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Sequential and Selective Buchwald−Hartwig Amination Reactions for the Controlled Functionalization of 6-Bromo-2-chloroquinoline: Synthesis of Ligands for the Tec Src Homology 3 Domain

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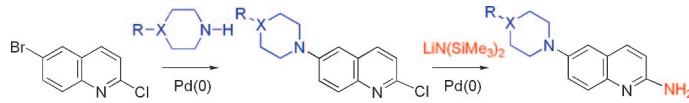

Src homology 3 (SH3) domains are highly conserved protein−protein interaction domains that mediate important biological processes and are considered valuable targets for the development of therapeutic agents. In this paper, we report the preparation of a range of new 6-heterocyclic substituted 2-aminoquinolines using Buchwald−Hartwig chemistry. 6-Heterocyclic substitution of the 2-aminoquinoline has provided ligands with increased binding affinity for the SH3 domain relative to the lead compound, 2-aminoquinoline, that are the highest affinity ligands prepared to date. The key step in the synthesis of these compounds required a selective Buchwald−Hartwig amination of an aryl bromide in the presence of an activated heteroaryl chloride. The optimization of reaction conditions to achieve the selective amination is discussed and has allowed for cross-coupling with a range of cyclic amines. Introduction of the amino functionality of the 6-heterocyclic 2-aminoquinolines involved additional Buchwald−Hartwig chemistry utilizing lithium bis(trimethylsilyl)amide as an ammonia equivalent.

Introduction

Src homology 3 (SH3) domains are small, highly conserved protein−protein interaction domains. The function of the SH3 domain is to mediate the assembly of large multiprotein complexes by binding to specific proline-rich sequences in target proteins. Protein complexes containing SH3 domains are found in a variety of signaling pathways controlling processes such as cell proliferation, apoptosis, and gene expression.[1−3] Proteins containing SH3 domains have been identified in deregulated signaling pathways associated with human diseases including cancer and osteoporosis, therefore making these domains valuable therapeutic targets. Previously, we have reported that a range of substituted 2-aminoquinoline derivatives display weak to moderate binding affinity with the Tec SH3 domain.[4−6] SAR information provided from 2-aminoquinoline (**1**) and a number of substituted 2-aminoquinolines has allowed for the development of a model for the mechanism of binding of these compounds to the Tec SH3 domain. This model involves $\pi-\pi$ stacking of the quinoline with the side chain of the tryptophan residue (W215) and a salt bridge between the positively charged ligand and the negatively charged aspartate residue (D196) under physiological conditions (Figure 1A).[6]

The highest affinity ligands identified to date (**2**−**4**) contain acetal functionality at the 6-position of the quinoline ring system and have equilibrium binding dissociation constants (K_d) in the range of 20−50 μM (Figure 2).[5] The acetal functionality of these ligands, however, is not suitable for use in therapeutic agents as the acetals hydrolyze to carbonyl compounds under physiological aqueous conditions.[5] We envisaged that replacement of the biologically labile acetal with an alternate heterocyclic substituent, as in **5**, would provide ligands with increased stability and may also provide ligands with similar or increased affinity for the SH3 domain relative to ligands **2**−**4** (Figure 2). Additionally, such ligands would provide information as to

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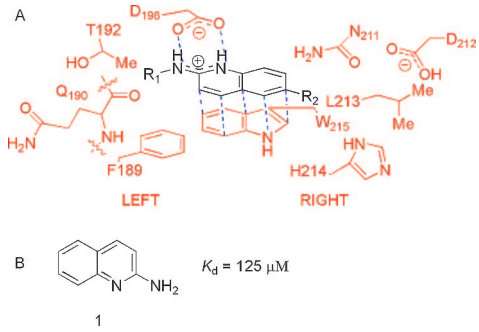


FIGURE 1. (A) Model for the mechanism of binding of **1** to the Tec SH3 domain and regions predicted to make contacts with substituents attached to the 2-aminoquinoline backbone on the "left" and "right" sides of the binding site. (B) Equilibrium binding dissociation constant (K_d) of **1**.[6]

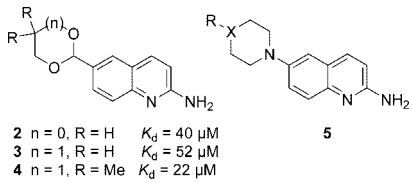


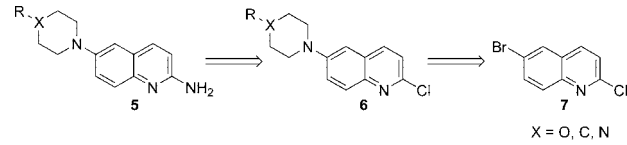
FIGURE 2. Equilibrium binding dissociation constants (K_d) of some 2-aminoquinolines reported previously.[5]

whether the nature of the heteroatom and its location in the heterocycle at the 6-position are important for increased binding affinity.

The preparation of **5** requires the formation of a C−N bond at the 6-position of the 2-aminoquinoline. Traditional methods for the synthesis of arylamines, such as nucleophilic aromatic substitution and Ullmann-type couplings, are typically conducted using relatively harsh reaction conditions and have limited generality.[7,8] On the other hand, the palladium-catalyzed C−N bond formation of arylamines (Buchwald−Hartwig amination) can be conducted under relatively mild conditions, is regioselective, and does not require activating groups.[9,10] Buchwald−Hartwig chemistry is a rapidly developing field of interest due to the importance of amino-substituted aryl derivatives and would allow for the synthesis of the target 2-aminoquinoline compounds. The use of Buchwald−Hartwig chemistry, however, requires the proper choice of catalyst (Pd source, ligand choice), base, and solvent, which is crucial for the success of a given amination reaction.

In this paper we report the synthesis of a range of new 6-heterocyclic substituted 2-aminoquinolines. The general approach employed was the synthesis of 2-chloroquinolines with appropriate 6-heterocyclic substitution introduced by Buchwald−Hartwig chemistry in the key step. A detailed investigation of the conditions for introducing substitution at the 6-position in the presence of an activated heteroaryl halide at the 2-position was conducted, and general reaction conditions for the selective cross-coupling with a range of cyclic amines are provided. Conversion of the 2-chloroquinolines to the corresponding 2-aminoquinolines was initially carried out using the method of Kóródi.[11] In addition, an improved method for this amination process is described using Buchwald−Hartwig chemistry and lithium bis(trimethylsilyl)amide (LHMDS) as an ammonia equivalent. The binding affinity of the prepared compounds with the Tec SH3 domain is also reported and the new SAR information discussed.

SCHEME 1. Retrosynthesis of 6-Substituted 2-Aminoquinolines



Results and Discussion

Synthesis of 6-Heterocyclic 2-Aminoquinolines. To prepare 6-heterocyclic 2-aminoquinolines of the general structure **5**, 6-bromo-2-chloroquinoline (**7**) was envisaged as the key intermediate (see Scheme 1). **7** can be prepared according to methods previously described[6] and contains halide functionality, allowing for the introduction of a heterocyclic substituent at the 6-position using Buchwald−Hartwig chemistry, producing 6-heterocyclic 2-chloroquinolines of the general structure **6**. Although there are two potential sites on **7** for palladium-catalyzed coupling (i.e., 6-Br vs 2-Cl), it was anticipated that selectivity for the 6-postion could be achieved in the presence of the activated chlorine at the 2-position. Once the heterocyclic substituent is introduced, the required 2-amino functionality can be subsequently incorporated utilizing the method of Kóródi.[11]

Introducing the Heterocyclic Substituent: Buchwald−Hartwig Amination. Initial exploration into the Buchwald−Hartwig reaction of **7** involved an investigation into the palladium catalytic system. Biphenyl-based "Buchwald ligands" [12,13] **9**−**14** were examined due to their high prevalence in palladium-catalyzed reactions (see Table 1).[14−16] These ligands are notable for being both bulky, which accelerates reductive elimination, and electron rich, which facilitates oxidative addition.[17] They also offer increased air stability relative to traditional phosphine ligands, and the development of such biphenyl ligands has expanded the substrate scope of Buchwald−Hartwig aminations.[13,16]

The biphenyl ligands were examined in combination with $Pd(OAc)_2$ and KO^{t}Bu in toluene at 110 °C overnight employing **a** as the model cyclic amine. Of these ligands, CyJohnPhos (**13**) was the most effective ligand and afforded a moderate conversion of the starting material to the desired product **6a** (54%). In addition to the desired product, however, substitution at the 2-position was also observed to produce compound **8a** under these conditions (see Table 1; formation of **8a** was observed with all the biphenyl ligands, excluding **14**). Ligands XPhos (**10**) and SPhos (**11**) demonstrated a reduced ability to afford the desired product **6a** under the reaction conditions employed.

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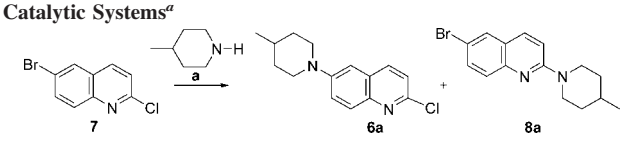
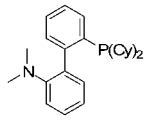
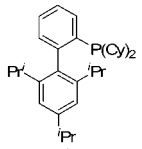
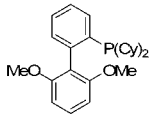
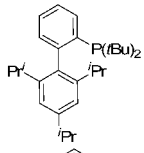
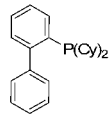
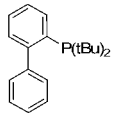
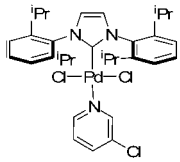
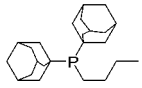
TABLE 1. Buchwald−Hartwig Amination of 7 with a Range of Catalytic Systems[a]



Ligand	Catalyst system[b]	Yield 6a (%)	Yield 8a (%)
9		15	15
10		40	20
11		31	15
12		0	21
13		54	16
14		0	0
15		0	[c]
16		57	14

[a] Reaction conditions: **7** (1 equiv), 4-methylpiperidine (**a**; 1.2 equiv), KO^{t}Bu (1.2 equiv), $Pd(OAc)_2$ (0.5 mol %), and ligand (1 mol %) in toluene at 110 °C. Yields were determined by ^{1}H NMR analysis of the crude material. The reaction employing **16** was carried out under pressure at 120 °C. [b] $Pd(OAc)_2$ was used as the source of palladium in all cases except for **15**. [c] Only **18** isolated.

Interestingly, ^{t}BuXPhos (**12**) and JohnPhos (**14**) were unsuccessful in affording any **6a.**

Use of the *N*-heterocyclic carbene (NHC) palladium complex PEPPSI (pyridine-enhanced precatalyst preparation stabilization and initiation, **15**) was also explored as it reportedly offers a number of advantages over traditional palladium complexes. It is stable to air and moisture and has been reported to have activity better than or comparable to that of known palladium catalysts in a range of coupling reactions including Buchwald−Hartwig aminations.[18,19] The use of **15** as a superior catalyst for C−N bond formation in the present context, specifically with improved selectivity for bromine, was explored again with **a** as the model amine. The reaction of **7** and **a** in the presence of **15** according to the method of Organ et al.[18,19] afforded 2-*tert*-butoxy-6-bromoquinoline (**18**) in almost quantitative yield in 1.5 h. However, repetition of this reaction with no catalyst produced a similar result. This indicates that **15** did not facilitate the desired C−N bond formation required and therefore was not suitable for this particular amination reaction.

Further studies on the Buchwald−Hartwig reaction of **7** utilized the CataCXium A ligand (**16**).[20] This class of sterically demanding phosphine ligands has been reported to be suitable for a range of palladium-catalyzed reactions,[20−22] including Buchwald−Hartwig aminations.[23] The use of **16** was examined using conditions reported by Tewari et al.[23] involving $Pd(OAc)_2$ and KO^{t}Bu in toluene at 120 °C under pressure overnight employing **a** as the amine for comparison (see Table 1). The use of **16** under these reaction conditions led to a slight improvement in the conversion of starting material to **6a** (57%; cf. 54% with **13**). In addition, a reduction in the amount of **8a** was also observed. The results of the ligand screen therefore indicated that ligand **16** was the most appropriate of the ligands tested for use in this particular Buchwald−Hartwig reaction and was employed for the preparation of a range of 6-substituted 2-chloroquinolines.

The use of **16**/$Pd(OAc)_2$ in the Buchwald−Hartwig reaction of **7** using the conditions above allowed for the amination of **7** with a number of cyclic amines, **a**−**m**, and afforded compounds **6a**−**m** in varying yields (1−94%) (see Table 2). In addition to the desired products, however, substitution at the 2-position was also observed to produce compounds **8**. In the reactions with heterocycles **c** and **l**, the expected reactivity was observed, with **6** predominating in good yields and none of **8** observed (see Table 2). However, in the reactions with heterocycles **b**, **d**−**f**, **h**−**k**, and **m**, low to moderate yields of **6** were obtained. In these reactions notable amounts of **8** were observed, and in many cases **8** was isolated in significant yield. In the case of heterocycle **g** only a trace amount of the desired product **6** was observed, and for heterocycle **m**, **8** was the only isolated product. The competing amination at chlorine and the resulting formation of compounds **8** in the presence of the more reactive bromine are due to the activation of the chlorine substituent from the adjacent quinoline nitrogen, which makes the 2-position more susceptible to nucleophilic attack. This also results in the formation of compounds **17** and **18**, which are seen in varying amounts and result from the displacement of the chloride by the base. In addition, in the reaction with **a** product **19** was observed, and in the reaction with **g** products **20** and **21** were also observed. The formation of these side products causes a reduction in the yield of the desired product and additionally complicates the purification process. In a number of cases the desired products were unable to be separated from the unwanted side products.

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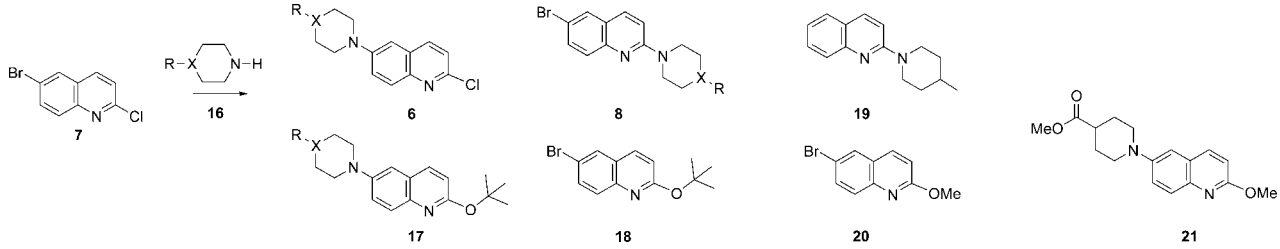
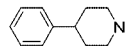
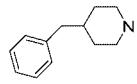
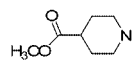
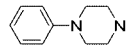
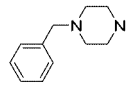
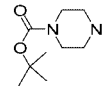
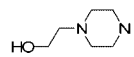
TABLE 2. Buchwald−Hartwig Amination of 7 with 16/Pd(OAc)$_2$[a] and a Range of Cyclic Amines Showing the Distribution of Products

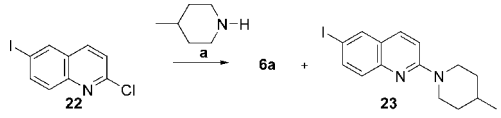


	Amine	6[b] (%)	6[c] (%)	8 (%)	17 (%)	Other (%)
a		57	44[d]	25	9[d]	**19**; 15
b		63	52	*e*	*f*	*g*
c		98	94			
d		65	54			
e		62	44	*e*	*c*	*g*
f		50	40[d]	*e*	7[d]	*g*
g		4	1[d]			**20**; 40 **21**[d]; 2
h		34	32[d]	*e*	*f*	**7**[d]; 5 *g*
i		63	58[d]	30[d]	10	*g*
j		57	44	15	*f*	
k		39	26[d]	11[d]	6	*g*
l		85	80		7	*g*
m		2		37		

[a] Reaction conditions: **7** (1 equiv), amine (1.2 equiv), KO^{t}Bu (1.2 equiv), Pd(OAc)$_2$ (0.5 mol %), and **16** (1 mol %) in toluene at 120 °C under pressure. [b] Yields were determined by ^{1}H NMR analysis of the crude material. [c] Isolated yield after chromatography. [d] Indicates isolated as a mixture which could not be separated; yields refer to individual components. [e] Observed by ^{1}H NMR analysis but not isolated. [f] **17** was also observed by ^{1}H NMR analysis but was not isolated. [g] **18** was also observed by ^{1}H NMR analysis but was not isolated.

Having prepared a range of 6-heterocylic 2-chloroquinoline compounds in significantly varied yields using this method, we turned our attention to improving the selectivity of this reaction for the 6-position. An initial attempt aimed at improving the selectivity involved replacement of the bromine atom at C-6 with an iodine atom, compound **22**, as the iodine equivalent should be more reactive (see Scheme 2). The Buchwald−Hartwig reaction with **a** using Pd(OAc)$_2$/**16**/NaO^{t}Bu in toluene afforded the desired product **6a** in only 38% yield, together with the corresponding 2-substituted compound **23** in 13% yield. This demonstrated that the reaction was less selective for the 6-position when **22** was employed as the aryl halide (cf. 44% yield with **7**), despite the anticipated increased reactivity of the iodine relative to bromine. This observation is consistent with several reports that show that aryl iodides are often less effective than their

SCHEME 2. Buchwald−Hartwig Amination of 21 with 16/Pd(OAc)$_2$[a]



[a] Reaction conditions: **22** (1 equiv), **a** (1.2 equiv), NaO^{t}Bu (1.2 equiv), Pd(OAc)$_2$ (0.5 mol %), and **16** (1 mol %) in toluene at 120 °C under pressure.

TABLE 3. Comparison of Buchwald−Hartwig Amination of 7 with CuBr Cocatalysis[a]

amine	yield of **6** (%), no CuBr	yield of **8** (%), no CuBr	yield of **6** (%), with CuBr	yield of **8** (%), with CuBr
a	57	30	72	6
f	50	10	58	47
h	34	22	78	0
j	57	26	9	50
k	39	11	45	45

[a] Reaction conditions: **7** (1 equiv), amine (1.2 equiv), KO^{t}Bu (1.2 equiv), Pd(OAc)$_2$ (0.5 mol %), **16** (1 mol %), and CuBr (10 mol %) (if required) in toluene at 120 °C under pressure. Yields were determined by ^{1}H NMR analysis of the crude material.

bromide equivalents and display significantly different reactivities in amination reactions.[15,24]

A number of authors have reported that coupling reactions of this type can be improved by the addition of a copper(I) salt as a cocatalyst.[25−27] The specific role of the copper in these reactions is not known, but it has been suggested that the copper may facilitate the transmetalation step.[25] We have investigated the effect of copper in the reaction of **7** with selected cyclic amines through the addition of CuBr (10 mol %) using the reaction conditions described for the preparation of compounds **6a**−**m**. The addition of Cu(I) improved the amount of **6** substantially when **a** and **h** were used as the amine and slightly in the cases of **f** and **k** (Table 3). In the case of **j**, a substantial decrease in the production of **6** was observed. In these reactions, the addition of Cu(I) decreased the amount of **8** substantially when **a** and **h** were used as the amine; however, in the cases of **f**, **j**, and **k** a substantial increase in the amount of **8** was observed. The use of Cu(I) in this particular palladium-catalyzed reaction therefore appeared to be inconsistent across the amines used. The addition of Cu(I), however, prevented the formation of corresponding compounds **17** and **18**, and little to none of these compounds were observed in all of the reactions involving CuBr. The absence of these side products is likely to be the main contribution to the improvement in the formation of **6** and **8** where they are observed.

A brief investigation of the effects of the base employed in these reactions involved a comparison of KO^{t}Bu with NaO^{t}Bu and Cs_2CO_3. In toluene, it was found that NaO^{t}Bu was effective for the amination reaction of **7**, displaying amounts of both **6a** and **8a** similar to those obtained when KO^{t}Bu was used as the base (see Table 4). The weak base Cs_2CO_3, on the other hand, was less effective in this reaction and resulted in a substantially lower yield of **6a** being obtained. It is however worth noting that in this case no **8a** was observed.

TABLE 4. Effect of Base on Buchwald−Hartwig Amination of 7[a]

base	yield of **6a** (%)	yield of **8a** (%)
KO^{t}Bu	57	14
NaO^{t}Bu	60	11
Cs_2CO_3	30	0

[a] Reaction conditions: **7** (1 equiv), **a** (1.2 equiv), base (1.2 equiv), Pd(OAc)$_2$ (0.5 mol %), and **16** (1 mol %) in toluene at 120 °C under pressure. Yields were determined by ^{1}H NMR analysis of the crude material.

Microwave-assisted organic synthesis has become increasingly popular over the past 20 years due to the potential improvements that can be achieved in chemical reaction times, yields, reaction purities, and selectivities. The use of microwave heating in palladium-catalyzed reactions, including Buchwald−Hartwig aminations, has been reported and has provided improvements in the yields and reaction times in many instances.[28,29] The Buchwald−Hartwig reaction was therefore investigated with the use of microwave irradiation using the catalytic system of **16**/Pd(OAc)$_2$ and **c** as a model cyclic amine in this instance. The reaction of **7** and **c** in toluene in the presence of NaO^{t}Bu afforded the desired product **6c** in 80% yield. Incomplete conversion of the starting material was observed and is likely a consequence of the inability of the reaction mixture to reach the required temperature of 150 °C in a short period of time.[30] Due to the poor heating ability of toluene for use in microwave reactions a number of alternate solvents were investigated including DME, DMF, DMF/water, and (trifluoromethyl)benzene. The reactions employing DMF and DMF/H_2O as the solvent lead to the formation of complex mixtures of products, with minor amounts of the desired product being observed. The use of DME, however, predominantly leads to the recovery of starting material. The use of (trifluoromethyl)benzene as a solvent has been shown to be effective in microwave-assisted Buchwald−Hartwig reactions as it could be heated rapidly and provided moderate to good yields of the desired coupled products.[31] The reaction of **7** with **c** was therefore examined with (trifluoromethyl)benzene as the solvent at 150 °C under microwave irradiation (see Table 5). The use of (trifluoromethyl)benzene allowed for rapid heating of the reaction mixture (typically 1 min) and for the consumption of all starting material. The reaction afforded the desired product **6c** in higher yield than the corresponding reaction in toluene (95%; cf. 80% in toluene). The yield obtained was also equivalent to the reaction of **7** with **c** conducted under thermal conditions in toluene; however, the reaction time was significantly reduced to 15 min. The reaction of **7** with other cyclic amines was also successful and provided the compounds **6e**,**f**,**h** in good to high yield. All of the yields obtained are improvements on the thermal reactions in toluene and were achieved in 20 min or less of microwave irradiation. It should be noted that these yields have not been optimized.

Due to the success of (trifluoromethyl)benzene as a solvent for the microwave reactions, the use of this solvent for thermal Buchwald−Hartwig aminations was considered (see Table 6).

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(26) Gomez-Bengoa, E.; Echavarren, A. M. *J. Org. Chem.* **1991**, *56*, 3497–3501.
(27) Tamayo, N.; Echavarren, A. M.; Paredes, M. C. *J. Org. Chem.* **1991**, *56*, 6488–6491.
(28) Majetich, G.; Hicks, R. *Res. Chem. Intermed.* **1994**, *20*, 61–77.
(29) Maes, B. U. W.; Loones, K. T. J.; Hostyn, S.; Diels, G.; Rombouts, G. *Tetrahedron* **2004**, *60*, 11559–11564.
(30) The reaction mixture reached a maximum of 130 °C after 15 min at maximum power (120 0W) in a MARS (CEM) microwave system. Differences in the heating profiles of common solvents and their use in various microwave systems have been investigated.[31]
(31) Loones, K. T. J.; Maes, B. U. W.; Rombouts, G.; Hostyn, S.; Diels, G. *Tetrahedron* **2005**, *61*, 10338–10348.

TABLE 5. Comparison of Buchwald−Hartwig Amination of 7 Using $C_6H_5CF_3$ with Microwave Irradiation and $C_6H_5CH_3$ under Thermal Conditions[a]

	yield of **6** (%)	
amine	$C_6H_5CH_3$	$C_6H_5CF_3$
c	94	95
e	44	50
f	40	78
h	32	50

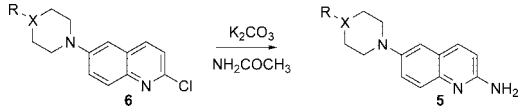
[a] Reaction conditions: **7** (1 equiv), amine (1.2 equiv), NaO^{t}Bu (1.2 equiv), $Pd(OAc)_2$ (0.5 mol %), and **16** (1 mol %). The reaction in toluene was conducted at 120 °C under pressure. The reaction in (trifluoromethyl)benzene was conducted at 150 °C with microwave irradiation for 15−20 min. Yields are not optimized and refer to isolated yields.

TABLE 6. Effect of Solvent on the Buchwald−Hartwig Amination of 7 under Thermal Conditions[a]

	yield of **6** (%)	
amine	$C_6H_5CH_3$	$C_6H_5CF_3$
a	57	93
c	98	95
e	62	80
f	50	88
h	34	80
j	57	91
k	39	90

[a] Reaction conditions: **7** (1 equiv), amine (1.2 equiv), NaO^{t}Bu (1.2 equiv), $Pd(OAc)_2$ (0.5 mol %), and **16** (1 mol %) in toluene at 120 °C or (trifluoromethyl)benzene at 100 °C under pressure. Yields were determined by ^{1}H NMR analysis of the crude material.

SCHEME 3. Amination of 6 Using the Kóródi[11] Method[a]



[a] Reaction conditions: 6 (1 equiv), NH_2COCH_3 (20−40 equiv), and K_2CO_3 (20 equiv) at 200 °C for 1−3 h.

Gratifyingly, employing (trifluoromethyl)benzene as a solvent in the amination of **7** with NaO^{t}Bu produced substantial increases in the yields of compounds **6** with a range of cyclic amines (see Table 6). In all instances, the conversion of starting material to **6** was 80% or greater (80−95%) and only minor of amounts **8** were observed. In addition, in most cases none of compound **17** or **18** was observed. These reaction conditions were therefore the optimal conditions for selectively aminating at the 6-bromine in the presence of the activated 2-chlorine and allowed for the preparation of compounds **6** in high yield.

Introducing the 2-Amino Functionality. Previous studies have utilized the method of Kóródi[11] to convert 2-chloroquinolines to 2-aminoquinolines.[5,6] Using this method, the 2-chloroquinolines prepared in this study (**6a−f**,**h−l**) were converted to 2-aminoquinolines **5a−f**,**h−l** (see Scheme 3). The yields obtained, however, varied substantially and in many cases were poor (see Table 7). A complex mixture of products was generally formed during these reactions and contributed to the low yields displayed in most cases. The complex mixture of products that was obtained from the Kóródi reactions also caused considerable difficulties in the purification process. Due to these difficulties and low yields an alternate method for amination was desirable.

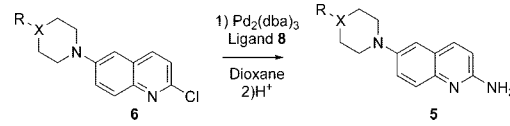
Recently, a few reports have described the use of LHMDS as an ammonia equivalent for palladium-catalyzed coupling of aryl halides to prepare simple anilines.[32−34] It was envisaged that this methodology could be applied to compounds such as **6** in the preparation of 2-aminoquinolines **5** (see Scheme 4). The reaction of a number of 2-chloroquinolines using the method described by Lee et al.[33] involving $Pd_2(dba)_3$ and DavePhos (**9**) in dioxane at 100 °C under pressure verified the usefulness of LHMDS for this type of amination process (see Table 7). In all instances **5** was obtained from workup of the reaction with only trace amounts of impurities observed (less than 2% impurities by NMR analysis in the cases of **5a**,**c**,**j**,**k** and less than 5% impurities by NMR analysis in the case of **5h**). **5** was afforded in high yield (88−98%) with an average improvement in yield of 70% compared to those of the corresponding Kóródi reactions. This method is therefore a significant improvement on the Kóródi reaction, which gave a complex mixture of products and low yields of **5**. In addition, this method provides an alternate pathway for the preparation of 2-aminoquinolines using palladium chemistry.

TABLE 7. Comparison of Methods for Amination of 2-Chloroquinolines

	yield of **5** (%)	
6	Kóródi amination	Pd-catalyzed amination
a	40	97[b,a]
b	56	
c	32	98[b]
d	64	
e	40	
f	25	
h	11	90[b]
i	26	
j	46	96[b]
k	4[a]	88[b]
l	47	

[a] Purified on C18 preparative TLC plates. [b] Yields were determined by ^{1}H NMR analysis of the crude material.

SCHEME 4. Amination of 6 Using LHMDS as an Ammonia Equivalent[a]



[a] Reaction conditions: **6** (1 equiv), LHMDS (2.2 equiv), $Pd_2(dba)_3$ (1 mol %), and **8** (1.2 mol %) in dioxane at 100 °C under pressure.

Binding Studies of 6-Substituted 2-Aminoquinolines with Murine Tec IV SH3 Domain. The 6-substituted 2-aminoquinolines **5a−f**,**h−k**[35] prepared were assayed for binding to the Tec SH3 domain by NMR chemical shift perturbation analysis utilizing (^{1}H, ^{15}N) heteronuclear single-quantum coherence (HSQC) experiments with uniformly ^{15}N-labeled SH3 protein, in the presence of the 2-aminoquinoline ligand. Changes in the chemical shifts for protein−ligand mixtures relative to the free protein indicate binding and allow for K_d values to be calculated. The use of this method for binding information of 2-aminoquinolines has been reported previously.[6]

The binding affinities of ligands **5** are shown in Table 8. All of the ligands **5** bound the Tec SH3 domain surface with

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(33) Lee, S.; Jorgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729–2732.
(34) Harris, M. C.; Huang, X.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 2885–2888.
(35) **5b** was not assayed due to its instability. **5l** was not assayed due to its insolubility in the assay medium.

TABLE 8. Equilibrium Dissociation Binding Constants (K_d) of 5 with the Tec SH3 Domain As Determined by NMR Chemical Shift Perturbation Experiments

ligand **5**	K_d[a] (μM)
a	12 ± 2
c	27 ± 3
d	91 ± 9
e	22 ± 4
f	9 ± 1
h	67 ± 18
i	28 ± 6
j	31 ± 5
k	28 ± 8

[a] Quoted values are the mean ± standard deviation over residues where ^{1}H (H−N) chemical shift changes of the SH3 domain were at least 0.1 ppm at or near saturation binding of the ligand.

improved affinity relative to the lead compound **1** (K_d = 125 μM). Introduction of a simple piperidine substituent, **5d**, displayed a small improvement in binding affinity (K_d = 90 μM). Further extension on the piperidine substituent in ligands **5a**, **5e**, and **5f** led to a greater improvement (6−10-fold, K_d = 9−22 μM) in binding relative to **1**. The incorporation of an oxygen in ligand **5c** displayed a similar improvement in binding affinity (K_d = 27 μM). Incorporation of piperazine in **5h** (K_d = 67 μM) gave an approximately 2-fold improvement in binding, with extension on the piperazine substituent similarly improving the binding affinity further (K_d = 28−31 μM). Ligands **5a** and **5f** are the highest affinity ligands for the Tec SH3 domain prepared to date.

The SAR information provided from the assay results suggests that the appended heterocycle makes an additional hydrophobic contact with the protein surface, which provides an improvement in binding affinity of compounds **5** relative to **1**. Extension on the heterocyclic substituent may provide a further contact with the protein surface, leading to a greater improvement in binding. The assay results also indicate that the second nitrogen in the piperazine ring appears to reduce the binding affinity of these compounds. Extension on the piperazine, however, regains some of the lost binding affinity presumably by making an additional contact with the protein surface.

The binding affinities of compounds **5** were compared to those of **2**−**4** (K_d = 40, 52, and 22 μM, respectively). Of the ligands assayed **5d** and **5h** displayed a reduced affinity for the Tec SH3 domain relative to ligands **2**−**4**. **5c**, **5e**, and **5i**−**k** showed affinity simlar to that of the acetal-substituted ligands, while **5a** and **5f** had improved affinities. The overall similarity of the binding affinities of ligands **5** with **2**−**4** is consistent with our prediction that the acetal functionality could be replaced with an alternate heterocycle. The replacement of the acetal with the above-mentioned heterocycles affords compounds with increased chemical stability and provides improvements in binding affinity relative to **1**.

Experimental Section

General Considerations. Compounds **7**[6] and **22**[6,36] were synthesized as previously described. ‡Indicates an unresolved *J* coupling.

General Procedure 1: Buchwald−Hartwig Amination in Toluene.[23] A pressure tube was loaded with $Pd(OAc)_2$ (0.5 mol %), ligand precursor (1 mol %), and base (1.2 equiv) under a nitrogen atmosphere. Anhydrous toluene was added, followed by **7** (1 equiv) and the amine (1.2 equiv). The tube was evacuated, backfilled with nitrogen, and sealed, and then the mixture was stirred for 18−26 h at 120 °C. After cooling, the mixture was diluted with an organic solvent and washed with water and/or brine. The organic phase was dried over $MgSO_4$ or Na_2SO_4, and then the solvent was removed under reduced pressure. The product was isolated by flash chromatography on silica gel with appropriate solvent mixtures.

General Procedure 2: Buchwald−Hartwig Amination in (Trifluoromethyl)benzene and 1,4-Dioxane.[23,31] General procedure 1 was employed with either (trifluoromethyl)benzene or 1,4-dioxane as the solvent except that the reaction was heated at 100 °C for the specified time. The product was isolated by flash chromatography on silica gel with appropriate solvent mixtures, or alternatively quantitative determinations were obtained by ^{1}H NMR analysis of the crude material.

General Procedure 3: Buchwald−Hartwig Amination in the Presence of CuBr.[27] General procedure 1 was employed with KO^{t}Bu as the base and with the addition of CuBr (10 mol %). Quantitative determinations of product yields were obtained by ^{1}H NMR analysis of the crude material.

General Procedure 4: Buchwald−Hartwig Amination with Microwave Irradiation.[31] A high-pressure microwave vessel was loaded with **7** (1 equiv) and amine (1.2 equiv) in anhydrous toluene or (trifluoromethyl)benzene. $Pd(OAc)_2$ (0.5 mol %), **16** (1 mol %), and NaO^{t}Bu (1.2 equiv) were added, and then the vessel was evacuated, backfilled with nitrogen, and sealed. The mixture was heated at the temperature and power indicated for 15−20 min (including the ramp time). After cooling, the mixture was filtered through Celite, and the solvent was removed under reduced pressure. The product was isolated by flash chromatography on silica gel with appropriate solvent mixtures.

General Procedure 5: Kóródi Amination of 2-Chloroquinolines.[11] The 2-chloroquinoline (1 equiv) was treated with acetamide (20−40 equiv) and potassium carbonate (20 equiv) and heated at 200 °C for 1−3 h. After cooling, water was added and the mixture extracted with either ethyl acetate or a solution of chloroform/2-propanol (3:1). The organic layers were washed with brine and dried over Na_2SO_4 and the solvent removed under reduced pressure. The product was isolated by flash chromatography with appropriate solvent mixtures.

General Procedure 6: Buchwald−Hartwig Amination of 2-Chloroquinolines Using LHMDS.[33] A pressure tube was loaded with $Pd_2(dba)_3$ (1 mol %), **9** (1.2 mol %), and the 2-chloroquinoline derivative (1.0 equiv). Dry 1,4-dioxane was added followed by lithium bis(trimethylsilyl)amide solution (1.0 M in THF, 2.2 equiv). The pressure tube was evacuated, backfilled with nitrogen, and sealed and the mixture stirred for 18−24 h at 100 °C. After being cooled to room temperature, the mixture was quenched with 1 M HCl and stirred for 10 min. The solution was then basified by the addition of NaOH. The aqueous phase was extracted with a solution of chloroform/2-propanol (3:1), washed with water, and dried over Na_2SO_4 and the solvent removed under reduced pressure. Quantitative determinations of product yields were obtained by ^{1}H NMR analysis.

General Procedure 7: Preparation of Maleate Salts. The 2-aminoquinoline (1.0 equiv) was dissolved in acetone, and a solution of maleic acid (1.0 equiv) in acetone was added dropwise at room temperature. The reaction mixture was then stirred at 0 °C for 1 h. The resulting precipitate was filtered and recrystallized from ethanol/water to afford the corresponding maleate salt.

2-Chloro-6-(4-methylpiperidin-1-yl)quinoline (6a). Synthesis Method i. Using general procedure 1, **7** (520 mg, 2.13 mmol) and **a** (300 μL, 2.56 mmol) were added to a mixture of $Pd(OAc)_2$ (2.4 mg, 10.6 μmol), **16** (7.6 mg, 21.3 μmol), and KO^{t}Bu (287 mg, 2.56 mmol) in toluene (3 mL). The reaction mixture was heated for 21 h. Extraction with ethyl acetate and chromatographic separation eluting with CH_2Cl_2/ethyl acetate (50:1) afforded the

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title compound as a 5:1 mixture with 2-*tert*-butoxy-6-(4-methylpiperidin-1-yl)quinoline (**17a**) (combined yield 297 mg; **6a**, 44%; **17a**, 9%). 6-Bromo-2-(4-methylpiperidin-1-yl)quinoline (**8a**) (yellow crystals, mp 76−80 °C, 140 mg, 25%) and 2-(4-methylpiperidin-1-yl)quinoline (**19**) (yellow oil, 71 mg, 15%) were also isolated. Data for **6a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.99 (3H, d, J = 6.6 Hz, CH_3), 1.37 (2H, dq, $J_{2'/6'eq,3'/5'ax}$ = 2.4 Hz, $J_{2'/6'ax,3'/5'ax}$ = $J_{3'/5'ax,3'/5'eq}$ = $J_{3'/5'ax,4'}$ = 12.6 Hz, 2 CH, H(3′/5′$_{ax}$)), 1.56 (1H, br m, CH, H(4′)), 1.77 (2H, br d‡, $J_{3'/5'ax,3'/5'eq}$ = $J_{2'/6'eq,3'/5'eq}$ = 12.6 Hz, 2 CH, H(3′/5′$_{eq}$)), 2.79 (2H, dt, $J_{2'/6'ax,3'/5'eq}$ = 2.4, $J_{2'/6'ax,2'/6'eq}$ = $J_{2'/6'ax,3'/5'ax}$ = 12.6 Hz, 2 CH, H(2′/6′$_{ax}$)), 3.77 (2H, br d‡, $J_{2'/6'ax,2'/6'eq}$ = $J_{2'/6'eq,3'/5'eq}$ =12.6 Hz, 2 CH, H(2′/6′$_{eq}$)), 6.97 (1H, d, J = 2.4 Hz, H5), 7.24 (1H, d, J = 9.0 Hz, H3), 7.47 (1H, dd, J = 2.4, 9.0 Hz, H7), 7.84 (1H, d, J = 9.0 Hz, H8), 7.87 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.7 (CH_3), 30.6 (C4′), 33.8 (C3′/5′), 49.6 (C2′/6′), 108.6 (C5), 122.2 (C3), 123.5 (C7), 128.1(C4a), 128.9 (C8), 137.3 (C4), 142.8 (C8a), 147.0 (C2), 150.0 (C6); IR (Nujol mull) ν/cm^{-1} 1654, 1616, 1600, and 1578. MS (EI) m/z 262 (M + H$^{\bullet+}$ [^{37}Cl], 30), 261 (M$^{\bullet+}$ [^{37}Cl], 40), 260 (M + H$^{\bullet+}$ [^{35}Cl], 100), 259 (M$^{\bullet+}$ [^{35}Cl], 100), 164 (6), 162 (18); HRMS (EI$^+$) m/z found 259.1000, $C_{15}H_{17}{}^{35}ClN_2$ − H requires 259.1002. Data for **8a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.98 (3H, d, J = 6.6 Hz, CH_3), 1.27 (2H, m, 2 CH, H(3′/5′$_{ax}$)), 1.69 (1H, br m, CH, H(4′)), 1.78 (2H, br d‡, $J_{3'/5'ax,3'/5'eq}$ = $J_{2'/6'eq,3'/5'eq}$ = 12.6 Hz, 2 CH, H(3′/5′$_{eq}$)), 2.98 (2H, br s‡, 2 CH, H(2′/6′$_{ax}$)), 4.53, (2H, br s‡, 2 CH, H(2′/6′$_{eq}$)), 6.73 (1H, d, J = 9.0 Hz, H3), 7.26 (1H, d, J = 1.2 Hz, H5), 7.39 (1H, br d‡, J = 9.0 Hz, H7), 7.68 (1H, d, J = 9.0 Hz, H8), 7.78 (1H, d, J = 9.0 Hz, H4); IR (Nujol mull) ν/cm^{-1} 1642, 1615, 1598, 1546, and 1493; MS (EI) m/z 306 (M$^{\bullet+}$ [^{81}Br], 50), 304 (M$^{\bullet+}$ [^{79}Br], 50), 277 (30), 263 (35), 261 (35), 249 (100), 237 (50), 235 (50), 224 (40), 222 (40), 208 (50), 127(50); HRMS (EI$^+$) m/z found 304.0575, $C_{15}H_{17}{}^{79}BrN_2$ requires 304.0575. Data for **17a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.99 (3H, d, J = 6.6 Hz, CH_3), 1.37 (2H, dq, $J_{2'/6'eq,3'/5'ax}$ = 2.4 Hz, $J_{2'/6'ax,3'/5'ax}$ = $J_{3'/5'ax,3'/5'eq}$ = $J_{3'/5'ax,4'}$ = 12.6 Hz, 2 CH, H(3′/5′$_{ax}$)), 1.56 (1H, br m, CH, H(4′)), 1.66 (9H, s, ^{t}Bu), 1.77 (2H, br d‡, $J_{3'/5'ax,3'/5'eq}$ = $J_{2'/6'eq,3'/5'eq}$ = 12.6 Hz, 2 CH, H(3′/5′$_{eq}$)), 2.73 (2H, m, 2 CH, H(2′/6′$_{ax}$)), 3.67, (2H, br d‡, $J_{2'/6'ax,2'/6'eq}$ = $J_{2'/6'eq,3'/5'eq}$ =12.6 Hz, 2 CH, H(2′/6′$_{eq}$)), 6.73 (1H, d, J = 9.0 Hz, H3), 7.26(1H, d, J = 1.2 Hz, H5), 7.39 (1H, br d‡, J = 9.0 Hz, H7), 7.68 (1H, d, J = 9.0 Hz, H8), 7.78 (1H, d, J = 9.0 Hz, H4); MS (EI) m/z 242 (M$^{\bullet+}$ − C_4H_8, 100). Data for **19**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.00 (3H, d, J = 6.6 Hz, CH_3), 1.27 (2H, dq, $J_{2'/6'eq,3'/5'ax}$ = 2.4 Hz, $J_{2'/6'ax,3'/5'ax}$ = $J_{3'/5'ax,3'/5'eq}$ = $J_{3'/5'ax,4'}$ = 12.6 Hz, 2 CH, H(3′/5′$_{ax}$)), 1.68 (1H, br m, CH, H(4′)), 1.77 (2H, br d‡, $J_{3'/5'ax,3'/5'eq}$ = $J_{2'/6'eq,3'/5'eq}$ = 12.6 Hz, 2 CH, H(3′/5′$_{eq}$)), 2.95 (2H, dt, $J_{2'/6'ax,3'/5'eq}$ = 2.4, $J_{2'/6'ax,2'/6'eq}$ = $J_{2'/6'ax,3'/5'ax}$ = 12.6 Hz, 2 CH, H(2′/6′$_{ax}$)), 4.53, (2H, br d‡, $J_{2'/6'ax,2'/6'eq}$ = $J_{2'/6'eq,3'/5'eq}$ =12.6 Hz, 2 CH, H(2′/6′$_{eq}$)), 7.00 (1H, d, J = 9.0 Hz, H3), 7.20 (1H, dt, J = 0.9, 7.8 Hz, H6), 7.39 (1H, dt, J = 1.5, 7.8 Hz, H7), 7.58 (1H, br d‡, J = 7.8 Hz, H8), 7.70 (1H, br d‡, J = 7.8 Hz, H5), 7.86 (1H, d, J = 9.0 Hz, H4); IR (Nujol mull) ν/cm^{-1} 3051, 1675, 1619, 1603, 1556, and 1505. MS (EI) m/z 226 (M$^{\bullet+}$, 100).

Synthesis Method ii. Using general procedure 2, the title compound was obtained in 93% yield as determined by ^{1}H NMR analysis. Data are as above.

Synthesis Method iii. Using general procedure 3, the title compound was obtained in 72% yield as determined by ^{1}H NMR analysis. Data are as above.

Method iv: Attempted Synthesis of 6a Using PEPPSI Catalyst.[18,19] **7** (50 mg, 0.21 mmol) was dissolved in dry DME and added to a reaction vessel loaded with KO^{t}Bu (35 mg, 0.32 mmol) and **15** (3 mg, 4.4 μmol) in DME under argon. **a** (27 μL, 0.23 mmol) was added dropwise, and then the solution was stirred at 50 °C for 1.5 h. After being cooled to room temperature, the mixture was extracted with a mixture of chloroform/2-propanol (3:1) and then washed with water and brine. The organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure to afford **18** as a pink glass (50 mg, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (9H, s, ^{t}Bu), 6.76 (1H, d, J = 9.0 Hz, H3), 7.65 (2H, s, H7, H8), 7.81 (1H, d, J = 2.7 Hz, H5), 7.83 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.7 (C(CH_3)$_3$), 80.7 (C(CH_3)$_3$), 116.2 (C3), 116.9 (C6), 125.9 (C4a), 129.4 (C5), 129.5 (C8), 132.4 (C7), 137.1 (C4), 145.3 (C8a), 162.3 (C2); IR (CH_2Cl_2 solution) ν/cm^{-1} 3384, 1667, 1613, 1602, and 1561; MS (EI) m/z 225 ([^{81}Br], 100), 223 ([^{79}Br], 100), 197 ([^{81}Br], 40), 195 ([^{79}Br], 40), 116 (75), 97 (20), 89 (45), 57 (30), 44 (35); HRMS (EI$^+$) m/z found 280.0332, $C_{13}H_{14}{}^{79}BrNO$ + H requires 280.0332.

Method v: Synthesis of 6a Employing Aryl Halide 22. Using general procedure 1, **22** (100 mg, 0.35 mmol) and **a** (35 μL, 0.41 mmol) were added to a mixture of $Pd(OAc)_2$ (0.4 mg, 1.8 μmol), **16** (1.2 mg, 3.5 μmol), and NaO^{t}Bu (40 mg, 0.41 mmol) in toluene (3 mL). The reaction mixture was heated for 21 h. Extraction with ethyl acetate and chromatographic separation eluting with CH_2Cl_2/ethyl acetate (50:1) afforded the title compound **6a** as a yellow solid (35 mg 38%). Data are as above. 6-Iodo-2-(4-methylpiperidin-1-yl)quinoline (**23**) was also isolated (yellow glass, 16 mg, 13%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, d, J = 6.3 Hz, CH_3), 1.28 (2H, dq, $J_{2'/6'eq,3'/5'ax}$ = 3.0 Hz, $J_{2'/6'ax,3'/5'ax}$ = $J_{3'/5'ax,3'/5'eq}$ = $J_{3'/5'ax,4'}$ = 12.3 Hz, 2 CH, H(3′/5′$_{ax}$)), 1.69 (1H, br m, CH, H(4′)), 1.80 (2H, br d‡, $J_{3'/5'ax,3'/5'eq}$ = $J_{2'/6'eq,\ 3'/5'eq}$ = 12.3 Hz, 2 CH, H(3′/5′$_{eq}$)), 3.00 (2H, br t‡, J = 12.6 Hz, 2 CH, H(2′/6′$_{ax}$)), 4.54, (2H, br d‡, $J_{2'/6'ax,2'/6'eq}$ = $J_{2'/6'eq,3'/5'eq}$ =12.3 Hz, 2 CH, H(2′/6′$_{eq}$)), 6.98 (1H, br d, J = 6.3 Hz, H3), 7.59 (1H, br d, J = 7.2 Hz, H8), 7.71−7.76 (2H, m, H4, H7), 7.92 (1H, d, J = 1.5 Hz, H5); IR (Nujol mull) ν/cm^{-1} 1646, 1615, 1598, 1560, and 1500; MS (EI) 352 (M$^{\bullet+}$, 100), 254 (30); HRMS (EI$^+$) m/z found 352.0435, $C_{15}H_{17}IN_2$ requires 352.0436.

2-Chloro-6-(pyrrolidin-1-yl)quinoline (6b). Using general procedure 1, **7** (140 mg, 0.58 mmol) and pyrrolidine (**b**; 58 μL, 0.69 mmol) were added to a mixture of $Pd(OAc)_2$ (0.65 mg, 2.9 μmol), **16** (2.1 mg, 5.8 μmol), and KO^{t}Bu (79 mg, 0.70 mmol) in toluene (2 mL). The mixture was heated for 20 h. Extraction with diethyl ether and chromatographic separation eluting with CH_2Cl_2/hexane (4:1) afforded the title compound as a brown solid which decomposed above 250 °C (70 mg, 52%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.07 (4H, tt, J = 3.3, 6.6 Hz, 2 CH_2, H(3′/4′)), 3.39 (4H, t, J = 6.6 Hz, 2 CH_2, H(2′/5′)), 6.60 (1H, d, J = 2.7 Hz, H5), 7.17 (1H, dd, J = 2.7, 9.0 Hz, H7), 7.22 (1H, d, J = 8.7 Hz, H3), 7.83 (1H, d, J = 9.0 Hz, H8), 7.86 (1H, d, J = 8.7 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.8 (C3′/4′), 48.3 (C2′/5′), 104.0 (C5), 119.8 (C3), 122.5 (C7), 128.7 (C4a), 129.3 (C8), 136.9 (C4), 143.2 (C8a), 149.2 (C2), 152.5 (C6); IR (Nujol mull) ν/cm^{-1} 3270, 1658, 1616, 1563, and 1517; MS (EI) m/z 234 (M$^{\bullet+}$ [^{37}Cl], 25), 233 (M − H$^{\bullet+}$ [^{37}Cl], 25), 232 (M$^{\bullet+}$ [^{35}Cl], 80), 231 (M − H$^{\bullet+}$ [^{35}Cl], 100), 176 (35); HRMS (EI$^+$) m/z found 232.0761, $C_{13}H_{13}{}^{35}ClN_2$ requires 232.0767. Anal. Calcd for $C_{13}H_{13}ClN_2$: C, 67.10; H, 5.63; N, 12.04. Found: C, 67.05; H, 5.63; N, 12.10.

2-Chloro-6-morpholinoquinoline (6c). Synthesis Method i. Using general procedure 1, **7** (102 mg, 0.42 mmol) and morpholine (**c**; 44 μL, 0.51 mmol) were added to a mixture of $Pd(OAc)_2$ (0.5 mg, 2.2 μmol), **16** (1.5 mg, 4.2 μmol), and KO^{t}Bu (57 mg, 0.51 mmol) in toluene (1 mL). The mixture was heated for 20 h. Extraction with ethyl acetate and chromatographic separation eluting with CH_2Cl_2 afforded the title compound as a yellow solid, mp 88−91 °C (98 mg, 94%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.26 (4H, br t, J = 4.8 Hz, 2 CH_2, H(2′/6′)), 3.90 (4H, br t, J = 4.8 Hz, 2 CH_2, H(3′/5′)), 6.98 (1H, d, J = 2.7 Hz, H5), 7.27 (1H, d, J = 8.7 Hz, H3), 7.45 (1H, d, J = 2.7, 9.6 Hz, H7), 7.88 (1H, d, J = 9.6 Hz, H8), 7.91 (1H, d, J = 8.7 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 49.1 (C2′/6′), 66.7 (C3′/5′), 110.4 (C5), 122.4 (C7), 122.5 (C3), 127.9 (C4a), 128.2 (C8), 137.1 (C4), 143.2 (C8a), 147.6 (C2), 149.5 (C6); IR (Nujol mull) ν/cm^{-1} 1652, 1621, 1563, and 1503; MS (EI) m/z 250 (M$^{\bullet+}$ [^{37}Cl], 15), 248 (M$^{\bullet+}$ [^{35}Cl], 50), 192 (30), 190 (100), 162 (20), 127 (20), 40 (30); HRMS (EI$^+$) m/z found 248.0707, $C_{13}H_{13}{}^{35}ClN_2O$ requires 248.0716. Anal. Calcd for $C_{13}H_{13}ClN_2O$: C, 62.78; H, 5.27; N, 11.26. Found: C, 62.80; H, 5.23; N, 11.26.

Synthesis Method ii. Using general procedure 2, the title compound was obtained in 95% yield as determined by ^{1}H NMR analysis. Data are as above.

Synthesis Method iii. Using general procedure 4, **7** (200 mg, 0.82 mmol) and **c** (86 μL, 0.98 mmol) were combined in toluene (10 mL). $Pd(OAc)_2$ (1.0 mg, 4.1 μmol), **16** (3.0 mg, 8.2 μmol), and NaO^{t}Bu (94 mg, 0.98 mmol) were added, and then the vessel was evacuated, backfilled with nitrogen, and sealed. The mixture was heated at 130 °C at 1200 W in a MARS microwave system for 15 min (including a 5 min ramp time). Chromatographic separation eluting with CH_2Cl_2 afforded the title compound as a yellow solid (195 mg, 80%). Data are as above.

Synthesis Method iv. Using general procedure 4, **7** (45 mg, 0.19 mmol) and **c** (20 μL, 0.23 mmol) were combined in (trifluoromethyl)benzene (2 mL). $Pd(OAc)_2$ (0.2 mg, 1.0 μmol), **16** (0.8 mg, 2.1 μmol), and NaO^{t}Bu (22 mg, 0.23 mmol) were added, and then the vessel was evacuated, backfilled with nitrogen, and sealed. The mixture was heated at 150 °C at 300 W in a Discover system for 15 min (including a 1 min ramp time). Workup afford the title compound as a yellow solid (45 mg, 95%). Data are as above.

2-Chloro-6-(piperidin-1-yl)quinoline (6d). Using general procedure 1, **7** (600 mg, 2.47 mmol) and piperidine (**d**; 300 μL, 3.03 mmol) were added to a mixture of $Pd(OAc)_2$ (2.8 mg, 12.5 μmol), **16** (9.1 mg, 25.4 μmol), and KO^{t}Bu (341 mg, 3.04 mmol) in toluene (2 mL). The reaction mixture was heated for 24 h. Extraction with ethyl acetate and chromatographic separation eluting with CH_2Cl_2/hexane (3:2) afforded the title compound as an orange solid, mp 127−130 °C (330 mg, 54%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (2H, m, CH_2, H4′), 1.74 (4H, br qn, J = 5.4 Hz, 2 CH_2, H(3′/5′)), 3.27 (4H, t, J = 5.4 Hz, 2 CH_2, H(2′/6′)), 6.99 (1H, br s, H5), 7.24 (1H, d, J = 8.4 Hz, H3), 7.48 (1H, dd, J = 2.7, 9.3 Hz, H7), 7.84 (1H, d, J = 9.3 Hz, H8), 7.88 (1H, d, J = 8.4 Hz, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4 (C4′), 25.8 (C3′/5′), 50.5 (C2′/6′), 109.0 (C5), 122.4 (C3), 123.7 (C7), 128.3 (C4a), 129.1 (C8), 137.5 (C4), 143.1 (C8a), 147.3 (C2), 150.4 (C6); IR (Nujol mull) ν/cm^{-1} 3280, 1685, 1620, 1583, and 1500; MS (EI) m/z 248 ($M^{\bullet+}$ [^{37}Cl], 25), 247 ($M - H^{\bullet+}$ [^{37}Cl], 100), 246 ($M^{\bullet+}$ [^{35}Cl], 80), 245 ($M - H^{\bullet+}$ [^{35}Cl], 100), 190 (25); HRMS (EI$^+$) m/z found 246.0915, $C_{14}H_{15}{}^{35}ClN_2$ requires 246.0924. Anal. Calcd for $C_{14}H_{15}ClN_2$: C, 68.15; H, 6.13; N, 11.35. Found: C, 68.13; H, 6.07; N, 11.52.

2-Chloro-6-(4-phenylpiperidin-1-yl)quinoline (6e). Synthesis Method i. Using general procedure 1, **7** (600 mg, 2.47 mmol) and 4-phenylpiperidine (**e**; 480 mg, 2.98 mmol) were added to a mixture of $Pd(OAc)_2$ (2.8 mg, 12.4 μmol), **16** (8.9 mg, 24.7 μmol), and KO^{t}Bu (332 mg, 2.96 mmol) in toluene (5 mL). The reaction mixture was heated for 20 h. Extraction with chloroform/2-propanol (3:1) and chromatographic separation eluting with CH_2Cl_2/hexane (4:1) afforded the title compound as a cream powder, mp 165−167 °C (346 mg, 44%). 6-Bromo-2-(4-phenylpiperidin-1-yl)quinoline (**8e**) was also observed in the crude material but was not isolated. Data for **6e**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.94 (2H, dq, $J_{2'/6'eq,3'/5'ax}$ = 3.6, $J_{2'/6'ax,3'/5'ax} = J_{3'/5'ax,3'/5'eq}$ = 12.0 Hz, 2 CH, H(3′/5′$_{ax}$)), 2.03 (2H, br d‡, $J_{2'/6'eq,3'/5'eq} = J_{3'/5'ax,3'/5'eq}$ = 12.0 Hz, 2 CH, H(3′/5′$_{eq}$)), 2.73 (1H, m, CH, H(4′)), 2.95 (2H, dt, $J_{2'/6'ax,3'/5'eq}$ = 2.4, $J_{2'/6'ax,2'/6'eq} = J_{2'/6'ax,3'/5'ax}$ = 12.0 Hz, 2 CH, H(2′/6′$_{ax}$)), 3.96, (2H, br d‡, $J_{2'/6'eq,3'/5'eq} = J_{2'/6'eq,2'/6'ax}$ = 12.0 Hz, 2 CH, H(2′/6′$_{eq}$)), 7.06 (1H, d, J = 2.4 Hz, H5), 7.23 (1H, tt, J = 1.8, 7.2 Hz, H4″), 7.26−7.29 (3H, m, H3, H(3″/5″), 7.34 (2H, tt, J = 1.8, 7.2 Hz, H(2″/6″), 7.55 (1H, dd, J = 3.0, 9.6 Hz, H7), 7.89 (1H, d, J = 9.6 Hz, H8), 7.93 (1H, d, J = 8.4 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.1 (C3/5′), 42.4 (C4′), 50.2 (C2′/6′), 109.0 (C5), 122.4 (C3), 123.7 (C7), 126.4 (C4″), 126.8 (C3″/5″), 128.2 (C4a), 128.6 (C2″/6″), 129.1 (C8), 137.4 (C4), 143.0 (C8a), 145.7 (C1″), 147.4 (C2), 150.0 (C6); IR (Nujol mull) ν/cm^{-1} 1618, 1574, and 1500; MS (EI) m/z 324 ($M^{\bullet+}$ [^{37}Cl], 35), 322 ($M^{\bullet+}$ [^{35}Cl], 100), 266 (20), 217 (50), 189 (40). Anal. Calcd for $C_{20}H_{19}ClN_2$: C, 74.41; H, 5.93; N, 8.68. Found: C, 74.57; H, 5.94; N, 8.62.

Synthesis Method ii. Using general procedure 2, the title compound was obtained in 80% yield as determined by ^{1}H NMR analysis. Data are as above.

Synthesis Method iii. Using general procedure 4, **7** (45 mg, 0.19 mmol) and **e** (37 mg, 0.23 mmol) were combined in (trifluoromethyl)benzene (2 mL). $Pd(OAc)_2$ (0.2 mg, 1.0 μmol), **16** (0.8 mg, 2.1 μmol), and NaO^{t}Bu (22 mg, 0.23 mmol) were added, and then the vessel was evacuated, backfilled with nitrogen, and sealed. The mixture was heated at 150 °C at 300 W in a Discover system for 17 min (including a 1 min ramp time). Chromatographic separation eluting with CH_2Cl_2/ethanol (48:1) afforded the title compound as a cream solid (30 mg, 50%). Data are as above.

2-Chloro-6-(4-benzylpiperidin-1-yl)quinoline (6f). Synthesis Method i. Using general procedure 1, **7** (600 mg, 2.47 mmol) and 4-benzylpiperidine (**f**; 530 μL, 2.98 mmol) were added to a mixture of $Pd(OAc)_2$ (2.8 mg, 12.4 μmol), **16** (8.9 mg, 24.7 μmol), and KO^{t}Bu (335 mg, 2.99 mmol) in toluene (5 mL), and the reaction was heated for 16 h. Extraction with chloroform/2-propanol (3:1) and chromatographic separation eluting with CH_2Cl_2/hexane (4:1) afforded the title compound as a 6:1 mixture with 2-*tert*-butoxy-6-(4-benzylpiperidin-1-yl)quinoline (**17f**) (yellow solid; combined yield 390 mg; **6f**, 40%; **17f**, 7%). An analytical sample of **6f** was obtained by recrystallization from hexane, mp 114−117 °C: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.44 (2H, dq, $J_{2'/6'eq,3'/5'ax}$ = 4.2, $J_{2'/6'ax,3'/5'ax} = J_{3'/5'ax,3'/5'eq}$ = 12.6 Hz, 2 CH, H(3′/5′$_{ax}$)), 1.74 (1H, m, CH, H(4′)), 1.80 (2H, br d‡, $J_{2'/6'eq,3'/5'eq} = J_{3'/5'ax,3'/5'eq}$ = 12.6 Hz, 2 CH, H(3′/5′$_{eq}$)), 2.60 (2H, d, J = 7.2 Hz, CH_2), 2.77 (2H, dt, $J_{2'/6'ax,3'/5'eq}$ = 4.2, $J_{2'/6'ax,2'6'eq} = J_{2'/6'ax,3'/5'ax}$ = 12.6 Hz, 2 CH, H(2′/6′$_{ax}$)), 3.80, (2H, br d‡, $J_{2'/6'eq,3'/5'eq} = J_{2'/6'eq,2'/6'ax}$ = 12.0 Hz, 2 CH, H(2′/6′$_{eq}$)), 6.98 (1H, d, J = 3.0 Hz, H5), 7.18 (2H, d, J = 7.8 Hz, H(2″/6″)), 7.22 (1H, t, J = 7.2 Hz, H4″), 7.26 (1H, d, J = 8.4 Hz, H3), 7.31 (2H, t, J = 7.8 Hz, H(3″/5″)), 7.48 (1H, dd, J = 3.0, 9.6 Hz, H7), 7.85 (1H, d, J = 9.6 Hz, H8), 7.90 (1H, d, J = 8.4 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.7 (C4′), 31.8 (C3′/5′), 43.1 (CH_2) 49.7 (C2′/6′), 108.8 (C5), 122.3 (C3), 123.6 (C7), 126.0 (C4″), 128.2 (C4a), 128.3 (C3″/5″), 129.0 (C8), 129.1 (C2″/6″), 137.4 (C4), 140.3 (C1″), 142.9 (C8a), 147.2 (C2), 150.4 (C6); IR (Nujol mull) ν/cm^{-1} 3330, 1653, 1558, and 1505; MS (EI) m/z 338 ($M^{\bullet+}$ [^{37}Cl], 30), 336 ($M^{\bullet+}$ [^{35}Cl], 100), 302 (20), 162 (16); HRMS (EI$^+$) m/z found 336.1388, $C_{21}H_{21}{}^{35}ClN_2$ requires 336.1393. Anal. Calcd for $C_{21}H_{21}ClN_2$: C, 74.88; H, 6.28; N, 8.32. Found: C, 75.05; H, 6.59; N, 8.08. Data for **17f**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.47 (2H, dq, $J_{2'/6'eq,3'/5'ax}$ = 4.2, $J_{2'/6'ax,3'/5'ax} = J_{3'/5'ax,3'/5'eq}$ = 12.6 Hz, 2 CH, H(3′/5′$_{ax}$)), 1.72 (1H, m, CH, H(4′)), 1.80 (2H, br d‡, $J_{2'/6'eq,3'/5'eq} = J_{3'/5'ax,3'/5'eq}$ = 12.6 Hz, 2 CH, H(3′/5′$_{eq}$)), 2.60 (2H, d, J = 7.2 Hz, CH_2), 2.68 (2H, dt, $J_{2'/6'ax,3'/5'eq}$ = 4.2, $J_{2'/6'ax,2'/6'eq} = J_{2'/6'ax,3'/5'ax}$ = 12.6 Hz, 2 CH, H(2′/6′$_{ax}$)), 3.69, (2H, br d‡, $J_{2'/6'eq,3'/5'eq} = J_{2'/6'eq,2'/6'ax}$ = 12.6 Hz, 2 CH, H(2′/6′$_{eq}$)), 6.72 (1H, d, J = 8.4 Hz, H3), 6.99 (1H, d, J = 3.0 Hz, H5), 7.18 (2H, d, J = 7.8 Hz, H(2″/6″)), 7.22 (1H, t, J = 7.2 Hz, H4″), 7.31 (2H, t, J = 7.8 Hz, H(3″/5″)), 7.36 (1H, dd, J = 3.0, 9.6 Hz, H7), 7.67 (1H, d, J = 9.6 Hz, H8), 7.77 (1H, d, J = 8.4 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.7 (C4′), 30.9 (CH_3), 32.1 (C3′/5′), 43.1 (CH_2), 50.9 (C2′/6′), 80.0 ($(CH_3)_3C$), 110.9 (C5), 115.0 (C3), 123.6 (C7), 125.0 (C4a), 125.9 (C4″), 128.0 (C8), 128.1 (C3″/5″), 129.1 (C2″/6″), 137.1 (C4), 140.5 (C1″), 141.5 (C8a), 147.5 (C6), 161.2 (C2); MS (EI) m/z 374 ($M^{\bullet+}$, 7), 318 (100), 144 (30).

Synthesis Method ii. Using general procedure 2, the title compound was obtained in 88% yield as determined by ^{1}H NMR analysis. Data are as above.

Synthesis Method iii. Using general procedure 3, the title compound was obtained in 58% yield as determined by ^{1}H NMR analysis. Data are as above.

Synthesis Method iv. Using general procedure 4, **7** (45 mg, 0.19 mmol) and **f** (41 μL, 0.23 mmol) were combined in (trifluoromethyl)benzene (2 mL). $Pd(OAc)_2$ (0.2 mg, 1.0 μmol), **16** (0.8 mg, 2.1 μmol), and NaO^{t}Bu (22 mg, 0.23 mmol) were added, and then the vessel was evacuated, backfilled with nitrogen, and sealed. The mixture was heated at 150 °C at 300 W in a Discover system for

20 min (including a 1 min ramp time). Chromatographic separation eluting with CH_2Cl_2 afforded the title compound as a yellow solid (50 mg, 78%). Data are as above.

Methyl 1-(2-Chloroquinolin-6-yl)piperidine-4-carboxylate (6g). Using general procedure 1, **7** (509 mg, 2.10 mmol) and methyl isonipecotate (**g**; 361 mg, 2.52 mmol) were added to a mixture of $Pd(OAc)_2$ (2.3 mg, 10.5 μmol), **16** (7.5 mg, 21.0 μmol), and KO^{t}Bu (283 mg, 2.52 mmol) in toluene (2 mL). The reaction mixture was heated for 22 h. Extraction with chloroform/2-propanol (3:1) and chromatographic separation on C18 silica eluting with water/methanol (1:1) afforded 6-bromo-2-methoxyquinoline (**20**), mp 96−98 °C (lit.[37] mp 98 °C) (200 mg, 40%). The title compound was isolated as an impure mixture with methyl 1-(2-methoxyquinolin-6-yl)piperidine-4-carboxylate (**21**) (combined yield 20 mg; **6g**, 1%; **21**, 2%). Data for **6g**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.94 (2H, m, 2 CH, H(3′/5′$_{ax}$)), 2.07 (2H, m, 2 CH, H(3′/5′$_{eq}$)), 2.53 (2H, m, CH, H(4′)), 2.93 (2H, dt, $J_{2'/6'ax,3'5'eq} = 3.0$, $J_{2'/6'ax,2'6'eq} = J_{2'/6'ax,3'5'ax} = 12.6$ Hz, 2 CH, H(2′/6′$_{ax}$)), 3.77, (2H, m, 2 CH, H(2′/6′$_{eq}$)), 4.03 (3H, s, OCH_3), 7.01 (1H, d, $J = 3.0$ Hz, H5), 7.27 (1H, d, $J = 9.0$ Hz, H3), 7.49 (1H, dd, $J = 3.0$, 9.6 Hz, H7), 7.87 (1H, d, $J = 9.0$ Hz, H8), 7.91 (1H, d, $J = 8.4$ Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.9 (C3′/5′), 40.8 (C4′), 48.9 (C2′/6′), 109.2 (C5), 122.4 (C3), 123.7 (C7), 128.1 (C4a), 129.2 (C8), 137.4 (C4), 143.1 (C8a), 147.5 (C2), 149.7 (C6); IR (Nujol mull) ν/cm^{-1} 3310, 1694, 1602, and 1503; MS (EI) *m*/*z* 306 (M$^{\bullet+}$ [^{37}Cl], 100), 304 (M$^{\bullet+}$ [^{35}Cl], 30), 269 (25); HRMS (EI$^+$) *m*/*z* found 304.0974, $C_{16}H_{17}{}^{35}ClN_2O_2$ requires 304.0978. Data for **20**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.06 (3H, s, OCH_3), 6.91 (1H, d, $J = 8.7$ Hz, H3), 7.67 (1H, dd, $J = 2.1$, 8.7 Hz, H7), 7.72 (1H, d, $J = 8.7$ Hz, H8), 7.85 (1H, d, $J = 2.1$ Hz, H5), 7.87 (1H, d, $J = 8.7$ Hz, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.5 (OCH_3), 114.1 (C3), 117.1 (C6), 126.3 (C4a), 129.0 (C8), 129.5 (C5), 132.7 (C7), 137.6(C4), 145.3 (C8a), 162.6 (C2); IR (Nujol mull) ν/cm^{-1} 1614, 1597, and 1567. Data for **21:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.94 (2H, m, 2 CH, H(3′/5′$_{ax}$)), 2.07 (2H, m, 2 CH, H(3′/5′$_{eq}$)), 2.48 (2H, m, CH, H(4′)), 2.84 (2H, dt, $J_{2'/6'ax,3'5'eq} = 3.0$, $J_{2'/6'ax,2'6'eq} = J_{2'/6'ax,3'5'ax} = 12.6$ Hz, 2 CH, H(2′/6′$_{ax}$)), 3.70, (2H, m, 2 CH, H(2′/6′$_{eq}$)), 4.03 (3H, s, OCH_3), 6.83 (1H, d, $J = 8.4$ Hz, H3), 7.04 (1H, d, $J = 2.4$ Hz, H5), 7.40 (1H, dd, $J = 2.4$, 9.6 Hz, H7), 7.73 (1H, d, $J = 9.6$ Hz, H8), 7.84 (1H, d, $J = 8.4$ Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.2 (C3′/5′), 40.9 (C4′), 49.9 (C2′/6′), 53.2 (OCH_3), 111.2 (C5), 113.0 (C3), 123.7 (C7), 125.7 (C4a), 128.1 (C8), 137.8 (C4), 143.1 (C8a), 148.1 (C6), 161.2 (C2), 175.0 (C═O); MS (EI) *m*/*z* 300 (M$^{\bullet+}$,100), 285 (20), 269 (9); HRMS (EI$^+$) *m*/*z* found 300.1471, $C_{17}H_{20}N_2O_3$ requires 300.1474.

2-Chloro-6-(4-methylpiperazin-1-yl)quinoline (6h). Synthesis Method i. Using general procedure 1, **7** (601 mg, 2.47 mmol) and 1-methylpiperazine (**h**; 330 μL, 2.96 mmol) were added to a mixture of $Pd(OAc)_2$ (2.8 mg, 12.5 μmol), **16** (8.8 mg, 24.7 μmol), and KO^{t}Bu (334 mg, 2.96 mmol) in toluene (2 mL). The reaction mixture was heated for 20 h. Extraction with chloroform/2-propanol (3:1) and chromatographic separation eluting with CH_2Cl_2 afforded the title compound as a 6:1 mixture with **7** (combined yield 241 mg; **6h**, 32%; **7**, 5%). Data for **6h**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.40 (3H, s, CH_3), 2.65 (4H, br t, $J = 4.8$ Hz, 2 CH_2, H(3′/5′)), 3.36 (4H, br t, $J = 4.8$ Hz, 2 CH_2, H(2′/6′)), 7.01 (1H, d, $J = 3.0$ Hz, H5), 7.29 (1H, d, $J = 9.0$ Hz, H3), 7.49 (1H, dd, $J = 3.0$, 9.0 Hz, H7), 7.88 (1H, d, $J = 9.0$ Hz, H8), 7.92 (1H, d, $J = 9.0$ Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 46.0 (CH_3), 48.8 (C2′/C6′), 54.8 (C3′/5′), 108.9 (C5), 123.1 (C3), 123.3 (C7), 128.0 (C4a), 129.2 (C8), 137.8 (C4), 143.2 (C8a), 147.6 (C2), 149.5 (C6); IR (Nujol mull) ν/cm^{-1} 3150, 1654, 1616, 1600, and 1578; MS (EI) *m*/*z* 263 (M$^{\bullet+}$ [^{37}Cl], 7), 261 (M$^{\bullet+}$ [^{35}Cl], 20), 245 (30), 243 (100), 241 (70), 208 (50), 208 (50); HRMS (EI$^+$) *m*/*z* found 261.1042, $C_{14}H_{16}{}^{35}ClN_3$ requires 261.1033.

Synthesis Method ii. Using general procedure 2, the title compound was obtained in 80% yield as determined by ^{1}H NMR analysis. Data are as above.

Synthesis Method iii. Using general procedure 3, the title compound was obtained in 78% yield as determined by ^{1}H NMR analysis. Data are as above.

Synthesis Method iv. Using general procedure 4, **7** (45 mg, 0.19 mmol) and **h** (26 μL, 0.23 mmol) were combined in (trifluoromethyl)benzene (2 mL). $Pd(OAc)_2$ (0.2 mg, 1.0 μmol), **16** (0.8 mg, 2.1 μmol), and NaO^{t}Bu (22 mg, 0.23 mmol) were added, and then the vessel was evacuated, backfilled with nitrogen, and sealed. The mixture was heated at 150 °C at 300 W in a Discover system for 20 min (including a 1 min ramp time). Chromatographic separation eluting with CH_2Cl_2/ethanol (49:1) afforded the title compound as a yellow solid (26 mg, 50%). Data are as above.

2-Chloro-6-(4-ethylpiperazin-1-yl)quinoline (6i). Using general procedure 1, **7** (502 mg, 2.06 mmol) and 1-ethylpiperazine (**i**; 314 μL, 2.47 mmol) were added to a mixture of $Pd(OAc)_2$ (2.3 mg, 10.3 μmol), **16** (7.4 mg, 20.6 μmol), and KO^{t}Bu (279 mg, 2.47 mmol) in toluene (2 mL). The reaction mixture was heated for 20 h. Extraction with ethyl acetate and chromatographic separation eluting with CH_2Cl_2/hexane (4:1) afforded the title compound as a 2.5:1 mixture with 6-bromo-2-(4-ethylpiperazin-1-yl)quinoline (**8i**) (combined yield 480 mg; **6i**, 58%; **8i**, 30%). Pure **8i** was also isolated, mp 140−144 °C (40 mg, 7%), along with 2-*tert*-butoxy-6-(4-ethylpiperazin-1-yl)quinoline (**17i**), mp 107−109 °C (63 mg, 10%). Data for **6i**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.16 (3H, t, $J = 7.2$ Hz, CH_3), 2.52 (2H, m, CH_2), 2.67 (4H, br t, $J = 4.8$ Hz, 2 CH_2, H(3′/5′)), 3.36 (4H, br t, $J = 4.8$ Hz, 2 CH_2, H(2′/6′)), 7.00 (1H, d, $J = 3.0$ Hz, H5), 7.27 (1H, d, $J = 9.0$ Hz, H3), 7.49 (1H, dd, $J = 2.4$, 9.0 Hz, H7), 7.87 (1H, d, $J = 9.0$ Hz, H8), 7.92 (1H, d, $J = 9.0$ Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.9 (CH_3), 48.8 (C2′/C6′), 52.4 (CH_2), 52.6 (C3′/5′), 108.7 (C5), 122.4 (C3), 123.0 (C7), 128.2 (C4a), 129.2 (C8), 137.1 (C4), 143.1 (C8a), 147.5 (C2), 149.6 (C6); IR (Nujol mull) ν/cm^{-1} 1650, 1618, 1600, 1582, and 1500; MS (EI) *m*/*z* 277 (M$^{+\cdot}$ [^{37}Cl], 30), 275 (M$^{\bullet+}$ [^{35}Cl], 85), 262 (20), 260 (60), 192 (15), 190 (35), 97 (40), 84 (100); HRMS (EI$^+$) *m*/*z* found 275.1186, $C_{15}H_{18}{}^{35}ClN_3$ requires 275.1189. Data for **8i**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.16 (3H, t, $J = 7.2$ Hz, CH_3), 2.52 (2H, m, CH_2), 2.59 (4H, br t, $J = 4.8$ Hz, 2 CH_2, H(3′/5′)), 3.80 (4H, br t, $J = 4.8$ Hz, 2 CH_2, H(2′/6′)), 6.97 (1H, d, $J = 9.3$ Hz, H3), 7.57 (1H, d, $J = 9.0$ Hz, H8), 7.57 (1H, dd, $J = 1.8$, 9.0 Hz, H7), 7.71 (1H, d, $J = 1.8$ Hz, H5), 7.80 (1H, d, $J = 9.3$ Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.9 (CH_3), 45.0 (C2′/C6′), 52.3 (CH_2) 54.5 (C3′/5′), 110.7 (C3), 115.2 (C6), 124.2 (C4a), 128.3 (C5), 129.1 (C8), 132.6 (C7), 137.1 (C4), 146.6 (C8a), 157.3 (C2); IR (Nujol mull) ν/cm^{-1} 1617, 1597, and 1542. MS (EI) *m*/*z* 321 (M$^{\bullet+}$ [^{81}Br], 100), 319 (M$^{\bullet+}$ [^{79}Br], 100), 306 (13), 304 (13); HRMS (EI$^+$) *m*/*z* found 319.0689, $C_{15}H_{18}{}^{79}BrN_3$ requires 319.0684. Data for **17i**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.16 (3H, t, $J = 7.2$ Hz, CH_3), 1.68 (9H, s, ^{t}Bu), 2.49 (2H, q, $J = 7.2$ Hz, CH_2), 2.67 (4H, t, $J = 4.8$ Hz, 2 CH_2, H(3′/5′)), 3.28 (4H, t, $J = 4.8$ Hz, 2 CH_2, H(2′/6′)), 6.75 (1H, d, $J = 8.8$ Hz, H3), 7.01 (1H, d, $J = 2.8$ Hz, H5), 7.37 (1H, dd, $J = 2.8$, 9.0 Hz, H7), 7.70 (1H, d, $J = 9.0$ Hz, H8), 7.80(1H, d, $J = 8.8$ Hz, H4); MS (EI) *m*/*z* 313 (40), 257 (100), 242 (60), 173 (20), 84 (65), 57 (45).

2-Chloro-6-(4-phenylpiperazin-1-yl)quinoline (6j). Synthesis Method i. Using general procedure 1, **7** (501 mg, 2.06 mmol) and 1-phenylpiperazine (**j**; 375 μL, 2.47 mmol) were added to a mixture of $Pd(OAc)_2$ (2.3 mg, 10.3 μmol), **16** (7.4 mg, 20.6 μmol), and KO^{t}Bu (279 mg, 2.47 mmol) in toluene (2 mL). The reaction mixture was heated for 20 h. Extraction with ethyl acetate and chromatographic separation eluting with CH_2Cl_2/hexane (4:1) afforded the title compound as a yellow solid, mp 182−185 °C (yield 290 mg, 44%). 6-Bromo-2-(4-phenylpiperazin-1-yl)quinoline (**8j**) was also isolated as a yellow solid, mp 155−159 °C (yield 110 mg, 15%). Data for **6j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (4H, br t, $J = 4.8$ Hz, 2 CH_2, H(3′/5′)), 3.47 (4H, br t, $J = 4.8$ Hz, 2 CH_2, H(2′/6′)), 6.92 (1H, t, $J = 7.2$ Hz, H4″), 7.01 (2H, d, $J =$

(37) Osborne, A. G.; Miller, L. A. D. *J. Chem. Soc., Perkin Trans. 1* **1993**, *2* (19), 81–184.

7.8 Hz, H(2″/6″)), 7.06 (1H, d, J = 2.4 Hz, H5), 7.31 (3H, m, H3, H(3″/5″)), 7.54 (1H, dd, J = 3.0, 9.0 Hz, H7), 7.91 (1H, d, J = 9.0 Hz, H8), 7.85 (1H, d, J = 8.4 Hz, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.2 (C2′/C6′), 49.3 (C3′/5′), 109.1 (C5), 116.4 (C2″/C5″), 120.3 (C4″), 122.5 (C3), 123.2 (C7), 128.0 (C4a), 129.2 (C8), 129.3 (C3″ /C5″), 137.5 (C4), 143.2 (C8a), 147.7 (C2), 149.5 (C1″), 151.0 (C6); IR (Nujol mull) ν/cm^{-1} 1669, 1615, 1600, and 1574; MS (EI) m/z 325 (M$^{\bullet+}$ [^{37}Cl], 15), 323 (M$^{\bullet+}$ [^{35}Cl], 50), 190 (30), 157 (50), 132 (100), 105 (50), 77 (25); HRMS (EI$^+$) m/z found 323.1185, $C_{19}H_{18}{}^{35}ClN_3$ requires 323.1189. Anal. Calcd for $C_{19}H_{18}ClN_3$: C, 70.47; H, 5.60; N, 12.98. Found: C, 70.37; H, 5.77; N, 12.62. Data for **8j**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.46 (4H, br t, J = 4.8 Hz, 2 CH_2, H(3′/5′)), 3.93 (4H, br t, J = 4.8 Hz, 2 CH_2, H(2′/6′)), 6.92 (1H, t, J = 7.2 Hz, H4″), 7.01 (2H, d, J = 8.1 Hz, H(2″/6″)), 7.06 (1H, d, J = 9.3 Hz, H3), 7.32 (2H, t, J = 8.1 Hz, H(3″/5″)), 7.62 (2H, br s, H7, H8), 7.76 (1H, br s, H5), 7.82 (1H, d, J = 9.3 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 45.2 (C2′/C6′), 49.4 (C3′/5′), 110.5 (C3), 115.4 (C6), 116.5 (C2″/C6″), 120.3 (C4″), 124.4 (C4a), 128.5 (C5), 129.2 (C8), 129.4 (C3″/C5″), 132.9 (C7), 136.7 (C4), 146.7 (C8a), 151.3 (C1″), 157.4 (C2); IR (Nujol mull) ν/cm^{-1} 1608, 1594, and 1545; MS (EI) 369 (M$^{\bullet+}$ [^{81}Br], 10), 367 (M$^{\bullet+}$ [^{79}Br], 10), 235 (100), 145 (20), 132 (30), 104 (25), 77 (20); HRMS (EI$^+$) m/z found 367.0677, $C_{19}H_{18}{}^{79}BrN_3$ requires 367.0684.

Synthesis Method ii. Using general procedure 2, the title compound was obtained in 91% yield as determined by ^{1}H NMR analysis. Data are as above.

Synthesis Method iii. Using general procedure 3, the title compound was obtained in 9% yield as determined by ^{1}H NMR analysis. Data are as above.

6-(4-Benzylpiperazin-1-yl)-2-chloroquinoline (6k). Synthesis Method i. Using general procedure 1, **7** (500 mg, 2.06 mmol) and 1-benzylpiperazine (**k**; 428 μL, 2.47 mmol) were added to a mixture of $Pd(OAc)_2$ (2.3 mg, 10.3 μmol), **16** (7.4 mg, 20.6 μmol), and KO^{t}Bu (277 mg, 2.47 mmol) in toluene (3 mL). The reaction mixture was heated for 20 h. Extraction with ethyl acetate and chromatographic separation eluting with CH_2Cl_2 afforded the title compound as a 2.5:1 mixture with 2-(4-benzylpiperazin-1-yl)-6-bromoquinoline (**8k**) (combined yield 260 mg; **6k**, 26%; **8k**, 11%). 2-*tert*-Butoxy-6-(4-benzylpiperazin-1-yl)quinoline (**17k**) was also isolated as a dark yellow solid, mp 127−131 °C (50 mg, 6%). Data for **6k**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.66 (4H, br t, J = 4.8 Hz, 2 CH_2, H(3′/5′)), 3.32 (4H, br t, J = 4.8 Hz, 2 CH_2, H(2′/6′)), 3.60 (2H, s, CH_2), 6.96 (1H, d, J = 2.4 Hz, H5), 7.25 (1H, d, J = 9.0 Hz, H3), 7.38 (5H, m, Ph), 7.42 (1H, dd, J = 2.4, 9.0 Hz, H7), 7.85 (1H, d, J = 9.0 Hz, H8), 7.92 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 48.8 (C2′/C6′), 52.8 (C3′/5′), 62.9 (CH_2), 108.7 (C5), 122.3 (C3), 123.0 (C7), 127.2 (C4″), 128.0 (C4a), 128.3 (C3″/C5″), 129.1 (C2″/C6″), 129.2 (C8), 137.4 (C4), 137.6 (C1″), 143.0 (C8a), 147.4 (C2), 149.6 (C6); IR (Nujol mull) ν/cm^{-1} 1650, 1615, 1576, and 1503; MS (EI) m/z 339 (M$^{\bullet+}$ [^{37}Cl], 30), 337 (M$^{\bullet+}$ [^{35}Cl], 90), 193 (25), 191 (70), 119 (20), 91 (100); HRMS (EI$^+$) m/z found 337.1345, $C_{20}H_{20}{}^{35}ClN_3$ requires 337.1346. Data for **8k**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.58 (4H, br t, J = 4.8 Hz, 2 CH_2, H(3′/5′)), 3.58 (2H, s, CH_2), 3.75 (4H, br t, J = 4.8 Hz, 2 CH_2, H(2′/6′)), 6.93 (1H, d, J = 9.0 Hz, H3), 7.28 (5H, m, Ph), 7.53 (1H, d, J = 9.0 Hz, H8), 7.55 (1H, dd, J = 2.4, 9.0 Hz, H7), 7.69 (1H, d, J = 2.4 Hz, H5), 7.73 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 44.8 (C2′/C6′), 52.8 (C3′/5′), 62.9 (CH_2), 110.2 (C3), 115.0 (C6), 124.1 (C4a), 127.2 (C4″), 128.3 (C3″/C5″), 129.1 (C5), 129.2 (C2″/C6″), 129.2 (C8), 132.5 (C7), 136.3 (C4), 137.6 (C1″), 146.6 (C8a), 157.3 (C2); MS (EI) 383 (M$^{\bullet+}$ [^{81}Br], 10), 381 (M$^{\bullet+}$ [^{79}Br], 10), 237 (30), 235 (30), 159 (50), 146 (90), 119 (20), 91 (100); HRMS (EI$^+$) m/z found 381.0842, $C_{20}H_{20}{}^{79}BrN_3$ requires 381.08412. Data for **17k**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (9H, s, $C(CH_3)_3$), 2.77 (4H, br s, 2 CH_2, H(3′/5′)), 3.33 (4H, br s, 2 CH_2, H(2′/6′)), 3.70 (2H, s, CH_2), 6.75 (1H, d, J = 9.0 Hz, H3), 7.01 (1H, d, J = 2.4 Hz, H5), 7.31−7.42 (6H, m, H7, Ph), 7.70 (1H, d, J = 9.0 Hz, H8), 7.80 (1H, d, J = 9.0 Hz, H4); IR (Nujol mull) ν/cm^{-1} 1654, 1597, 1560, and 1505.

Synthesis Method ii. Using general procedure 2, the title compound was obtained in 90% yield as determined by ^{1}H NMR analysis. Data are as above.

Synthesis Method iii. Using general procedure 3, the title compound was obtained in 45% yield as determined by ^{1}H NMR analysis. Data are as above.

***tert*-Butyl 4-(2-Chloroquinolin-6-yl)piperazine-1-carboxylate (6l).** Using general procedure 1, **7** (510 mg, 2.10 mmol) and *tert*-butyl piperazine-1-carboxylate (**l**; 472 mg, 2.52 mmol) were added to a mixture of $Pd(OAc)_2$ (2.3 mg, 10.5 μmol), **16** (7.5 mg, 21.0 μmol), and KO^{t}Bu (284 mg, 2.53 mmol) in toluene (3 mL). The reaction mixture was heated for 20 h. Extraction with ethyl acetate and chromatographic separation eluting with CH_2Cl_2 afforded the title compound as a yellow glass (580 mg, 80%). *tert*-Butyl 4-(2-*tert*-butoxyquinolin-6-yl)piperazine-1-carboxylate (**17l**) was also isolated as a brown solid, mp 119−122 °C (52 mg, 7%). Data for **6l**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.50 (9H, s, ^{t}Bu), 3.27 (4H, br t, J = 4.8 Hz, 2 CH_2, H(2′/6′)), 3.64 (4H, br t, J = 4.8 Hz, 2 CH_2, H(3′/5′)), 7.03 (1H, br s, H5), 7.30 (1H, d, J = 9.0 Hz, H3), 7.48 (1H, br d, J = 9.0 Hz, H7), 7.90 (1H, d, J = 9.0 Hz, H8), 7.93 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.4 (C(CH$_3$)$_3$), 43.2 (C3′/5′), 49.2 (C2′/6′), 80.1 (C(CH$_3$)$_3$), 109.6 (C5), 122.5 (C3), 123.4 (C7), 127.9 (C4a), 129.3 (C8), 137.5 (C4), 143.3 (C8a), 147.9 (C2), 149.4 (C6), 154.6 (C═O); IR (Nujol mull) ν/cm^{-1} 3310, 1694, 1602, and 1503; MS (EI) m/z 349 (M$^{\bullet+}$ [^{37}Cl], 15), 347 (M$^{\bullet+}$ [^{35}Cl], 15), 293 (15), 291 (50), 247 (20), 219 (10), 217 (30), 207 (30), 205 (100), 190 (20), 57 (20); HRMS (EI$^+$) m/z found 347.1397, $C_{18}H_{22}ClN_3O_2$ requires 347.1401. Data for **17l**: ^{1}H NMR (600 MHz, DMSO) δ 1.42 (9H, s, ^{t}Bu), 1.62 (9H, s, ^{t}Bu), 3.12 (4H, br t, J = 4.8 Hz, 2 CH_2, H(2′/6′)), 3.48 (4H, br t, J = 4.8 Hz, 2 CH_2, H(3′/5′)), 6.76 (1H, d, J = 9.0 Hz, H3), 7.14 (1H, d, J = 2.4 Hz, H5), 7.43 (1H, dd, J = 2.4, 9.0 Hz, H7), 7.57 (1H, d, J = 9.0 Hz, H8), 7.96 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (150 MHz, DMSO) δ 28.0 (C(CH$_3$)$_3$), 28.3 (C(CH$_3$)$_3$), 43.2 (C3′/5′), 49.0 (C2′/6′), 79.0 (C(CH$_3$)$_3$), 78.9 (C(CH$_3$)$_3$), 110.5 (C5), 114.6 (C3), 122.2 (C7), 124.8 (C4a), 127.4 (C8), 137.7 (C4), 140.6 (C8a), 147.3 (C6), 153.8 (C═O), 159.9 (C2); IR (Nujol mull) ν/cm^{-1} 3295, 1706, 1694, and 1602.

Attempted Synthesis of 2-Chloro-6-(4-(2-hydroxy)ethylpiperazin-1-yl)quinoline (6m). Using general procedure 1, **7** (507 mg, 2.10 mmol) and 1-(2-hydroxyethyl)piperazine (**m**; 310 μL, 2.52 mmol) were added to a mixture of $Pd(OAc)_2$ (2.3 mg, 10.5 μmol), **16** (7.5 mg, 21.0 μmol), and KO^{t}Bu (287 mg, 2.56 mmol) in toluene (2 mL). The reaction mixture was heated for 22 h. Extraction with chloroform/2-propanol (3:1) and chromatographic separation on C18 silica eluting with water/methanol (2:3) did not afford the title compound; however, 6-bromo-2-(4-(2-hydroxy)ethylpiperazin-1-yl)quinoline (**8m**) was obtained, mp 75−80 °C (241 mg, 37%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.58 (4H, br t, J = 4.4 Hz, 2 CH_2, H(3′/5′)), 2.84 (2H, t, J = 6.0 Hz, CH_2N), 2.93 (4H, br t, J = 4.4 Hz, 2 CH_2, H(2′/6′)), 4.62 (2H, t, J = 6.0 Hz, CH_2OH), 6.94 (1H, d, J = 8.7 Hz, H3), 7.68 (2H, br s, H7, H8), 7.86 (1H, br s, H5), 7.88 (1H, d, J = 8.7 Hz, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.8 (C2′/C6′), 52.4 (C3′/5′), 53.1 (2 CH_2), 57.2 (CH_2N), 63.3 (CH_2OH), 114.4 (C3), 117.4 (C6), 126.4 (C4a), 129.1 (C5), 129.6 (C8), 132.9 (C7), 137.9 (C4), 145.2 (C8a), 162.1 (C2); IR (Nujol mull) ν/cm^{-1} 3455, 3379, 3236, 1659, 1613, 1597, and 1567; MS (EI) m/z 225 ([^{81}Br], 20), 223 ([^{79}Br], 20), 210 (20), 208 (20), 140 (20), 127 (40), 112, (100), 99 (80), 84 (30), 70 (100), 56 (60), 42 (20); HRMS (EI$^+$) m/z found 336.0714, $C_{15}H_{18}{}^{79}BrN_3O$ + H requires 336.0706.

6-(4-Methylpiperidin-1-yl)quinolin-2-amine (5a). Synthesis Method i. Using general procedure 5, impure **6a** (290 mg, 0.93 mmol) was treated with acetamide (1.31 g, 22.2 mmol) and potassium carbonate (760 mg, 5.55 mmol) for 2 h. Extraction with chloroform/2-propanol (3:1) and chromatographic separation eluting with ethanol/CH_2Cl_2 (1:19) afforded the title compound as a pale orange solid, mp 166−174 °C (90 mg, 40%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.99

(3H, d, J = 6.6 Hz, CH_3), 1.41 (2H, dq, $J_{2'/6'eq,3'5'ax}$ = 2.4 Hz, $J_{2'/6'ax,3'5'ax} = J_{3'/5'ax,3'5'eq} = J_{3'5'ax,4'}$ = 12.6 Hz, 2 CH, H(3′/5′$_{ax}$)), 1.52 (1H, m, CH, H4′), 1.78 (2H, m, Hz, 2 CH, H(3′/5′$_{eq}$)), 2.71 (2H, dt, $J_{2'/6'ax,3'5'eq}$ = 2.4, $J_{2'/6'ax,2'6'eq} = J_{2'/6'ax,3'5'ax}$ = 12.6 Hz, 2 CH, H(2′/6′$_{ax}$)), 3.66, (2H, br d[‡], $J_{2'/6'ax,2'6'eq} = J_{2'/6'eq,3'5'eq}$ =12.6 Hz, 2 CH, H(2′/6′$_{eq}$)), 4.66 (2H, br s, NH_2), 6.67 (1H, d, J = 8.7 Hz, H3), 6.97 (1H, d, J = 2.4 Hz, H5), 7.38 (1H, dd, J = 2.4, 9.0 Hz, H7), 7.58 (1H, d, J = 9.0 Hz, H8), 7.76 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.9 (CH_3), 30.7 (C4′), 34.2 (C3′/5′), 50.8 (C2′/6′), 111.1 (C5), 111.6 (C3), 123.6 (C7), 124.2 (C4a), 126.4 (C8), 137.3 (C4), 142.2 (C8a), 147.8 (C6), 155.2 (C2); IR (Nujol mull) ν/cm^{-1} 3441, 3295, 3105, 2354, 1645, 1600, 1557, and 1505; MS (EI) m/z 241 (M$^{\bullet+}$ 100), 171 (40); HRMS (EI$^+$) found 241.1572, $C_{15}H_{19}N_3$ requires 241.1579. **5a** was converted to the corresponding maleate salt, mp 190−200 °C, using general procedure 7 for the purpose of obtaining an elemental analysis. Anal. Calcd for $C_{19}H_{23}N_3O_4 \cdot 0.5H_2O$: C, 62.28; H, 6.60; N, 11.47. Found: C, 62.32; H, 6.58; N, 11.39.

Synthesis Method ii. Using general procedure 6, $Pd_2(dba)_3$ (1.9 mg, 2.1 μmol), **9** (1.0 mg, 2.5 μmol), and **6a** (55 mg, 0.21 mmol) were combined in 1,4-dioxane (1 mL). LHMDS solution (1.0 M in THF, 460 μL) was added, and then the reaction was heated for 22 h. Workup afforded the title compound (49 mg, 97%). Data are as above.

6-(Pyrrolidin-1-yl)quinolin-2-amine (5b). Using general procedure **6b** (160 mg, 0.66 mmol) was treated with acetamide (3.34 g, 56.60 mmol) (note the deviation in the amount of acetamide used in this reaction) and potassium carbonate (477 mg, 3.45 mmol) for 1.5 h. Extraction with ethyl acetate and chromatographic separation eluting with ethanol/CH_2Cl_2 (1:9) afforded the title compound as a yellow solid (79 mg, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04 (4H, t, J = 6.6 Hz, 2 CH_2, H(3′/4′)), 3.32 (4H, t, J = 6.6 Hz, 2 CH_2, H(2′/5′)), 6.42 (2H, br s, NH_2), 6.56 (1H, d, J = 2.4 Hz, H5), 6.88 (1H, d, J = 9.0 Hz, H3), 7.02 (1H, dd, J = 2.4, 9.0 Hz, H7), 7.58 (1H, d, J = 9.0 Hz, H8), 7.82 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.78 (C3′/4′), 48.1 (C2′/5′), 105.8 (C5), 112.5 (C3), 119.3 (C7), 122.5 (C4a), 124.1 (C8), 133.3 (C4), 139.7 (8a), 145.2 (C6), 153.3 (C2); IR (Nujol mull) ν/cm^{-1} 3392, 1673, 1618, and 1523; MS (EI) m/z 213 (M$^{\bullet+}$, 100), 170 (20), 157 (20), 143 (20), 87 (20), 71 (20), 57 (30), 47 (30); HRMS (EI$^+$) m/z found 213.1260, $C_{13}H_{15}N_3$ requires 213.1266. This compound decomposed at room temperature and was therefore unable to be assayed for binding to the Tec SH3 domain by NMR chemical shift perturbation analysis utilizing (^{1}H, ^{15}N) HSQC experiments with uniformly ^{15}N-labeled SH3 protein.

6-Morpholinoquinolin-2-amine (5c). Synthesis Method i. Using general procedure 5, **6c** (370 mg, 1.49 mmol) was treated with acetamide (1.76 g, 29.8 mmol) and potassium carbonate (1.03 g, 7.4 mmol) for 2.5 h. Extraction with ethyl acetate and chromatographic separation eluting with ethanol/CH_2Cl_2 (1:9) afforded the title compound as a pale orange solid, mp 224−228 °C (111 mg, 32%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.20 (4H, t, J = 4.8 Hz, 2 CH_2, H(2′/6′)), 3.90 (4H, t, J = 4.8 Hz, 2 CH_2, H(3′/5′)), 5.46 (2H, br s, NH_2), 6.71 (1H, d, J = 9.0 Hz, H3), 6.97 (1H, d, J = 2.4 Hz, H5), 7.33 (1H, dd, J = 2.4, 9.0 Hz, H7), 7.61 (1H, d, J = 9.0 Hz, H8), 7.80 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.2 (C2′/6′), 66.9 (C3′/5′), 110.8 (C5), 112.1 (C3), 122.5 (C7), 124.0 (C4a), 126.1 (C8), 137.7 (C4), 141.7 (C8a), 147.1 (C6), 155.4 (C2); IR (Nujol mull) ν/cm^{-1} 3379, 3300, 3154, 1661, 1603, and 1567; MS (EI) m/z 229 (M$^{\bullet+}$, 60), 171 (100); HRMS (EI$^+$) m/z found 229.1208, $C_{13}H_{15}N_3O$ requires 229.1215. **5c** was converted to the corresponding maleate salt, mp 194−200 °C, using general procedure 7 for the purpose of obtaining an elemental analysis. Anal. Calcd for $C_{17}H_{19}N_3O_5 \cdot 0.5H_2O$: C, 57.62; H, 5.69; N, 11.86. Found: C, 57.47; H, 5.39; N, 11.66.

Synthesis Method ii. Using general proceedure 6, $Pd_2(dba)_3$ (1.9 mg, 2.1 μmol), **9** (1.0 mg, 2.5 μmol) and **6c** (52 mg, 0.21 mmol) were combined in 1,4-dioxane (3 mL). LHMDS solution (1.0 M in THF, 460 μL) was added, and then the reaction was heated for 22 h. Workup afforded the title compound (47 mg, 98%). Data are as above.

6-(Piperidin-1-yl)quinolin-2-amine (5d). Using general procedure 5, **6d** (300 mg, 1.2 mmol) was treated with acetamide (1.42 g, 24.0 mmol) and potassium carbonate (830 mg, 6.0 mmol) for 1.5 h. Extraction with ethyl acetate and chromatographic separation eluting with ethyl acetate/CH_2Cl_2 (2:3) afforded the title compound as a pale brown solid, mp 120−122 °C (175 mg, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (2H, br d,[‡] J = 4.8 Hz, CH_2, H4′), 1.72 (4H, br d[‡], J = 4.8 Hz, 2 CH_2, H(3′/5′)), 3.16 (4H, br t, J = 4.8 Hz, 2 CH_2, H (2′/6′)), 5.82 (2H, br s, NH_2), 6.83 (1H, d, J = 8.7 Hz, H3), 6.97 (1H, d, J = 2.7 Hz, H5), 7.38 (1H, dd, J = 2.7, 9.0 Hz, H7), 7.60 (1H, d, J = 9.0 Hz, H8), 7.82 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7 (C4′), 29.6 (C3′/5′), 51.0 (C2′/6′), 111.4 (C5), 113.1 (C3), 120.8 (C8), 122.6 (C4a), 124.1 (C7), 134.3 (C8a), 139.7 (C4), 148.9 (C6), 154.2 (C2); IR (Nujol mull) ν/cm^{-1} 3400, 3210, 1685, and 1618; MS (EI) m/z 227 (M$^{\bullet+}$, 100), 171 (50), 143 (30), 116 (20); HRMS (EI$^+$) m/z found 227.1428, $C_{14}H_{17}N_3$ requires 227.1422.

6-(4-Phenylpiperidin-1-yl)quinolin-2-amine (5e). Using general procedure 5, **6e** (132 mg, 0.41 mmol) was treated with acetamide (486 mg, 8.23 mmol) and potassium carbonate (283 mg, 2.05 mmol) for 2 h. Extraction with chloroform/2-propanol (3:1) and chromatographic separation eluting with ethanol/CH_2Cl_2 (1:19) afforded the title compound as a pale yellow powder, mp 187−194 °C (50 mg, 40%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.95 (2H, dq, $J_{2'/6'eq,3'5'ax}$ = 3.0, $J_{2'/6'ax,3'5'ax} = J_{3'/5'ax,3'5'eq}$ = 12.0 Hz, 2 CH, H(3′/5′$_{ax}$)), 2.01 (2H, br d[‡], $J_{2'/6'eq,3'5'eq} = J_{3'/5'ax,3'5'eq}$ = 12.0 Hz, 2 CH, H(3′/5′$_{eq}$)), 2.65 (1H, m, CH, H4′), 2.85 (2H, dt, $J_{2'/6'ax,3'5'eq}$ = 3.0, $J_{2'/6'ax,2'6'eq} = J_{2'/6'ax,3'5'ax}$ = 12.0 Hz, 2 CH, H(2′/6′$_{ax}$)), 3.84, (2H, br d[‡], $J_{2'/6'eq,3'5'eq} = J_{2'/6'eq,2'6'ax}$ = 12.0 Hz, 2 CH, H(2′/6′$_{eq}$)), 4.66 (2H, br s, NH_2), 6.69 (1H, d, J = 9.0 Hz, H3), 7.03 (1H, d, J = 3.0 Hz, H5), 7.22 (1H, t, J = 7.2 Hz, C4″), 7.27 (2H, m, C3″/5″), 7.32 (2H, t, J = 7.2 Hz, C2″/6″), 7.42 (1H, dd, J = 3.0, 9.0 Hz, H7), 7.60 (1H, d, J = 9.0 Hz, H8), 7.79 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.4 (C3′/5′), 42.5 (C4′), 51.4 (C2′/6′), 111.4 (C5), 111.7 (C3), 123.6 (C7), 124.2 (C4a), 126.3 (C4″), 126.5 (C8), 126.9 (C3″/5″), 128.5 (C2″/6″), 137.4 (C4), 142.4 (C8a), 146.0 (C1″), 147.6 (C6), 155.3 (C2); IR (Nujol mull) ν/cm^{-1} 1618, 1574, and 1500; MS (EI) m/z 303 (M$^{\bullet+}$, 100), 198 (30), 171 (40), 143 (20); HRMS (EI$^+$) m/z found 303.173, $C_{20}H_{21}N_3$ requires 303.174. **5e** was converted to the corresponding maleate salt, mp 197−207 °C, using general procedure 7 for the purpose of obtaining an elemental analysis. Anal. Calcd for $C_{24}H_{25}N_3O_4 \cdot H_2O$: C, 65.89; H, 6.22; N, 9.60. Found: C, 65.45; H, 6.01; N, 9.35.

6-(4-Benzylpiperidin-1-yl)quinolin-2-amine (5f). Using general procedure 5, an impure mixture of **6f** (390 mg, 1.0 mmol) was treated with acetamide (1.20 g, 20.3 mmol) and potassium carbonate (698 mg, 5.0 mmol) for 2.5 h. Extraction with chloroform/2-propanol (3:1) and chromatographic separation eluting with CH_2Cl_2 afforded the title compound as a yellow/brown solid, mp 169−174 °C (78 mg, 25%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.47 (2H, dq, $J_{2'/6'eq,3'5'ax}$ = 4.2, $J_{2'/6'ax,3'5'ax} = J_{3'/5'ax,3'5'eq}$ = 12.6 Hz, 2 CH, H(3′/5′$_{ax}$)), 1.70 (1H, m, CH, H(4′)), 1.79 (2H, br d[‡], $J_{2'/6'eq,3'5'eq} = J_{3'/5'ax,3'5'eq}$ = 12.6 Hz, 2 CH, H(3′/5′$_{eq}$)), 2.60 (2H, d, J = 7.2 Hz, CH_2), 2.69 (2H, dt, $J_{2'/6'ax,3'5'eq}$ = 4.2, $J_{2'/6'ax,2'6'eq} = J_{2'/6'ax,3'5'ax}$ = 12.6 Hz, 2 CH, H(2′/6′$_{ax}$)), 3.68, (2H, br d[‡], $J_{2'/6'eq,3'5'eq} = J_{2'/6'eq,2'6'ax}$ = 12.0 Hz, 2 CH, H(2′/6′$_{eq}$)), 4.59 (2H, br s, NH_2), 6.66 (1H, d, J = 9.0 Hz, H3), 6.95 (1H, d, J = 2.4 Hz, H5), 7.18 (1H, t, J = 7.2 Hz, C4″), 7.21 (2H, m, C2″/6″), 7.30 (2H, t, J = 7.2 Hz, C3″/5″), 7.35 (1H, dd, J = 2.4, 9.0 Hz, H7), 7.56 (1H, d, J = 9.0 Hz, H8), 7.76 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 32.1 (C3′/5′), 37.8 (C4′), 43.2 (CH_2), 50.8 (C2′/6′), 111.2 (C5), 111.7 (C3), 123.6 (C7), 124.3 (C4a), 125.9 (C4″), 126.5 (C8), 128.2 (C3″/5″), 129.2 (C2″/6″), 137.3 (C4), 140.5 (C1″), 142.5 (C8a), 147.7 (C6), 155.3 (C2); IR (Nujol mull) ν/cm^{-1} 3456, 3309, 3120, 1650, 1601, 1566, and 1502; MS (EI) m/z 317 (M$^{\bullet+}$, 100), 224 (40), 198 (20), 172 (30), 71 (30), 170 (30), 143 (20); HRMS (EI$^+$) m/z found

317.1884, $C_{21}H_{23}N_3$ requires 317.1892. **5f** was converted to the corresponding maleate salt, mp 188−195 °C, using general procedure 7 for the purpose of obtaining an elemental analysis. Anal. Calcd for $C_{25}H_{27}N_3O_4 \cdot 0.5H_2O$: C, 67.86; H, 6.38; N, 9.50. Found: C, 67.69; H, 6.38; N, 9.33.

6-(4-Methylpiperazin-1-yl)quinolin-2-amine (5h). Synthesis Method i. Using general procedure 5, impure **6h** (200 mg, 0.77 mmol) was treated with acetamide (912 mg, 15.3 mmol) and potassium carbonate (527 mg, 3.84 mmol) for 2.5 h. Extraction with chloroform/2-propanol (3:1) and chromatographic separation on C18 silica eluting with water/methanol (2:3) afforded the title compound as a pale yellow powder, mp 171−181 °C (20 mg, 11%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.39 (3H, s, CH_3), 2.64 (4H, t, J = 4.8 Hz, 2 CH_2, H(3′/5′)), 3.26 (4H, t, J = 4.8 Hz, 2 CH_2, H(2′/6′)), 4.94 (2H, br s, NH_2), 6.70 (1H, d, J = 8.6 Hz, H3), 6.98 (1H, d, J = 2.6 Hz, H5), 7.36 (1H, dd, J = 2.6, 9.0 Hz, H7), 7.60 (1H, d, J = 9.0 Hz, H8), 7.79 (1H, d, J = 8.6 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 46.1 (CH_3), 49.8 (C2′/6′), 55.1 (C3′/5′), 111.0 (C5), 111.9 (C3), 122.9 (C7), 124.0 (C4a), 126.0 (C8), 137.8 (C4), 141.5 (C8a), 147.1 (C6), 155.2 (C2); IR (Nujol mull) ν/cm^{-1} 3299, 3181, 1603, and 1505; MS (EI) m/z 242 ($M^{\bullet+}$, 20), 144 (100), 117 (50); HRMS (EI$^+$) m/z found 242.1531, $C_{14}H_{18}N_4$ requires 242.1531.

Synthesis Method ii. Using general proceedure 6, $Pd_2(dba)_3$ (1.7 mg, 1.9 μmol), **9** (0.9 mg, 2.2 μmol), and **6h** (65 mg, 0.19 mmol) were combined in 1,4-dioxane (1 mL). LHMDS solution (1.0 M in THF, 420 μL) was added, a nd then the reaction was heated for 24 h. Workup afforded the title compound (41 mg, 90%). Data are as above.

6-(4-Ethylpiperazin-1-yl)quinolin-2-amine (5i). Using general procedure 5, impure **6i** (220 mg, 0.80 mmol) was treated with acetamide (946 mg, 16.0 mmol) and potassium carbonate (553 mg, 4.0 mmol) for 2.5 h. Extraction with chloroform/2-propanol (3:1) and chromatographic separation on C18 silica eluting with water/methanol (2:3) afforded the title compound as a pale yellow powder, mp 166−169 °C (17 mg, 8%). Additional product was also isolated as a mixture that could not be purified further (combined yield 45 mg; **5i**, 18%). Data for **5i**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.15 (3H, t, J = 7.2 Hz, CH_3), 2.51 (2H, q, J = 7.2 Hz, CH_2), 2.67 (4H, t, J = 4.8 Hz, 2 CH_2, H(3′/5′)), 3.27 (4H, t, J = 4.8 Hz, 2 CH_2, H(2′/6′)), 4.68 (2H, br s, NH_2), 6.68 (1H, d, J = 9.0 Hz, H3), 6.97 (1H, d, J = 2.4 Hz, H5), 7.36 (1H, dd, J = 2.4, 9.0 Hz, H7), 7.59 (1H, d, J = 9.0 Hz, H8), 7.78 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.9 (CH_3), 49.9 (C2′/6′), 52.3 (CH_2), 52.9 (C3′/5′), 110.9 (C5), 111.8 (C3), 122.8 (C7), 124.2 (C4a), 126.5 (C8), 137.4 (C4), 142.4 (C8a), 147.1 (C6), 155.3 (C2); IR (Nujol mull) ν/cm^{-1} 3466, 3730, 3210, 1639, and 1601; MS (EI) m/z 256 ($M^{\bullet+}$, 100), 241 (50), 172 (40), 84 (40), 57 (30); HRMS (EI$^+$) m/z found 256.1688, $C_{15}H_{20}N_4$ requires 256.1688.

6-(4-Phenylpiperazin-1-yl)quinolin-2-amine (5j). Synthesis Method i. Using general procedure 5, impure **6j** (150 mg, 0.46 mmol) was treated with acetamide (550 mg, 9.3 mmol) and potassium carbonate (320 mg, 2.3 mmol) for 1.5 h. Extraction with chloroform/2-propanol (3:1) and chromatographic separation eluting with ethanol/CH_2Cl_2 (1:19) afforded the title compound as a yellow powder, mp 233−240 °C (65 mg, 46%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.39 (8H, br s, 4 CH_2), 5.38 (2H, br s, NH_2), 6.70 (1H, d, J = 9.0 Hz, H3), 6.92 (1H, t, J = 7.2 Hz, H4″), 7.00 (2H, d, J = 8.1 Hz, H(2″/6″)), 7.05 (1H, d, J = 2.7 Hz, H5), 7.29 (2H, m, H(3″/5″)), 7.43 (1H, dd, J = 2.7, 9.0 Hz, H7), 7.65 (1H, d, J = 9.0 Hz, H8), 7.87 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 49.7 (C2′/6′), 50.4 (C3′/5′), 111.5 (C3), 112.1 (C4″), 116.6 (C2″/C6″), 120.3 (C5), 123.3 (C7), 124.3 (C4a), 126.7 (C8), 129.4 (C3″/C5″), 142.5 (C4), 142.5 (C8a), 147.3 (C6), 151.5 (C1″), 155.6 (C2); IR (Nujol mull) ν/cm^{-1} 3435, 3301, 3112, 1646, and 1602; MS (EI) m/z 304 ($M^{\bullet+}$, 100), 171 (60), 132 (60), 105 (30); HRMS (EI$^+$) m/z found 304.1682, $C_{19}H_{20}N_4$ requires 304.1688. Anal. Calcd for $C_{19}H_{20}N_4 \cdot 0.5H_2O$: C, 72.82; H, 6.75; N, 17.88. Found: C, 72.56; H, 6.63; N, 17.42.

Synthesis Method ii. Using general proceedure 6, $Pd_2(dba)_3$ (1.4 mg, 1.5 μmol), **9** (0.7 mg, 1.8 μmol), and **6j** (50 mg, 0.15 mmol) were combined in 1,4-dioxane (1 mL). LHMDS solution (1.0 M in THF, 330 μL) was added, and then the reaction was heated for 18 h. Workup afforded the title compound (44 mg, 96%). Data are as above.

6-(4-Benzylpiperazin-1-yl)quinolin-2-amine (5k). Synthesis Method i. Using general procedure 5, impure **6k** (575 mg, 1.71 mmol) was treated with acetamide (2.0 g, 34.1 mmol) and potassium carbonate (1.18 g, 8.5 mmol) for 2.0 h. Extraction with chloroform/2-propanol (3:1) and chromatographic separation on C18 silica eluting with water/methanol (1:4) afforded the title compound as an impure mixture (90 mg). Additional attempts to purify the product on C18 preparative plates afforded a small amount of the title pure compound as a cream powder, mp 194−196 °C (20 mg, 4%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.64 (4H, m, 2 CH_2, H(3′/5′)), 3.23 (4H, t, J = 4.8 Hz, 2 CH_2, H(2′/6′)), 3.58 (2H, s, CH_2), 4.66 (2H, br s, NH_2), 6.66 (1H, d, J = 9.0 Hz, H3), 6.94 (1H, d, J = 3.0 Hz, H5), 7.25−7.37 (6H, m, H (C7, Ph)), 7.57 (1H, d, J = 9.0 Hz, H8), 7.75 (1H, d, J = 9.0 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 49.9 (C2′/6′), 53.1 (C3′/5′), 63.0 (CH_2), 110.8 (C5), 112.8 (C3), 121.9 (C7), 124.2 (C4a), 126.7 (C8), 127.1 (C4″), 128.3 (C2″/C6″), 129.1 (C3″/C5″), 137.9 (C4), 138.15 (C1″), 142.8 (C8a), 147.0 (C6), 155.5 (C2); IR (Nujol mull) ν/cm^{-1} 3439, 3301, 2354, 1647, 1599, and 1560; MS (EI) m/z 318 ($M^{\bullet+}$, 100), 172 (70), 146 (30), 91 (50); HRMS (EI$^+$) m/z found 318.1847, $C_{20}H_{22}N_4$ requires 318.1844.

Synthesis Method ii. Using general proceedure 6, $Pd_2(dba)_3$ (2.6 mg, 2.8 μmol), **9** (1.3 mg, 3.3 μmol), and **6k** (96 mg, 0.15 mmol) were combined in 1,4-dioxane (1 mL). LHMDS solution (1.0 M in THF, 620 μL) was added, a nd then the reaction was heated for 24 h. Workup afforded the title compound (80 mg, 88%). Data are as above.

***tert*-Butyl 4-(2-Aminoquinolin-6-yl)piperazine-1-carboxylate (5l).** Using general procedure 5, **6l** (200 mg, 0.58 mmol) was treated with acetamide (685 mg, 11.6 mmol) and potassium carbonate (400 mg, 2.9 mmol) for 1.5 h. Extraction with chloroform/2-propanol (3:1) and chromatographic separation eluting with ethanol/CH_2Cl_2 (1:9) afforded the title compound as a green-brown solid, mp 220−228 °C (90 mg, 47%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.26 (9H, s, $C(CH_3)_3$), 3.22 (4H, t, J = 4.8 Hz, CH_2, H(2′/6′)), 3.66 (4H, t, J = 4.8 Hz, 2 CH_2, H(3′/5′)), 5.17 (2H, br s, NH_2), 6.74 (1H, d, J = 8.4 Hz, H3), 6.97 (1H, d, J = 2.4 Hz, H5), 7.35 (1H, dd, J = 2.4, 9.0 Hz, H7), 7.62 (1H, d, J = 9.0 Hz, H8), 7.81 (1H, d, J = 8.4 Hz, H4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.7 ($C(CH_3)_3$), 41.4 (C3′/5′), 49.9 (C2′/6′), 80.10 ($C(CH_3)_3$), 111.9 (C5), 112.2 (C3), 123.4 (C7), 123.8 (C4a), 125.9 (C8), 135.1 (C4), 138.0 (C8a), 146.8 (C6), 155.4 (C2), 169.0 (C═O); IR (Nujol mull) ν/cm^{-1} 3336, 3157, 1658, 1621, and 1604; MS (EI) m/z 270 ($M^+ - {}^t$Bu, 90), 198 (100), 185 (30), 170 (50) 143 (30), 83 (30), 56 (30); HRMS (EI$^+$) m/z found 328.1895, $C_{18}H_{24}N_4O_2$ requires 328.1899.

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Supporting Information Available: General experimental considerations and NMR spectra for characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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