 10.6 (s, 1H), 9.16 (s, 1H), 8.36 (d, J = 2.2 Hz, 1H), 8.15 (dd, J = 8.5, 2.0 Hz, 1H), 7.96 (s, 1H), 7.93 (d, J = 9.4 Hz, 1H), 7.86 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.42 (br s, 1H), 2.93 (d, J = 4.7 Hz, 3H), 2.37 (s, 3H). HRMS $(C_{24}H_{19}ClF_3N_4O)^+$: calcd, 471.119 40; found, 471.118 95. Anal. ($C_{24}H_{18}ClF_3N_4O\cdot H_2O$) C, N. H: calcd, 4.12; found, 3.69.

***N*-(4-Chloro-2-methyl-3-(trifluoromethyl)phenyl)-4-methyl-3-(2-(methylamino)quinazolin-6-yl)benzamide (31).** Boronate **4f** (0.128 g, 0.283 mmol), 6-bromo-*N*-methylquinazolin-2-amine (0.074 g, 0.31 mmol), Pd(dppf)$Cl_2\cdot CH_2Cl_2$ (0.021 g, 0.028 mmol), Na_2CO_3 (0.43 mL, 2.0 M solution in water), and dioxane (1.9 mL) were combined in a resealable tube. The tube was sealed and heated to 80 °C overnight. Upon completion (as judged by LCMS), the reaction mixture was diluted with ethyl acetate and water. The aqueous layer was separated and extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (90:10:1 $CH_2Cl_2/CH_3OH/NH_4OH$ in CH_2Cl_2) provided the title compound (0.078 g, 57%). HPLC purity: 98% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.27 (s, 1H), 9.16 (s, 1H), 7.96 (s, 1H), 7.93 (dd, J = 8.2, 1.7 Hz, 1 H), 7.86 (d, J = 1.8 Hz, 1H), 7.76 (dd, J = 8.7, 2.0 Hz, 1H), 7.58 (m, 3H), 7.52 (d, J = 8.0 Hz, 1H), 7.42 (br s, 1H), 2.93 (d, J = 4.7 Hz, 3H), 2.37 (s, 3H), 2.35 (q, J = 3.3 Hz, 3H). HRMS $(C_{25}H_{21}ClF_3N_4O)^+$: calcd, 485.135 05; found, 485.134 99. Anal. ($C_{25}H_{20}ClF_3N_4O$) C, H, N.

4-Methyl-3-(2-(methylamino)quinazolin-6-yl)-*N*-(2-(1-methylpiperidin-4-yloxy)-5-(trifluoromethyl)phenyl)benzamide (32). The title compound was prepared from boronate **4g** and bromide **3b**, using a method analogous to the preparation of compound **33**. Yield: 0.435 g, 63%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 1H), 9.14 (s, 1H), 8.27 (d, J = 1.8 Hz, 1H), 7.86−7.91 (m, 3H), 7.78 (dd, J = 8.8, 1.8 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.48−7.55 (m, 2H), 7.44 (s, 1H), 7.33 (d, J = 8.6 Hz, 1H), 4.66 (s, 1H), 2.93 (d, J = 4.8 Hz, 3H), 2.40−2.48 (m, 2H), 2.38 (s, 3H), 2.15−2.26 (m, 2H), 1.99 (s, 3H), 1.85−1.94 (m, 2H), 1.71−1.80 (m, 2H). HRMS $(C_{30}H_{31}F_3N_5O_2)^+$: calcd, 550.24244; found: 550.24249. Anal. ($C_{30}H_{30}F_3N_5O_2\cdot CH_3OH$) C, H. N: calcd, 12.04; found, 11.48.

4-Methyl-3-(2-(methylamino)quinazolin-6-yl)-*N*-(2-(piperidin-1-yl)-5-(trifluoromethyl)phenyl)benzamide (33). To a resealable glass tube was added boronate **4h** (0.30 g, 0.61 mmol), bromide **3b** (0.097 g, 0.41 mmol), and K_2CO_3 (0.34 g, 2.5 mmol), followed by CH_3CN (3 mL) and H_2O (1 mL). Pd(dppf)$Cl_2\cdot CH_2Cl_2$ (0.030 g, 0.041 mmol) was then added, and the tube was sealed. The mixture was heated to 60 °C for 3 h. After cooling to room temperature, the mixture was partitioned between CH_2Cl_2 and brine, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified on the Gilson MPLC system, using CH_3CN/H_2O/0.1% TFA as the solvent system. The product fractions were collected and basified with saturated aqueous $NaHCO_3$. The product was extracted with CH_2Cl_2, and the organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the title compound (0.09 g, 27%) as an amorphous yellow solid. HPLC purity: 97% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.72 (s, 1H), 9.15 (s, 1H), 8.44 (s, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.87 (s, 2H), 7.81 (dd, J = 8.7, 2.0 Hz, 1H), 7.58 (t, J = 7.9 Hz, 2H), 7.49 (dd, J = 8.5, 2.0 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 2.94−2.87 (m, 8H), 2.40 (s, 3H), 1.66 (m, 4H), 1.50 (m, 2H). HRMS $(C_{29}H_{29}F_3N_5O)^+$: calcd, 520.2318; found, 520.231 71. Anal. ($C_{29}H_{28}F_3N_5O\cdot0.5CH_3OH$) C, H, N.

4-Methyl-*N*-(2-(3-methyl-2-oxoimidazolidin-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(methylamino)quinazolin-6-yl)-benzamide (34). The title compound was prepared from boronate **4i** and bromide **3b**, using a method analogous to the preparation of compound **33**. Yield: 0.135 g, 81%. HPLC purity: 100% (system A). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.53 (s, 1H), 9.14 (s, 1H), 8.24 (s, 1H), 7.89−7.43 (m, 9H), 3.90 (t, J = 7.7 Hz, 2H), 3.49 (t, J = 7.7 Hz, 2H), 2.92 (d, J = 4.4 Hz, 3H), 2.71 (s, 3H), 2.37 (s, 3H). HRMS $(C_{28}H_{26}F_3N_6O_2)^+$: calcd, 535.206 39; found, 535.206 16. Anal. ($C_{28}H_{25}F_3N_6O_2\cdot H_2O$) H, N. C: calcd, 60.86; found, 61.34.

1-(2-(4-Methyl-3-(2-(methylamino)quinazolin-6-yl)benzamido)-4-(trifluoromethyl)phenyl)-3-(2-morpholinoethyl)urea (35). The title compound was prepared from boronate **4j** and bromide **3b**, using a method analogous to the preparation of compound **33**. Yield: 0.055 g, 30%. HPLC purity: 100% (system A). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.20 (s, 1H), 9.12 (s, 1H), 8.32 (s, 1H), 8.15 (d, J = 5.5 Hz, 1H), 8.00−7.91 (m, 2H), 7.90−7.65 (m, 3H), 7.61−7.42 (m, 4H), 6.91 (br s, 1H), 3.49 (m, 4H), 3.15 (m, 2H), 2.87 (d, J = 4.5 Hz, 3H), 2.38−2.20 (m, 9H). HRMS $(C_{31}H_{33}F_3N_7O_3)^+$: calcd, 608.259 15; found, 608.258 79. Anal. ($C_{31}H_{32}F_3N_7O_3\cdot H_2O$) C, H, N.

***N*-(2-(2-(Diethylamino)acetamido)-5-(trifluoromethyl)phenyl)-4-methyl-3-(2-(methylamino)quinazolin-6-yl)benzamide (36).** The title compound was prepared from boronate **4k** and bromide **3b**, using a method analogous to the preparation of compound **33**. Yield: 0.060 g, 25%. HPLC purity: 100% (system A). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.84 (s, 1H), 9.69 (s, 1H), 8.99 (s, 1H), 8.24 (s, 1H), 8.02−7.82 (m, 2H), 7.77−7.61 (m, 3H), 7.51−7.35

(m, 3H), 5.36 (br s, 1H), 3.25−3.09 (m, 5H), 2.70−2.55 (m, 4H), 2.38 (s, 3H), 1.11−0.96 (m, 6H). HRMS $(C_{30}H_{32}F_3N_6O_2)^+$: calcd, 565.253 34; found, 565.253 32. Anal. ($C_{30}H_{31}F_3N_6O_2$) H, N. C: calcd, 63.82; found, 63.01.

***N*-(2-(3,3-Dimethyl-2-oxoazetidin-1-yl)-5-(trifluoromethyl)-phenyl)-4-methyl-3-(2-(methylamino)quinazolin-6-yl)benzamide (37).** The title compound was prepared from boronate **4l** and bromide **3b** using a method analogous to the preparation of compound **33**. Yield: 0.09 g, 56%. HPLC purity: 100% (system A). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (s, 1H), 9.14 (s, 1H), 8.13 (s, 1H), 7.95−7.84 (m, 3H), 7.82−7.76 (m, 1H), 7.75−7.71 (m, 1H), 7.65−7.50 (m, 3H), 7.44 (br s, 1H), 3.66 (s, 2H), 2.92 (d, J = 4.6 Hz, 3H), 2.38 (s, 3 H), 1.29 (s, 6H). HRMS $(C_{29}H_{27}F_3N_5O_2)^+$: calcd, 534.211 14; found, 534.211 34. Anal. ($C_{29}H_{26}F_3N_5O_2\cdot CH_3OH$) C, N. H: calcd, 5.56; found, 5.06.

3-(2-(Methylamino)quinazolin-6-yl)-*N*-(3-(trifluoromethyl)-phenyl)benzamide (38). The title compound was prepared from 3-((3-(trifluoromethyl)phenyl)carbamoyl)phenylboronic acid and bromide **3b** using a method analogous to the preparation of compound **39**. Purification by silica gel chromatography (gradient, 5−9% acetone/CH_2Cl_2) provided the title compound as a light-yellow amorphous solid. Yield: 0.024 g, 48%. HPLC purity: 100% (system A); 99.7% (system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.67 (s, 1H), 9.19 (s, 1H), 8.35 (s, 1H), 8.28 (s, 1H), 8.24 (s, 1H), 8.17−8.09 (m, 2H), 8.02−7.95 (m, 2H), 7.70−7.45 (m, 5H), 2.92 (d, J = 4.4 Hz, 3H). HRMS $(C_{23}H_{18}F_3N_4O)^+$: calcd, 423.142 72; found, 423.142 96.

3-(2-Aminoquinazolin-6-yl)-*N*-(3-(trifluoromethyl)phenyl)-benzamide (39). To a stirring suspension of 3-iodobenzoic acid (10.0 g, 40.3 mmol) in CH_2Cl_2 (300 mL) at 0 °C was added 3 drops of DMF followed by oxalyl chloride (3.52 mL, 40.3 mmol). The mixture was allowed to warm to room temperature over several hours and was allowed to stir overnight. The solvent was removed in vacuo, and the residue was taken up in THF (200 mL). 3-(Trifluoromethyl)benzenamine (5.09 mL, 40.7 mmol) was added, resulting in a slight exotherm that was controlled by a water bath. After 5 h, the mixture was concentrated in vacuo and the residue purified by silica gel chromatography (10% EtOAc/hexanes) to give 3-iodo-*N*-(3-(trifluoromethyl)phenyl)benzamide (5.20 g, 33%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.93−7.83 (m, 5H), 7.51 (dd, J = 8.0, 8.0 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.26 (dd, J = 7.8, 7.8 Hz, 1H). MS, m/z ($C_{14}H_8F_3INO$): calcd, 390.1; found, 391.9 (MH).

To a solution of 3-iodo-*N*-(3-(trifluoromethyl)phenyl)benzamide (0.43 g, 1.1 mmol) in THF (30 mL) under argon at 0 °C was added MeMgCl (3.0 M solution in THF, 1.9 mL, 5.6 mmol) dropwise. The resulting light-yellow solution was stirred for 45 min and cooled to −78 °C, and *t*-BuLi (1.7 M solution in pentane, 3.3 mL, 5.6 mmol) was added dropwise. The solution was allowed to stir for 5 min, and trimethoxyborane (1.2 mL, 10 mmol) was added dropwise. The solution was allowed to stir for 90 min and was then sealed and stored at 0 °C overnight. The reaction was quenched by addition of saturated aqueous Na_2SO_3 (5 mL) and 10% aqueous $NaHSO_4$ (25 mL). Additional saturated aqueous Na_2SO_3 was added until the yellow color disappeared. The aqueous material was extracted four times with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (gradient, 2.5−10% CH_3OH in CH_2Cl_2) provided the title compound (0.27 g, 82%) as a yellow foam. The material was homogeneous by HPLC but exhibited a complex ^{1}H NMR spectrum, presumably due to the presence of anhydrides. MS, m/z ($C_{14}H_{10}BF_3NO_3$): calcd, 308.0; found, 310.1 (MH).

A mixture of 3-((3-(trifluoromethyl)phenyl)carbamoyl)phenylboronic acid (0.033 g, 0.110 mmol), bromide **3a** (0.024 g, 0.11 mmol), $Pd(PPh_3)_4$ (0.004 g, 0.003 mmol), Na_2CO_3 (2.0 M solution in water, 0.110 mL, 0.210 mmol), EtOH (0.100 mL), and toluene (0.700 mL) was heated in a sealed tube at 90 °C for 2 h. The mixture was cooled to room temperature and was added to EtOAc and 2.0 M aqueous Na_2CO_3. The organic layer was washed once with brine, dried with Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (gradient, 40−100% EtOAc/hexanes, then 1% NEt_3 in EtOAc) provided the title compound (0.030 g, 68%) as a yellow solid. HPLC purity: 99.3% (system A); 99.7% (system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.67 (s, 1H), 9.21 (s, 1H), 8.33 (s, 1H), 8.27 (s, 1H), 8.23 (s, 1H), 8.15−8.09 (m, 2H), 8.01−7.95 (m, 2H), 7.70−7.47 (m, 4H), 6.97 (s, 2H). HRMS $(C_{22}H_{16}F_3N_4O)^+$: calcd, 409.127 07; found, 409.127 013.

5-(2-Aminoquinazolin-6-yl)-2-fluoro-*N*-(3-(trifluoromethyl)-phenyl)benzamide (40). 2-Fluoro-5-iodo-*N*-(3-(trifluoromethyl)-phenyl)benzamide was prepared from 2-fluoro-5-iodobenzoic acid, using a method analogous to the preparation of 3-iodo-*N*-(3-(trifluoromethyl)phenyl)benzamide. Yield: 2.4 g, 52%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (dd, J = 7.3, 2.3 Hz, 1H), 8.45 (s, 1H), 7.96 (s, 1H), 7.87−7.83 (m, 2H), 7.52 (dd, J = 7.7, 7.7 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.00 (dd, J = 11.8, 8.5 Hz, 1H). MS, m/z ($C_{14}H_8F_4INO$): calcd, 409.12; found, 409.9 (MH).

A mixture of 2-fluoro-5-iodo-*N*-(3-(trifluoromethyl)phenyl)benzamide (0.095 g, 0.23 mmol), boronate **17a** (0.066 g, 0.23 mmol), $Pd(PPh_3)_4$ (0.013 g, 0.010 mmol), Na_2CO_3 (2.0 M solution in water, 0.35 mL, 0.69 mmol), 0.5 mL of EtOH, and 3 mL of toluene was heated in a sealed tube at 80 °C for 16 h. The mixture was cooled to ambient temperature and was added to EtOAc and water. The aqueous layer was extracted once with EtOAc. The combined organic layers were washed once with brine, dried with $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (7/7/7/1 CH_2Cl_2/hexanes/*t*-BuOMe/CH_3OH/NH_4OH) provided the title compound (0.057 g, 58%) as an orange solid. HPLC purity: 95% (system A). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.12 (s, 1H), 8.65 (d, J = 16.5 Hz, 1H), 8.50 (dd, J = 7.4, 2.5 Hz, 1H), 8.05−7.95 (m, 3H), 7.90−7.81 (m, 2H), 7.69 (d, J = 8.8 Hz, 1H), 7.54 (dd, J = 7.9 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.35 (dd, J = 11.9, 8.6 Hz, 1H), 5.27 (s, 2H). HRMS $(C_{22}H_{15}F_4N_4O)^+$: calcd, 427.117 65; found, 427.117 62. Anal. ($C_{22}H_{14}F_4N_4O$) C, H, N.

3-(2-Aminoquinazolin-6-yl)-4-chloro-*N*-(3-(trifluoromethyl)-phenyl)benzamide (41). 3-Bromo-4-chloro-*N*-(3-(trifluoromethyl)-phenyl)benzamide was prepared from 3-bromo-4-chlorobenzoic acid and 3-(trifluoromethyl)benzoyl chloride using a method analogous to the preparation of *N*-(3-iodo-4-methylphenyl)-3-(trifluoromethyl)-benzamide (step 1 of the preparation of **13**). Yield: 0.085 g, 14%. ^{1}H NMR (400 MHz, CH_3OH-d_4): δ 8.30 (d, J = 4.0 Hz, 1H), 8.16 (d, J = 4.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.45 (m, 1H).

A heterogeneous mixture of 3-bromo-4-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (0.085 g, 0.22 mmol), boronate **17a** (0.090 g, 0.34 mmol), 2.2 M K_2CO_3 (0.30 mL, 0.67 mmol), ethylene glycol dimethyl ether (1.0 mL), and Pd(dppf)$Cl_2\cdot CH_2Cl_2$ (0.0090 g, 0.011 mmol) was heated to 80 °C for 15 h. The cooled reaction mixture was diluted with EtOAc and washed with brine, dried with Na_2SO_4, and concentrated to dryness. The solid residue was purified by preparative TLC (90:10:1, CH_2Cl_2:CH_3OH:NH_4OH) to afford the title compound (0.012 g, 12%) as a light-yellow solid. HPLC purity: 98.3% (system A); 99% (system B). ^{1}H NMR (400 MHz, CH_3OH-d_4): δ 9.12 (s, 1H), 8.13 (s, 1H), 8.00 (d, J = 2.3 Hz, 1H), 7.94−7.89 (m, 3H), 7.87 (dd, J = 8.6, 2.0 Hz, 1H), 7.67 (d, J = 8.597 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H). HRMS $(C_{22}H_{15}ClF_3N_4O)^+$: calcd, 443.088 10; found, 443.087 84.

2-Fluoro-4-methyl-5-(2-(methylamino)quinazolin-6-yl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (42). The title compound was prepared from boronate **4m** and bromide **3b**, using a method analogous to the preparation of compound **33**. Yield: 0.064 g, 84%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.70 (s, 1H), 9.14 (s, 1H), 8.20 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.75 (dd, J = 8.7, 2.1 Hz, 1H), 7.65−7.52 (m, 3H), 7.46 (m, 1H), 7.44 (br s, 1H), 7.39 (m, 1H), 2.92 (d, J = 4.8 Hz, 3H), 2.36 (s, 3H). HRMS $(C_{24}H_{19}F_4N_4O)^+$: calcd, 455.148 95; found, 455.149 26. Anal. ($C_{24}H_{18}F_4N_4O\cdot CH_3OH$) C, H, N.

5-(2-Aminoquinazolin-6-yl)-2-fluoro-4-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide (43). The title compound was prepared from boronate **4m** and bromide **3a**, using a method analogous to the preparation of compound **33**. Yield: 0.083 g, 79%. HPLC

purity: 99% (system A). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.69 (s, 1H), 9.16 (s, 1H), 8.20 (s, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 1.9 Hz, 1H), 7.75 (dd, J = 8.7, 2.0 Hz, 1H), 7.64−7.59 (m, 2H), 7.52−7.48 (m, 2H), 7.39 (d, J = 11.4 Hz, 1H), 6.93 (s, 2H), 2.36 (s, 3H). HRMS $(C_{23}H_{17}F_4N_4O)^+$: calcd, 441.133 30; found, 441.133 59. Anal. ($C_{23}H_{16}F_4N_4O$) C, H. N: calcd, 12.72; found: 13.42.

3-(2-Aminoquinazolin-6-yl)-2-methyl-*N*-(3-(trifluoromethyl)-phenyl)benzamide (44). 3-Iodo-2-methyl-*N*-(3-(trifluoromethyl)-phenyl)benzamide was prepared from 3-iodo-2-methylbenzoic acid and 3-(trifluoromethyl)benzenamine, using a method analogous to the preparation of 3-iodo-*N*-(3-(trifluoromethyl)phenyl)benzamide. Yield: 0.073 g, 30%. HPLC purity: 95% (system A). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.63 (s, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 6.95 (t, J = 8.0 Hz, 1H), 2.55 (s, 3H). MS, *m*/*z* ($C_{15}H_{11}F_3INO$): calcd, 405.15; found, 406.0 (MH).

The title compound was prepared from boronate **17a** and 3-iodo-2-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide, using a method analogous to the preparation of compound **40**. Purification by silica gel chromatography (3% CH_3OH in CH_2Cl_2) provided the title compound as an off-white amorphous solid. Yield: 0.073 g, 30%. HPLC purity: 95% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.77 (s, 1H), 9.18 (s, 1H), 8.28 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 4.0 Hz, 1H), 7.69 (dd, J = 12.0, 4.0 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.42−7.52 (m, 5H), 6.93 (s, 2H), 2.28 (s, 3H). HRMS $(C_{23}H_{18}F_3N_4O)^+$: calcd, 423.142 72; found, 423.143 18. Anal. ($C_{23}H_{17}F_3N_4O$) C, H, N.

6-*o*-Tolylquinazolin-2-amine (45). A mixture of bromide **3a** (3.02 g, 13.5 mmol), *o*-tolylboronic acid (2.2 g, 16 mmol), Na_2CO_3 (6.0 g, 57 mmol), and $Pd(PPh_3)_2Cl_2$ (0.055 g, 0.80 mmol) in 7:3:2 DME/H_2O/EtOH (120 mL) was heated at 80 °C. After 3 h, the reaction mixture was cooled to room temperature and partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine and dried over Na_2SO_4. Purification by silica gel chromatography (10−100% EtOAc in hexanes) afforded the title compound (2.0 g, 62%) as a yellow amorphous solid. HPLC purity: 94% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 1H), 7.76 (d, J = 1.9 Hz, 1 H), 7.69 (dd, J = 8.7, 1.9 Hz, 1H), 7.47 (d, J = 8.7 Hz, 1H), 7.35−7.27 (m, 4H), 6.88 (s, 2H), 2.28 (s, 3H). HRMS $(C_{15}H_{14}N_3)^+$: calcd, 236.118 22; found, 236.118 47. Anal. ($C_{15}H_{13}N_3 \cdot 0.33H_2O$) C, H, N.

3-(2-Aminoquinazolin-6-yl)-4-methyl-*N*-(2-methyl-3-(trifluoromethyl)phenyl)benzamide (46). To a flame-dried disposable sealed tube was added acid **18a** (0.15 g, 0.54 mmol) followed by 3 mL of $SOCl_2$. The mixture was purged with N_2, and the tube was sealed and heated at 80 °C for 1 h, then allowed to cool to room temperature. The mixture was then transferred to a 50 mL pear-shaped flask with anhydrous CH_2Cl_2 and concentrated. At this point, 6 mL of anhydrous toluene was added and the mixture was concentrated (repeat). The resulting crude acid chloride was then taken up in 4 mL of CH_2Cl_2, and NEt_3 (0.23 mL, 1.6 mmol) was added followed by 2-methyl-3-(trifluoromethyl)benzenamine (0.12 g, 0.67 mmol) and an additional 1 mL of CH_2Cl_2. The mixture was stirred at room temperature for 2.5 h, concentrated, and purified using MPLC (ISCO, 0−3% CH_3OH/CH_2Cl_2 over 30 min, 3−5% over 15 min), providing the title compound (0.15 g, 65%) as an off-white solid. HPLC purity: 100% (system A). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.16 (s, 1H), 9.17 (s, 1H), 7.97−7.91 (m, 2H), 7.86 (d, J = 1.9 Hz, 1H), 7.77 (dd, J = 8.6, 2.1 Hz, 1H), 7.62 (dd, J = 7.8, 2.6 Hz, 2H), 7.52 (s, 1H), 7.50 (s, 1H), 7.44 (t, J = 7.8 Hz, 1H), 6.94 (s, 2H), 2.36 (s, 3H), 2.31 (s, 3H). HRMS $(C_{24}H_{20}F_3N_4O)^+$: calcd, 437.158 37; found, 437.159 07. Anal. ($C_{24}H_{19}F_3N_4O \cdot H_2O$) C, H, N.

4-Methyl-3-(2-(2-morpholinoethylamino)quinazolin-6-yl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (47). The title compound was prepared from boronate **4a** and bromide **3d**, using a method analogous to the preparation of compound **33**. Yield: 0.050 g, 17%. HPLC purity: 100% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.52 (s, 1H), 9.17 (s, 1H), 8.24 (s, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.97 (s, 1H), 7.94 (dd, J = 7.7, 1.9 Hz, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.78 (dd, J = 8.7, 1.9 Hz, 1H), 7.63−7.50 (m, 3H), 7.46 (d, J = 8.3 Hz, 1H), 7.32−7.26 (m, 1H), 3.62−3.57 (m, 4H), 3.54 (q, J = 6.6 Hz, 2H), 2.56 (t, J = 6.6 Hz, 2H), 2.46 (s, 4H), 2.37 (s, 3H). HRMS $(C_{29}H_{29}F_3N_5O_2)^+$: calcd, 536.226 79; found, 536.226 28. Anal. ($C_{29}H_{28}F_3N_5O_2 \cdot 0.5H_2O$) C, H. N: calcd, 12.86; found, 12.19.

4-Methyl-*N*-(2-methyl-3-(trifluoromethyl)phenyl)-3-(2-(2-morpholinoethylamino)quinazolin-6-yl)benzamide (48). The title compound was prepared from boronate **4b** and bromide **3d**, using a method analogous to the preparation of compound **33**. Yield: 0.092 g, 97%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.16 (s, 1H), 9.17 (s, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.94 (dd, J = 8.0, 2.0 Hz, 1H), 7.86 (d, J = 1.9 Hz, 1H), 7.78 (dd, J = 8.0, 1.9 Hz, 1H), 7.65−7.60 (m, 2H), 7.58−7.50 (m, 2H), 7.48−7.42 (m, 1H), 7.27 (br m, 1H), 3.59 (m, 4H), 3.53 (m, 2H), 2.56 (m, 2H), 2.46 (m, 4H), 2.37 (s, 3H), 2.32 (s, 3H). HRMS $(C_{30}H_{31}F_3N_5O_2)^+$: calcd, 550.242 44; found, 550.242 71. Anal. ($C_{30}H_{30}F_3N_5O_2 \cdot CH_3OH$) C, H, N.

4-Methyl-*N*-(2-methyl-3-(trifluoromethyl)phenyl)-3-(2-(3-morpholinopropylamino)quinazolin-6-yl)benzamide (49). The title compound was prepared from boronate **4b** and bromide **3e**, using a method analogous to the preparation of compound **33**. Yield: 0.089 g, 82%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.17 (s, 1H), 9.16 (s, 1H), 7.96 (s, 1H), 7.93 (dd, J = 8.1, 1.8 Hz, 1H), 7.85 (d, J = 1.8 Hz, 1H), 7.77 (dd, J = 8.6, 2.0 Hz, 1H), 7.63 (dd, J = 7.7, 3.7 Hz, 2H), 7.56−7.49 (m, 3H), 7.45 (t, J = 7.8 Hz, 1H), 3.62−3.57 (m, 4H), 3.43 (q, J = 6.6 Hz, 2H), 2.42−2.35 (m, 9H), 2.32 (s, 3H), 1.84−1.70 (m, 2H). HRMS $(C_{31}H_{33}F_3N_5O_2)^+$: calcd, 564.258 09; found, 564.257 58. Anal. ($C_{31}H_{32}F_3N_5O_2 \cdot H_2O$) C, H, N.

4-Methyl-3-(2-(methyl(3-morpholinopropyl)amino)quinazolin-6-yl)-*N*-(2-methyl-3-(trifluoromethyl)phenyl)benzamide (50). The title compound was prepared from boronate **4b** and bromide **3f**, using a method analogous to the preparation of compound **33**. Yield: 0.063 g, 45%. HPLC purity: 100% (system A); 100% (system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 9.29 (d, J = 18.1 Hz, 1H), 7.99−7.80 (m, 4H), 7.67−7.45 (m, 5H), 3.95 (m, 2H), 3.87 (m, 1H), 3.80 (m, 1H), 3.61 (m, 2H), 3.56 (m, 1 H), 3.46 (m, 2H), 3.30 (br s, 1H), 3.26 (br s, 1H), 3.17 (m, 1H), 2.57 (s, 3H), 2.40 (s, 3H), 2.34 (s, 3H), 2.13 (m, 1H), 0.97 (m, 1H). HRMS $(C_{32}H_{35}F_3N_5O_2)^+$: calcd, 578.27374; found: 578.27136.

4-Methyl-*N*-(2-methyl-3-(trifluoromethyl)phenyl)-3-(2-(2-(piperidin-1-yl)ethylamino)quinazolin-6-yl)benzamide (51). The title compound was prepared from boronate **4b** and bromide **3g**, using a method analogous to the preparation of compound **33**. Yield: 0.094 g, 67%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.16 (s, 1H), 9.15 (s, 1H), 7.93−7.75 (m, 4H), 7.60−7.43 (m, 5H), 7.22 (br s, 1H), 3.50 (m, 2H), 2.40−2.37 (m, 6H), 2.35 (s, 3H), 2.29 (s, 3H), 1.49 (m, 4H), 1.38 (m, 2H). HPLC purity: 99%. HRMS $(C_{31}H_{33}F_3N_5O)^+$: calcd, 548.263 17; found, 548.263 28. Anal. ($C_{31}H_{32}F_3N_5O \cdot CH_3OH$) C, N. H: calcd, 6.26; found, 5.85.

4-Methyl-*N*-(2-methyl-3-(trifluoromethyl)phenyl)-3-(2-(2-(pyrrolidin-1-yl)ethylamino)quinazolin-6-yl)benzamide (52). The title compound was prepared from boronate **4b** and bromide **3h**, using a method analogous to the preparation of compound **33**. Yield: 0.061 g, 57%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.17 (s, 1H), 9.17 (s, 1H), 7.96 (s, 1H), 7.93 (dd, J = 8.1, 1.5 Hz, 1H), 7.85 (d, J = 1.8 Hz, 1H), 7.76 (dd, J = 8.6, 2.0 Hz, 1H), 7.63 (dd, J = 8.0, 4.2 Hz, 2H), 7.56−7.49 (m, 2H), 7.45 (t, J = 7.8 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 3.91−3.80 (m, 1H), 2.78 (d, J = 10.9 Hz, 2H), 2.37 (s, 3H), 2.32 (s, 3H), 2.19 (s, 3H), 2.07−1.97 (m, 2H), 1.95−1.87 (m, 2H), 1.65−1.52 (m, 2H). HRMS $(C_{30}H_{31}F_3N_5O)^+$: calcd, 534.247 52; found, 534.247 29. Anal. ($C_{30}H_{30}F_3N_5O \cdot H_2O$) H, N. C: calcd, 65.32; found, 65.93.

4-Methyl-*N*-(2-methyl-3-(trifluoromethyl)phenyl)-3-(2-(1-methylpiperidin-4-ylamino)quinazolin-6-yl)benzamide (53). The title compound was prepared from boronate **4b** and bromide **3i**, using a method analogous to the preparation of compound **33**.

Yield: 0.090 g, 85%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.29 (s, 1H), 9.29 (s, 1H), 8.08−8.04 (m, 2H), 7.97 (d, J = 1 Hz, 1H), 7.90−7.88 (dd, J = 8.0, 1.0 Hz, 1H), 7.77−7.73 (m, 2H), 7.68−7.50 (m, 4H), 3.97 (m, 1H), 2.90 (m, 2H), 2.49 (s, 3H), 2.44 (s, 3H), 2.31 (s, 3H), 2.17−2.11 (m, 2H), 2.05−2.00 (m, 2H), 1.76−1.67 (m, 2H). HRMS $(C_{30}H_{31}F_3N_5O)^+$: calcd, 534.247 52; found, 534.247 48. Anal. ($C_{30}H_{30}F_3N_5O\cdot H_2O$) C, H. N: calcd, 12.70; found, 12.17.

4-Methyl-*N*-(2-methyl-3-(trifluoromethyl)phenyl)-3-(2-(phenylamino)quinazolin-6-yl)benzamide (54). The title compound was prepared from boronate **4b** and bromide **3c**, using a method analogous to the preparation of compound **33**. Yield: 0.020 g, 12%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 9.96 (s, 1H), 9.38 (s, 1H), 8.01 (m, 4H), 7.96 (dd, J = 8.2, 2.0 Hz, 1H), 7.91 (dd, J = 8.6, 2.0 Hz, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.63 (m, 2H), 7.54 (d, J = 8.1 Hz, 1H), 7.45 (m, 1H), 7.35 (m, 2H), 7.01 (m, 1H), 2.40 (s, 3H), 2.33 (s, 3H). HRMS $(C_{30}H_{24}F_3N_4O)^+$: calcd, 513.189 67; found, 513.190 08. Anal. ($C_{30}H_{23}F_3N_4O$) C, H. N: calcd, 10.93; found, 10.45.

3-(2-(Cyclopropylamino)quinazolin-6-yl)-4-methyl-*N*-(2-methyl-3-(trifluoromethyl)phenyl)benzamide (55). The title compound was prepared from boronate **4b** and bromide **3j**, using a method analogous to the preparation of compound **33**. Yield: 0.086 g, 91%. HPLC purity: 99% (system A). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.17 (s, 1H), 9.18 (s, 1H), 7.97 (s, 1H), 7.94 (dd, J = 7.9, 1.6 Hz, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.79 (dd, J = 8.7, 2.0 Hz, 1H), 7.67 (d, J = 3.8 Hz, 1H), 7.64−7.60 (m, 3H), 7.51 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 2.92−2.86 (m, 1H), 2.37 (s, 3H), 2.32 (s, 3H), 0.77−0.72 (m, 2H), 0.57−0.54 (m, 2H). HRMS $(C_{27}H_{24}F_3N_4O)^+$: calcd, 477.18967; found, 477.19025. Anal. ($C_{27}H_{23}F_3N_4O\cdot 0.5CH_3OH$) C, H, N.

Biological Materials and Methods. Lck Kinase Assay. The Lck HTRF kinase assay involves ATP-dependent phosphorylation of a biotinylated substrate peptide of gastrin in the presence or absence of inhibitor compound. The final concentration of gastrin was 1.2 μM. The final concentration of ATP was 0.5 μM ($K_{m(app)}$ = 0.6 μM ± 0.1), and the final concentration of Lck (a GST-kinase domain fusion (AA 225−509)) was 250 pM. Buffer conditions were as follows: 50 mM HEPES, pH 7.5, 50 mM NaCl, 20 mM MgCl, 5 mM MnCl, 2 mM DTT, 0.05% BSA. The assay was quenched and stopped with 160 μL of detection reagent. Detection reagents were as follows: buffer made of 50 mM Tris, pH 7.5, 100 mM NaCl, 3 mM EDTA, 0.05% BSA, 0.1% Tween-20. Prior to reading, streptavidin allophycocyanin (SA-APC) was added at a final concentration in the assay of 0.0004 mg/mL, along with europilated anti-phosphotyrosine Ab (Eu-anti-PY) at a final concentration of 0.025 nM. The assay plate was read in a Discovery fluorescence plate reader with excitation at 320 nm and emission at 615 and 655 nm.

Assays for other kinases were done in a similar way as described above, varying the concentrations of enzyme, peptide substrate, and ATP added to the reaction, depending on the specific activity of the kinase and measured K_m values for the substrates.

Human Mixed Lymphocyte Reaction (MLR). The purpose of this assay is to test the potency of T cell activation inhibitors in an in vitro model of allogeneic T cell stimulation. Human peripheral blood lymphocytes (hPBL, 2 × 10^5/well) were incubated with mitomycin C-treated B lymphoblastoid cells (JY cell line (ATCC, Rockville, MD), 1 × 10^5/well) as allogeneic stimulators in the presence or absence of dilutions of potential inhibitor compound in 96-well round-bottom tissue culture plates. These cultures were incubated at 37 °C in 5% CO_2 for 6 days total. The proliferative response of the hPBL was measured by [^{3}H]thymidine incorporation overnight between days 5 and 6 after initiation of culture. Cells were harvested onto glass fiber filters, and [^{3}H]thymidine incorporation into DNA was analyzed by liquid scintillation counter.

Anti-CD3/CD28-Induced T Cell IL-2 Secretion and Proliferation Assay (IL-2). The purpose of this assay was to test the potency of T cell receptor (TCR, CD3) and CD28 signaling pathway inhibitors in human T cells. T cells were purified from human peripheral blood lymphocytes and preincubated with or without compound prior to stimulation with a combination of an anti-CD3 and an anti-CD28 antibody in 96-well tissue culture plates (1 × 10^5 T cells/well). Cells were cultured for ∼20 h at 37 °C in 5% CO_2, and then secreted IL-2 in the supernatants was quantified by cytokine ELISA (Pierce/Endogen, St. Louis, MO). The cells remaining in the wells were then pulsed with [^{3}H]thymidine overnight to assess the T cell proliferative response. Cells were harvested onto glass fiber filters, and [^{3}H]thymidine incorporation into DNA was analyzed by a liquid scintillation counter. For comparison purposes, phorbol myristic acid (PMA) and calcium ionophore can be used in combination to induce IL-2 secretion from purified T cells. Potential inhibitor compounds can be tested for inhibition of this response as described above for anti-CD3 and -CD28 antibodies.

Human whole-blood anti-CD3/CD28-induced IL-2 secretion assays were run in a similar fashion as described above using whole blood from normal volunteers diluted 50% in tissue culture medium prior to stimulation.

Human Whole-Blood LPS-Induced TNFα. Compounds were preincubated with heparinized human whole blood diluted in RPMI 1640 with L-glutamine (GIBCO) supplemented with 10% v/v human serum AB (Gemini BioSciences) and 1% pen/strep at a final whole-blood dilution of 50% in 96-well flat-bottom plates (Falcon) for 1 h at 37 °C. LPS (List Biological Laboratories, 0.1 μg/mL final) was subsequently added. Plates were then incubated overnight (18 h) at 37 °C. Secreted cytokines were measured by ELISA.

Pharmacokinetic Studies. Male Sprague-Dawley rats were administered the compound intravenously as a solution in DMSO or orally as a suspension in 2% hydroxypropylmethylcellulose with 1% Tween-80, at the indicated doses. Samples were taken at various times after dosing and analyzed for parent compound by LCMS.

Anti-CD3 Induced IL-2 Production in Mice. The 12 week old (20 g) BALB/c mice were dosed, per os, 1 h prior to challenge with compound (8 per group) at the indicated doses in 2% hydroxypropylmethylcellulose with 1% Tween-80. Mice were then challenged intravenously with antimouse CD3 monoclonal antibody (145.2C11, BD PharMingen, San Diego, CA; 3 μg/mouse) diluted in PBS. Ninety minutes after anti-CD3 challenge, blood was collected via cardiac puncture. IL-2 levels were measured in serum by ELISA (BioSource, Camarillo, CA). Data points represent the mean IL-2 levels/group ± the standard error. P values were determined vs vehicle control by the Mann−Whitney U-test.

SIF Solubility Assay. The solubility media was fasted state simulated intestinal fluid (SIF), pH 6.8, containing 5 mM sodium taurochol, 1.5 mM lecithin, 2.9 mM KH_2PO_4, and 0.22 M KCl. The Symyx solubility system (Santa Clara, CA) consisted of a liquid handling robot and an Agilent 1100 HPLC. An experiment template was created for solubility measurements of 24 compounds on a 96-well plate. Samples were prepared assuming a screening criterion of 200 μg/mL solubility. A stock solution was first prepared for each of the 24 compounds on a 24-well plate. A mixed solution of 50/50 CH_3OH/DME (v/v) was used as the stock solvent. The weight of the solid sample (i.e., 1 mg, to the nearest 0.01 mg) was directly imported, and the appropriate volume of the stock solvent was calculated and dispensed into the 4 mL vial for each compound by the liquid handing robot to obtain a stock concentration of 500 μg/mL. From each of the 24 compound stock solutions, volumes of 200, 250, 250, and 250 μL were robotically transferred to an array of four 1 mL glass vials on a 96-well plate: one vial for the calibration standard and the other three vials for solubility samples. After evaporation of the stock solvent using a centrifugal evaporator, 500 μL of the solubility media was added to the corresponding sample vials on the 96-well plate for each compound to give a calculated concentration of 250 μg/mL. A stir bar was added to each vial using a 96-well stir bar dispenser, and the vials were sealed with a 96-well cap mat. The samples were equilibrated by stirring at 100 rpm for 24 h and subsequently left standing unstirred for an additional 24−48 h at room temperature. After equilibration, 500 μL of 50/50 CH_3OH/DME was added to the corresponding standard vials on the same plate for each compound to give a calibration

concentration of 200 μg/mL. Immediately before solubility measurement by HPLC, the sealed 96-well plate was centrifuged at 1650 rpm for 10 min using a plate centrifuge to allow separation of the compound supernatant from undissolved solid. The solubility samples and the calibration standards in 1 mL vials on a 96-well plate were injected directly onto the HPLC column after centrifuging. A fast gradient method was developed for HPLC throughput starting with 100% water containing 0.04% trifluoroacetic acid (TFA) and holding for 0.1 min, then ramping to 100% acetonitrile containing 0.04% TFA in 0.1 min and holding for 1.0 min. A Phenomenex Synergi Hydro-RP C-18 column (10 mm × 2.0 mm, 2 μm) was chosen for retention and resolution of both polar and nonpolar compounds. The injection volume was 2 μL, with a detection wavelength of 220 nm. For each compound, its solubility was quantified through individual standard peak area calibration at a concentration equal to the solubility screening criterion (i.e., 200 μg/mL).

Protein Binding Assay. Plasma filtrate was used for the calibration curve and QC samples. To generate plasma filtrate, an aliquot of plasma was filtered through Millipore Centriplus (a filter) by spinning at 3000*g* (4980 rpm) at 4 °C for 24 h with a Beckman Avanti J-251 ultracentrifuge. An aliquot of 10 μL of test compound (1 mg/mL in DMSO) was added to 1990 μL of human, rat, and mouse plasma to give final concentration of 5 mg/mL (12.9 μM). Separate QC samples were prepared by adding 10 μL of the test compound spiked plasma sample (5 μg/mL) to 490 μL of plasma filtrate, in duplicate. The plasma samples including the QC samples were then incubated at 37 °C for 15 min. Following incubation, 800 μL was transferred to the centrifuge tube (in duplicate) and spun at 120 000 rpm for 3 h at 37 °C with a TLA-120.2 rotor (Optima TLX ultracentrifuge, Beckman Coulter). The top portion below the lipid layer of the centrifuged plasma sample was aspirated (100 μL in triplicate) for LCMS analysis. The QC samples (100 μL in duplicate) were also aspirated for LCMS analysis. The concentrations of the samples ($n = 6$) and QCs ($n = 2$) were determined from a linear regression of peak area ratios (analyte peak area/IS peak area) versus the theoretical concentrations of the calibration standards. The percent of binding was calculated as

$$\%\ \text{protein binding} = 1 - \frac{\text{concentration of the centrifuged plasma sample}}{\text{mean concentration of the QC}} \times 100$$

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Supporting Information Available: Elemental analysis and HPLC data, X-ray methods and data, exposures for **32** and **47**, and additional references. This material is available free of charge via the Internet at http://pubs.acs.org.

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