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Synthesis of novel quinolone and quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amides: A late-stage diversification approach to potent $5HT_{1B}$ antagonists

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Abstract—Multiparallel amenable syntheses of 6-methoxy-8-amino-4-oxo-1,4-dihydroquinoline-2-carboxylic acid-(4-morpholin-4-yl-phenyl)amides (**I**) and 4-amino-6-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amides (**II**) which facilitate late-stage diversification at the 8-position of (**I**) and at the 4- and 8-positions of (**II**) are described. The resulting novel series were determined to contain potent $5HT_{1B}$ antagonists. Preliminary SAR data are presented.
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1. Introduction

The 5-hydroxytryptamine$_1$ ($5HT_1$) receptor family consists of five receptor subtypes ($5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$, $5HT_{1E}$, and $5HT_{1F}$) all of which are G-protein coupled, seven transmembrane receptors.[1] It is thought that there are potentially four distinct signal transduction mechanisms for these receptors. They both activate and inhibit adenylate cyclase, modulate potassium channel activity in the hippocampus, and activate phosphoinositide (PI) metabolism.[1b] The $5HT_{1A}$ receptor has been studied extensively for its potential in the treatment of depression, anxiety, and psychosis.[1a,2] The $5HT_{1B,D,F}$ receptors have been primarily indicated in the treatment of migraine.[1a] However, the $5HT_{1B}$ receptor has recently been targeted for its potential in the treatment of depression, anxiety, and other serotoninergic neurotransmission related psychiatric disorders.[2b,3] The release of 5-HT is regulated by autoreceptors on the 5-HT nerve terminals. It has been suggested that antagonists of the terminal $5HT_1$ autoreceptors ($5HT_{1B/1D}$) which block terminal $5HT_{1B}$ receptors may effect immediate 5-HT release, thereby increasing 5-HT transmission at the synapses and ultimately providing faster clinical antidepressant activity than currently available therapies.[2,4] Recent studies on $5HT_{1B}$ selective antagonists are beginning to substantiate this hypothesis.[5] Two $5HT_{1B}$ antagonists have been shown to be active in animal models for anxiolytic and antidepressant effects.[6]

In a continuation of our efforts to discover an orally active $5HT_{1B}$ antagonist for the treatment of anxiety and depression, we sought to improve on AR-A000002, a selective $5HT_{1B}$ antagonist (Fig. 1) which has been shown to have potential as both an antidepressive and an anxiolytic agent.[6a,7] Pharmacophore model scoring opposite AR-A000002 and other known $5HT_{1B}$ antagonists led to the identification of the quinolone and quinoline cores as potential replacements to the 2-aminotetralin core (Fig. 2).

We wished then to evaluate the novel quinoline series as a new class of $5HT_{1B}$ antagonists. This necessitated

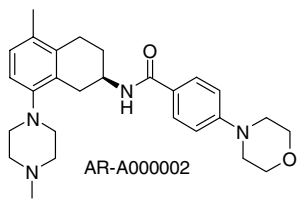

Figure 1. The legacy compound, AR-A000002, served as a starting point for the quinoline series.

Keywords: $5HT_{1B}$ antagonist; 8-Amino-4-oxo-1,4-dihydroquinoline-2-carboxylic acid amides; 4-Aminoquinoline-2-carboxylic acid amide.
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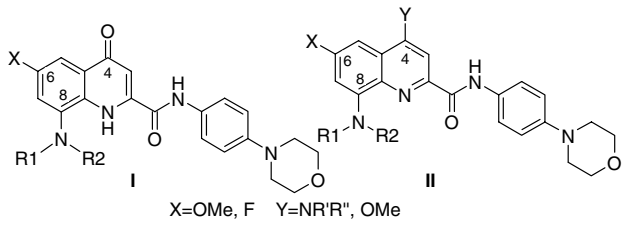
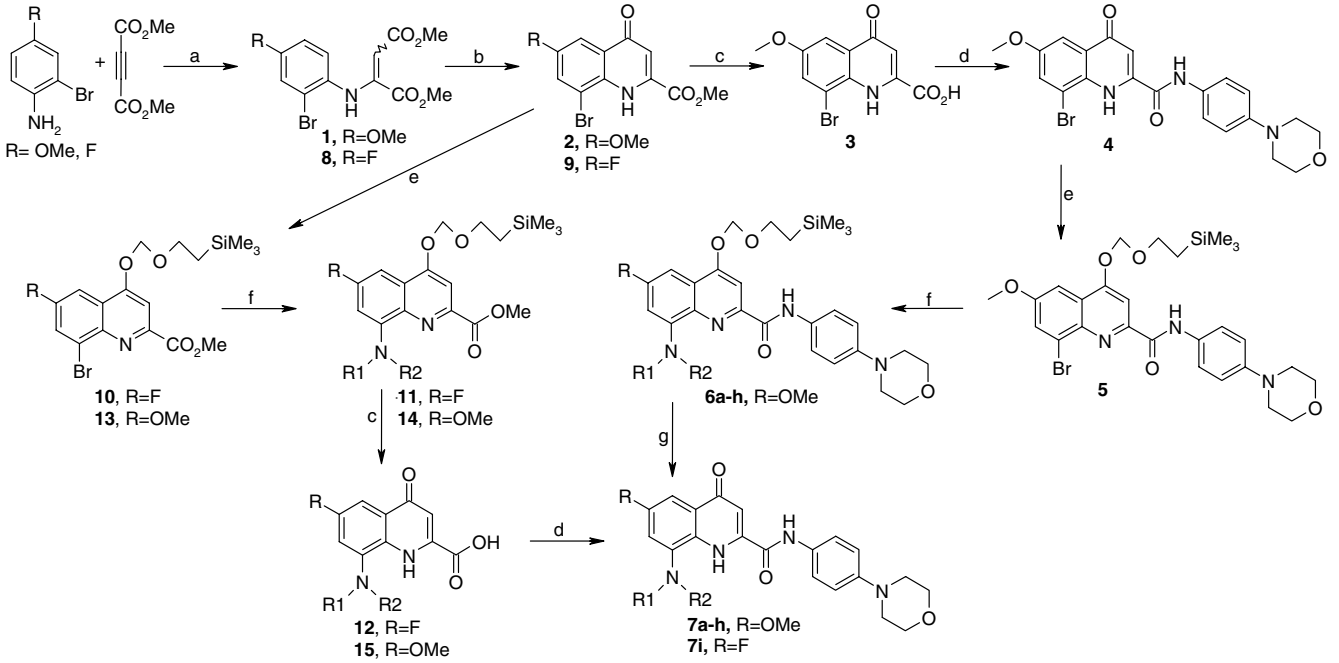


Figure 2. The quinolone and quinoline cores were targeted as stable potential $5HT_{1B}$ antagonists.

syntheses which would allow late-stage diversification of the 4-oxo-1,4-dihydroquinolines (**I**) at the 8-position and of the quinolines (**II**) at the 4- and 8-positions. The chemistry developed for these series allowed for exploration of portions of the molecule which were more difficult to explore in the 2-aminotetralin core. Within, we describe multiparallel amenable syntheses (MPS) which allowed for the expedient evaluation of several quinoline derivatives as $5HT_{1B}$ antagonists.

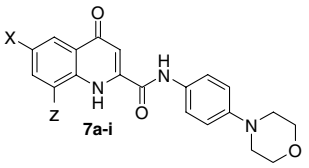
2. Discussion

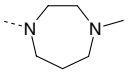
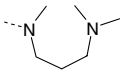
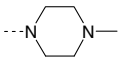
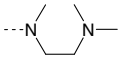
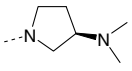
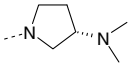
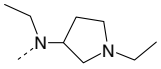
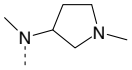
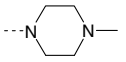
The synthesis of the 4-oxo-1,4-dihydroquinolines was initiated by addition of dimethyl acetylenedicarboxylate to a solution of 2-bromo-4-methoxy aniline[8] in anhydrous methanol, followed by heating at reflux to afford 2-(2-bromo-4-methoxy-phenylamino)-but-2-enedioic acid dimethyl ester (**1**). The key quinolone intermediate **2** (Scheme 1) was obtained by adaptation of the procedure of Heindel et al.[9] Cyclization of **1** in DowTherm® A provided the 8-bromo-6-methoxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid methyl ester (**2**) in much better yield than the corresponding cyclization in polyphosphoric acid.[9] The methyl ester was hydrolyzed to the acid (**3**) using lithium hydroxide. The required 8-bromo-6-methoxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (**4**) was prepared through standard coupling of **3** and 4-morpholinoaniline. The Buchwald–Hartwig reaction[10] was envisaged as the means of rapidly introducing a variety of 8-amino groups into **I** and **II**. Attempts to obtain **7** from the unprotected quinolone **4** using tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$), ±2,2-bis(diphenylphospino)-1,1′-binaphthalene (BINAP), and cesium carbonate (Cs_2CO_3) or potassium fluoride (KF) failed to elucidate a means of direct conversion. It was conjectured that under the strongly basic reaction conditions, the increased electron density of the deprotonated quinolone ring[11] was preventing the desired reaction from occurring. Protection of the 4-oxo group of **4** was accomplished by introduction of a 2-trimethylsilanylethoxymethoxy (SEM) group under standard conditions to afford 8-bromo-6-methoxy-4-(2-trimethylsilanylethoxymethoxy) quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (**5**). Complete regioselectivity was confirmed by 2D HMBC NMR experiments. Intermediate **5** was then sucessfully employed in the coupling reaction to introduce a variety of amines in generally excellent yields (Table 1). The desired 6-methoxy-8-amino-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amides **7a**–**h** were then obtained by the removal of the SEM group in the presence of HCl.



Scheme 1. Synthesis of 4-oxo-1,4-dihydroquinolines **7a**–**i**. Reagents and conditions: (a) MeOH, reflux, 8 h, 82–93%; (b) DowTherm® A, 240–245 °C, 45 min, 78%; (c) 3 equiv $LiOH{\cdot}H_2O$, 3:1:1 THF/MeOH/H_2O, RT, 5 h, 95–100%; (d) 2.4 equiv TBTU, 2.4 equiv HOBt, 1.3 equiv 4-morpholinoaniline, 4.3 equiv DIEA, DMF, RT, 16 h, 43–58%; (e) 1.5 equiv NaH, 1.3 equiv SEMCl, NMP, RT, 4.5 h, 78–100%; (f) 1.6 equiv appropriate amine, 5 mol % $Pd_2(dba)_3$, 0.3 equiv BINAP, 4 equiv Cs_2CO_3, 4 Å molecular sieves, toluene, reflux, 17 h, 75–92%; (g) 0.05 N aq HCl, MeOH, RT, 45 min, 13–80% (yield from **5**).

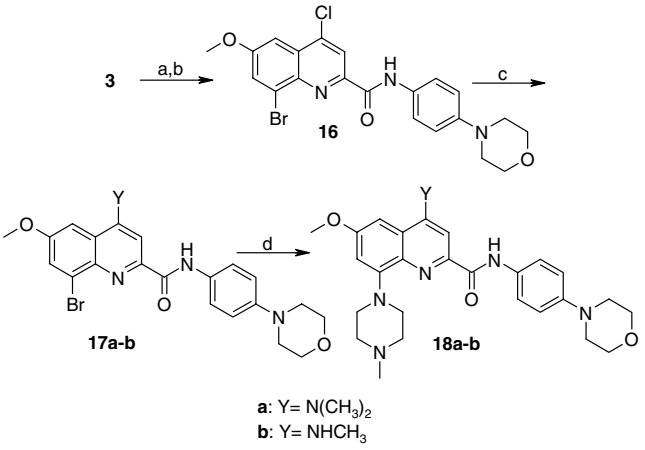
Table 1. Structure–activity relationships of quinolones **7a–i**



Compound	X	Z	K_i[a] (nM)	Yield[b] %
7a	OMe		0.9 (n = 3)	81
7b	OMe		292	79
7c	OMe		3.5	85[c]
7d	OMe		392	78
7e	OMe		35	100
7f	OMe		>1000 (n = 2)	100
7g	OMe		170	100
7h	OMe		>1000	50
7i	F		9.3	88[d]

[a] $5HT_{1B}$ binding affinity was determined as described in Refs. 5d and 13. Geometric mean values reported for multiple experiments.
[b] Yield of Buchwald–Hartwig coupling reaction from **5**.
[c] Yield from **13**.
[d] Yield from **10**.

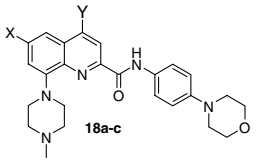
The 6-fluoroquinolone **7i** was prepared in a similar fashion from 2-bromo-4-fluoroaniline. As shown in Scheme 1, the steps in the synthesis for this compound were rearranged such that 8-bromo-6-fluoro-4-oxo-1,4-dihydroquinoline-2-carboxylic acid methyl ester **9** was protected as the SEM derivative **10** and then subjected to the Buchwald–Hartwig coupling reaction to give 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-(2-trimethylsilanylethoxymethoxy)-quinoline-2-carboxylic acid methyl ester **11**. The ester was hydrolyzed with concurrent loss of the SEM group to give the quinolone carboxylic acid **12**. Subsequent conversion to the amide provided the desired 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide **7i**. This alternative route was also employed for the methoxy derivatives as exemplified in the alternate synthesis of **7a** which is included in Section 4. The route offers the advantage of potential late-stage diversification at the amide position versus at the 8-amino quinoline position should that be of interest.



Scheme 2. Diversification at the 4- and 8-positions of the quinolines **18**. Reagents and conditions: (a) 9.8 equiv oxalyl chloride, cat. DMF, CH_2Cl_2, reflux, 2 h, reaction concentrated; (b) 1.1 equiv 4-morpholino aniline, 3.5 equiv DIEA, CH_2Cl_2, RT, 1 h, 49% (from **3**); (c) 2.0 M appropriate amine in THF, 100 °C, 60–80 psi, 18 h, 87–92%; (d) 1.5 equiv N-methylpiperizine, 6 mol % $Pd_2(dba)_3$, 0.3 equiv BINAP, 4.7 equiv Cs_2CO_3, 4 Å molecular sieves, toluene, reflux, 20 h, 57–67%.

The synthesis of the desired quinolines **18a** and **18b** also employed carboxylic acid **3** (Scheme 2). Diversification at both the 4- and 8-positions was achieved by treatment of **3** with oxalyl chloride in methylene chloride and catalytic DMF, followed by isolation of the 4-chloro quinoline acid chloride. Subsequent addition of 4-morpholinoaniline and diisopropylethylamine provided 8-bromo-4-chloro-6-methoxyquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (**16**). Intermediate **16** could then be diversified by sequential displacement of the 4-chloro group under thermal conditions, followed by catalytic coupling of amino moities at the 8-bromo position. Our initial evaluation required displacement of the chloro group with N,N-dimethyl amine and N-methyl amine. The 8-bromo-substituted aminoquinolines **17** proved competent substrates for the Buchwald–Hartwig reaction affording the 4-amino-6-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl- phenyl)amides **18a** and **18b** in acceptable yields (Table 2).

Table 2. Structure–activity relationships of quinolines **18a–c**

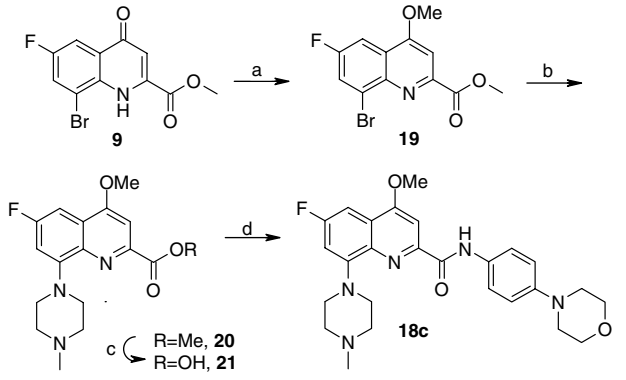


Compound	X	Y	K_i[a] (nM)	Yield %
18a	OMe	NMe_2	51	67[b]
18b	OMe	NHMe	1300	57[b]
18c	F	OMe	30	90[c]

[a] $5HT_{1B}$ binding affinity was determined as described in Refs. 5d and 13. Geometric mean values reported for multiple experiments.
[b] Yield of Buchwald–Hartwig coupling from **17**.
[c] Yield of **18c** from **19**.

The synthesis of 6-fluoro-4-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide **18c** was carried out in a similar manner (Scheme 3). Sequential treatment of 8-bromo-6-fluoro-4-oxo-1,4-dihydroquinoline-2-carboxylic acid methyl ester (**9**) with sodium hydride and iodomethane afforded 8-bromo-6-fluoro-4-methoxyquinoline-2-carboxylic acid methyl ester (**19**). Buchwald–Hartwig coupling conditions were employed on the methoxy quinoline compound to introduce the *N*-methyl piperazine group. Hydrolysis of **20** and subsequent coupling of the acid **21** with 4-morpholinoaniline afforded the desired 6-fluoro-4-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide **18c**.

Piperazine side chains commonly appear as elements of $5HT_{1B}$ antagonists.[12,5c,3a] However, the available structure activity relationship (SAR) information surrounding this substituent is actually rather limited. We wished to explore a variety of amines as potential piperazine surrogates. Binding affinities were determined using a stably transfected Chinese hamster ovary (CHO) cell line expressing $5HT_{1B}$ receptors. The compounds were evaluated in competition assays using [^{3}H]-GR125743 and K_i values were determined as described.[5d,13] It is interesting to note that homopiperazine **7a** is more active than the corresponding piperazine derivative **7c** (Table 1). Replacement of either the homopiperazine or piperazine with an analogous, noncyclic amine (**7b** and **7d**, respectively) resulted in significant loss of activity, indicating that the rigidity of the cyclic amine was required in these systems. The chirality of the amines also appeared to be important as exemplified by **7e** and **7f**. The (3R)-(+)-3-(dimethylamino)-pyrrolidine derivative **7e** demonstrated potent activity while the (*S*)-enantiomer **7f** was inactive. To our knowledge, such strong chirality effects have not been previously reported opposite the $5HT_{1B}$ receptor. The *N*,*N*′dieth-



Scheme 3. Synthesis of 6-fluoro-4-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (**18c**). Reagents and conditions: (a) 1.1 equiv NaH, 1.2 equiv CH_3I, NMP, 2 h, 98% or 1.5 equiv K_2CO_3, 2 equiv CH_3I, DMSO, 70 °C, 1 h, 93%; (b) 1.1 equiv *N*-methyl piperizine, 2 mol% $Pd_2(dba)_3$, 0.12 equiv BINAP, 1.4 equiv Cs_2CO_3, 4 Å molecular sieves, toluene, reflux, 36 h, 90%; (c) 1.1 equiv $LiOH{\cdot}H_2O$, THF:MeOH:H_2O, RT, 1 h, 95%; (d) 1.2 equiv 4-morpolinoaniline, 2.0 equiv TBTU, 2.0 equiv HOBt, 4.0 equiv DIEA, DMF, RT, 18 h, 93%.

yl-3-amino-pyrrolidine derivative **7g** exhibited modest activity while the *N*,*N*′-dimethyl-3-amino-pyrrolidine derivative **7h** did not. This result made it apparent that small changes such as an extra methylene group can have a dramatic effect on activity.

The intrinsic affinity of **7a**, **7c**, and **7i** was evaluated using a GTPγS (a hydrolysis resistant analog of guanosine triphosphate) binding assay in order to confirm antagonist properties. Agonist stimulated GTP binding was measured in a stably transfected CHO cell line expressing $5HT_{1B}$ receptors using [^{35}S]GTPγS as previously described.[13,14] Maximal intrinsic affinity (IA) was defined as the percent maximal 5-HT-induced stimulation by 10 μM compound in the absence of 5-HT with a negative number indicating full antagonism. All three compounds were determined to be full antagonists. (The intrinsic affinities ranged from −28 to −34.) Thus, potent $5HT_{1B}$ antagonists were obtained within the 4-oxo-1,4-dihydroquinoline series. The DMPK (disposition metabolism pharmacokinetic) properties of this series, however, were somewhat disappointing. In particular, the compounds were found to have no oral activity as determined in a guinea pig agonist induced hypothermia model.[13,15]

The quinoline compounds **18a**–**c** (Table 2) were expected to exhibit better DMPK properties than the quinolones allowing for better blood–brain barrier penetration and subsequent oral bioavailability due to their reduced polar surface area[16] and decreased basicity. In the quinoline series, the piperazine side chain at the 8-position was held constant and the functional group at the 4-position was examined (Table 2). Replacement of the carbonyl of the quinolones with an *N*,*N*-dimethylamino group (**7c** vs **18a**) resulted in a diminution of activity. The *N*-methyl amino derivative **18b** was inactive, implying that the presence of a hydrogen-bond donor at the 4-position is detrimental to binding. This is also consistent with the decreased basicity of the quinoline nitrogen of **18a** relative to **18b** due to unfavorable peri–steric interactions, which result in poor orbital overlap of the periplanar dimethyl amino group with the π orbitals of the ring system. Subsequently, the electron density at the quinoline nitrogen in **18a** is decreased versus **18b**.[17] Consistent with this hypothesis, the even less basic methoxy compound **18c**[18] demonstrated improved activity over **18a**. The intrinsic affinity of **18c** was determined to be −28 using the GTPγS binding assay, demonstrating this compound to be a full antagonist. It is believed that the quinoline compounds may have better physical properties. At present, activity in the guinea pig hypothermia model remains to be determined for quinoline **18c**; a positive outcome in this test would be consistent with achievement of CNS penetration.

3. Conclusions

We have developed robust synthetic routes to the desired quinolones and quinolines. In both cases, the routes are suitable for MPS and late-stage diversification at the 4- and/or 8-position. Diversification of the

compounds at the amide position is feasible as well. The quinolones and quinolines have proven to be potent new $5HT_{1B}$ antagonists. Preliminary SAR has revealed new areas for optimization of these compounds. The binding affinities seen within the relatively small subset of potential cyclic amines tested for the quinolone series suggest that a variety of amines may potentially serve as surrogates for the traditional piperazine side chain. The homopiperazine appears to be particularly promising. The pyrrolidine examples provide new evidence that the chirality of the amines may have dramatic effects on $5HT_{1B}$ receptor binding affinity.

4. Experimental

4.1. General methods

All chemicals were reagent grade and were used without further purification. Solvents were HPLC (high performance liquid chromatography) or anhydrous grade. Reactions were performed under inert (N_2) atmosphere. Column chromatography was performed manually or on an ISCO CombiFlash™ Optix 10. Proton and carbon nuclear magnetic resonance (NMR) spectra were acquired on a Bruker Avance 300 spectrometer using a 5 mm QNP probe operating at 300.13 MHz for proton and 75.5 MHz for carbon-13 or a Bruker Avance 400 spectrometer using a 5 mm inverse broadband probe operating at 400.13 MHz for proton and 100.6 MHz for carbon-13. For advanced experiments, NMR spectra were acquired on a Bruker Avance 500 spectrometer using the 5 mm Bruker triple resonance cryogenically cooled probe (Cryoprobe™) equipped with Z-gradient. Proton spectra were acquired at 500.13 MHz and carbon-13 assignments were made based on two- and three-bond proton-carbon couplings observed in 2D HMBC spectra. The heteronuclear multiple bond correlation (HMBC) experiments were typically run on a sample with less than 1 mg of compound dissolved in 0.6 mL $CDCl_3$, using a gradient pulse sequence. The enhanced sensitivity of the Cryoprobe™ allowed acquisition of the HMBC data in less than 30 min. The same level of signal using the Avance 400 conventional probe required more than 6 h of acquisition time. Low resolution mass spectra were obtained on a Micromass LCZ using an APCI (atmospheric pressure chemical ionization) detection mode and a Zorbax 50 mm × 2.1 mm Stablebond C8 column with a solvent gradient of 5% B to 90% B over 4 min at 1.4 mL/min where solvent A = 0.05% TFA in H_2O and solvent B = 90% CH_3CN/10% H_2O/0.05% TFA. High resolution electrospray mass spectrometric data were acquired by direct infusion of the compounds in DMSO or MeOH solution (20 μg/mL) on a Micromass QTOF-1 mass spectrometer operated in the positive ionization mode. The compounds were diluted with a solution containing Leucine Enkephalin (approximately 25 μg/mL) dissolved in water/MeOH (3:7). The infusion rate was 5 μl/min and the positioning of the electrospray probe was adjusted such that the signal abundances of the protonated molecular ions from the analytes and the lock mass (Leu-Enkephalin) were not subject to dead time correction. The instrument was scanned, in the continuum mode, between 110 and 1100 Da in 1 s (total cycle time was 1.1 s) using a cone voltage of 30 V. The resultant mass spectra were centered by setting the measured mass for the Leu-Enkephalin protonated molecular ion to its known accurate mass of 556.2766 Da. This yielded accurate mass determinations for the analyte related mass spectral ions.

4.2. Synthesis of quinolines 7a–7h

4.2.1. 2-(2-Bromo-4-methoxyphenylamino)-but-2-enedioic acid dimethyl ester (1). A solution of 2-bromo-4-methoxy aniline (6.02 g, 29.8 mmol) in 125 mL anhydrous methanol was treated with dimethyl acetylenedicarboxylate (3.70 mL, 30.2 mmol) and the solution was heated at reflux under nitrogen for 8 h. The reaction mixture was cooled, concentrated, and dissolved in hot methanol. Yellow crystals were obtained by filtration (6.93 g, 68%). A second crop of crystals was obtained from ethanol (0.942 g, 9%). The filtrates were combined and purified by flash chromatography on silica gel using 4:1 hexanes/ethyl acetate to afford an additional 1.63 g (16%) of product for a total yield of 93%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H, N*H*), 7.26 (d, 1H, J_m = 2.7 Hz, ArH_3), 6.93 (dd, 1H, J_o = 8.7, J_m = 2.7 Hz, ArH_5), 6.87 (d, 1H, J_o = 8.7 Hz, ArH_6), 5.34 (s, 1H, C=C*H*), 3.76 (s, 3H, OCH_3), 3.68 (s, 3H, $CHCO_2CH_3$), 3.66 (s, 3H, $CNCO_2CH_3$); Mass Spec.: Calcd for $[C_{13}H_{14}BrNO_5 + H]^+$ Theor. *m*/*z* = 344, 346; Obs. = 344, 346.

4.2.2. 8-Bromo-6-methoxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid methyl ester (2). DowTherm® A (175 mL) was heated to 244 °C and **1** (9.50 g, 27.6 mmol) was added as a solid in portions over 7 min while maintaining a temperature of 230–240 °C. The brown reaction mixture was heated at 240–245 °C for 45 min and then cooled to room temperature. A yellow precipitate formed upon cooling. Approximately 100 mL of hexanes was added to the mixture and the solids were isolated by filtration, washed with additional hexanes, and dried under high vacuum to afford the product as a yellow solid (6.73 g, 78%). ^{1}H NMR (300 MHz, DMSO, d_6) δ 12.01 (s, 1H, N*H*), 7.86 (d, 1H, J_m = 2.7 Hz, ArH_5), 7.52 (s, 1H, C=C*H*), 7.48 (d, 1H, J_m = 2.7 Hz, ArH_7), 3.93 (s, 6 H, OCH_3 and CO_2CH_3); Mass Spec.: Calcd for $[C_{12}H_{10}BrNO_4 + H]^+$ Theor. *m*/*z* = 312, 314; Obs. = 312, 314.

4.2.3. 8-Bromo-6-methoxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (3). To a solution of **2** (3.53 g, 11.3 mmol) in 75 mL 3:1:1 tetrahydrofuran/methanol/water was added lithium hydroxide monohydrate (1.367 g, 32.6 mmol). The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated and then poured into water. The solution was acidified to pH 2 with 1 N HCl and the resulting solids were isolated by filtration. The solids were then suspended in methanol and filtered to afford the desired product as a pale yellow solid (2.673 g, 80%). An additional 0.577 g (17%) of product was isolated from the methanol filtrates. ^{1}H NMR (300 MHz, DMSO-d_6, TFA Shake) δ 7.86 (d, 1H, J_m = 2.7 Hz, ArH_5), 7.55 (d, 1H, J_m = 2.7 Hz, ArH_7), 7.32 (s, 1H, C=C*H*), 3.94

(s, 3H, OCH_3); Mass Spec.: Calcd for $[C_{11}H_8BrNO_4 + H]^+$ Theor. m/z = 298, 300; Obs. = 298, 300.

4.2.4. 8-Bromo-6-methoxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (4). To a yellow suspension of **3** (3.446 g, 11.56 mmol), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate (TBTU) (9.039 g, 28.15 mmol), and 1-hydroxybenzotriazole hydrate (HOBt) (3.757 g, 27.8 mmol) in 100 mL dimethylformamide (DMF) were added 4-morpholinoaniline (2.733 g, 15.3 mmol) and DIEA (8.2 mL, 50.2 mmol). The resulting maroon solution was stirred at room temperature under nitrogen for 16 h during which time the reaction became greenish brown and formed a large amount of precipitate. The reaction mixture was filtered and the solids washed with DMF, water, and methanol. Drying under high vacuum afforded the desired product as a yellow solid (3.09 g, 58%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.13 (s, 1H, NH), 10.18 (s, 1H, C(O)NH), 7.90 (d, 1H, J_m = 2.7 Hz, ArH_5), 7.68 (d, 2H, J_o = 9.0 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.63 (s, 1H, C=CH), 7.51 (d, 1H, J_m = 2.7 Hz, ArH_7), 7.00 (d, 2H, J_o = 9.0 Hz, Ar$H_{3'}$ and $H_{5'}$), 3.94 (s, 3H, OCH_3), 3.75 (t, 4H, J = 4.8 Hz, OCH_2CH$_2$N), 3.10 (t, 4H, J = 4.8 Hz, OCH$_2$CH_2N); Mass Spec.: Calcd for $[C_{21}H_{20}BrN_3O_4 + H]^+$ Theor. m/z = 458, 460; Obs. = 458, 460.

4.2.5. 8-Bromo-6-methoxy-4-(2-trimethylsilanylethoxymethoxy)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (5). A yellow suspension of **4** (3.092 g, 6.75 mmol) in 40 mL *N*-methylpyrrolidinone (NMP) was treated with sodium hydride (60% dispersion in oil, 0.410 g, 10.24 mmol). Gas evolution and warming were observed and the suspension became light brown and almost clear. The reaction mixture was stirred for 10 min at room temperature under nitrogen. Addition of 2-(trimethylsilyl)ethoxymethyl chloride (1.6 mL, 9.1 mmol) resulted in a slightly cloudy, lighter brown solution. After 4.5 h at room temperature, the reaction mixture was poured into 300 mL water, stirred for 15 min, and then stored at 0 °C overnight. The solids were isolated by filtration, suspended in methanol, filtered again, and dried under high vacuum to afford the product as a yellow solid (3.19 g, 80%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.18 (s, 1H, C(O)NH), 7.95 (d, 1H, J_m = 2.4 Hz, ArH_7), 7.83 (s, 1H, ArH_3), 7.69 (d, 2H, J_o = 9.0 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.51 (d, 1H, J_m = 2.7 Hz, ArH_5), 7.00 (d, 2H, J_o = 9.0 Hz, Ar$H_{3'}$ and $H_{5'}$), 5.69 (s, 2H, OCH$_2$O), 3.95 (s, 3H, OCH_3), 3.85 (t, 2H, J = 8.0 Hz, OCH_2CH$_2$Si), 3.75 (t, 4H, J = 4.7 Hz, OCH_2CH$_2$N), 3.10 (t, 4H, J = 4.7 Hz, OCH$_2$CH_2N), 0.94 (t, 2H, J = 8.0 Hz, OCH$_2$CH_2Si), −0.04 (s, 9 H, Si(CH_3)$_3$); Mass Spec.: Calcd for $[C_{27}H_{34}BrN_3O_5Si + H]^+$ Theor. m/z = 588, 590; Obs. = 588, 590. 2D HMBC: H_3 and H_5 correlate with C_4; OCH_2O correlate with C_4.

4.2.6. 6-Methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-(2-trimethylsilanylethoxymethoxy)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (6a). To a yellow-green suspension of **5** (1.155 g, 1.96 mmol), *N*-methylhomopiperazine (0.39 mL, 3.14 mmol), and 4 Å molecular sieves in 30 mL anhydrous toluene were added tris(dibenzylidineacetone)dipalladium(0) ($Pd_2(dba)_3$) (90.0 mg, 0.098 mmol) and racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) (0.358 g, 0.58 mmol). The resulting reddish brown mixture became lighter in color upon treatment with cesium carbonate (2.544 g, 7.81 mmol). The reaction mixture was heated at reflux under nitrogen for 17 h. The clear brown solution was cooled to room temperature, concentrated, and then purified by flash chromatography on silica gel using a slow gradient of 95:5 to 50:50 methylene chloride:methanol to afford the desired product (0.989 g, 81%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.88 (s, 1H, NH), 7.73 (s, 1H, ArH_3), 7.68 (d, 2H, J_o = 8.9 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.00 (d, 2H, J_o = 8.9 Hz, Ar$H_{3'}$ and $H_{5'}$), 6.94 (d, 1H, J_m = 2.7 Hz, ArH_5), 6.66 (d, 1H, J_m = 2.7 Hz, ArH_7), 5.62 (s, 2H, OCH_2O), 3.87 (s, 3H, OCH_3), 3.80 (t, 2H, J = 8.0 Hz, OCH_2CH$_2$Si), 3.73 (t, 4H, J = 4.7 Hz, OCH_2CH$_2$N), 3.63 (t, 2H, J = 5.9 Hz, ArNCH_2CH$_2$CH$_2$NCH$_3$), 3.33 (br s, 2H, ArNCH_2CH$_2$NCH$_3$), 3.09 (t, 4H, J = 4.7 Hz, OCH$_2$CH_2N), 2.97 (br s, 2H, ArNCH$_2$CH_2NCH$_3$), 2.69 (br s, 2H, ArNCH$_2$CH$_2$CH_2NCH$_3$), 2.35 (s, 3H, NCH_3), 2.09 (br s, 2 H ArNCH$_2$CH_2CH$_2$NCH$_3$), 0.94 (t, 2H, J = 8.0 Hz, OCH$_2$CH_2Si), −0.03 (s, 9H, Si(CH_3)$_3$); Mass Spec.: Calcd for $[C_{33}H_{47}N_5O_5Si + H]^+$ Theor. m/z = 622; Obs. = 622.

4.2.7. 6-Methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (7a). A solution of **6a** (0.989 g, 1.59 mmol) in 20 mL methanol was poured into 300 mL 0.05 N hydrochloric acid. The clear dark yellow solution became cloudy within 5 min. The mixture was stirred at room temperature for 45 min and then adjusted to pH 7 with 10% sodium hydroxide. The resulting yellow precipitate was isolated by filtration, washed with water, and dried under high vacuum to afford the desired product as a yellow solid (0.629 g, 80%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.97 (br s, 1H, C(O)NH), 7.67 (d, 2H, J_o = 8.8 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.47 (br s, 1H, ArH_5), 7.00 (s, 1H, C=CH), 6.99 (d, 2H, J_o = 8.8 Hz, Ar$H_{3'}$ and $H_{5'}$), 6.71 (br s, 1H, ArH_7), 3.85 (s, 3H, OCH_3), 3.75 (t, 4H, J = 4.6 Hz, OCH_2CH$_2$N), 3.70 (br s, 2H, ArNCH_2CH$_2$CH$_2$NCH$_3$), 3.55 (br s, 2H, ArNCH_2CH$_2$NCH$_3$), 3.09 (t, 4H, J = 4.6 Hz, OCH$_2$CH_2N), 2.95 (br s, 2H, ArNCH$_2$CH_2NCH$_3$), 2.73 (br s, 2H, ArNCH$_2$CH$_2$CH_2NCH$_3$), 2.36 (s, 3H, NCH_3), 2.07 (br s, 2H, ArNCH$_2$CH_2CH$_2$NCH$_3$); Mass Spec.: Calcd for $[C_{27}H_{33}N_5O_4 + H]^+$ Theor. m/z = 492.2605; Obs. = 492.2616. Analysis for $C_{27}H_{33}N_5O_4 \cdot 1.0HCl \cdot 0.3H_2O$: Calculated C, 60.79; H, 6.54; N, 13.13. Found C, 60.82; H, 6.53; N, 13.17.

4.3. Alternate Synthesis of 7a

4.3.1. 8-Bromo-6-methoxy-4-(2-trimethylsilanylethoxymethoxy)-quinoline-2-carboxylic acid methyl ester (13). A brown solution of **2** (6.73 g, 21.6 mmol) in 100 mL *N*-methylpyrrolidinone was treated with sodium hydride (60% dispersion in oil, 1.028 g, 25.7 mmol). Gas evolution and warming were observed. The reaction mixture was stirred for 10 min at room temperature

under nitrogen. Addition of 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) (5.00 mL, 28.3 mmol) resulted in a slightly cloudy, light brown solution. After 2.5 h at room temperature, the reaction mixture was poured into 800 mL water and stirred for 15 min. The resulting precipitate was isolated by filtration, washed with water, and dried under high vacuum to afford the product as a cream colored solid (9.70 g, quantitative yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.97 (d, 1H, J_m = 2.7 Hz, ArH_7), 7.79 (s, 1H, C=CH), 7.53 (d, 1H, J_m = 2.7 Hz, ArH_5), 5.70 (s, 2H, OCH_2O), 3.99 (s, 6H, OCH_3 and CO_2CH_3), 3.88 (t, 2H, J = 8.0 Hz, OCH_2CH$_2$Si), 0.97 (t, 2H, J = 8.0 Hz, OCH$_2$CH_2Si), −0.04 (s, 9H, Si(CH_3)$_3$); Additional 2D NMR data were used to confirm regioselectivity. HMBC experiments confirmed the proton and carbon assignments and the presence of proton–carbon coupling between the OCH_2O of the SEM group and the C4 of the quinoline ring system which can only be present with O-alkylation.; Mass Spec.: Calcd for [$C_{18}H_{24}BrNO_5Si$ + H]$^+$ Theor. m/z = 442, 444; Obs. = 442, 444. Analysis for $C_{18}H_{24}BrNO_5Si$·0.15-H_2O: Calculated C, 48.57; H, 5.50; N, 3.15. Found C, 48.09; H, 4.94; N, 3.21.

4.3.2. 6-Methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-(2-trimethylsilanylethoxymethoxy)-quinoline-2-carboxylic acid methyl ester (14). To a clear, light brown solution of **13** (1.01 g, 2.28 mmol), *N*-methylhomopiperazine (0.32 mL, 2.57 mmol), and 4 Å molecular sieves in 30 mL anhydrous toluene were added $Pd_2(dba)_3$ (43.8 mg, 0.048 mmol) and BINAP (169.8 mg, 0.27 mmol). The resulting wine colored solution was treated with cesium carbonate (1.124 g, 3.45 mmol). The reaction mixture was heated at reflux under nitrogen for 21 h. The resulting pea green reaction mixture was cooled to room temperature and concentrated. The crude mixture was purified by flash chromatography on silica gel using a gradient of 95:5 to 40:60 methylene chloride/methanol to afford the desired product as a yellow foam (1.004 g, 92%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.67 (s, 1H, ArH_3), 6.94 (d, 1H, J_m = 2.4 Hz, ArH_5), 6.66 (d, 1H, J_m = 2.4 Hz, ArH_7), 5.60 (s, 2H, OCH_2O), 3.94 (s, 3H, CO_2CH_3), 3.88 (s, 3H, OCH_3), 3.82 (t, 2H, J = 8.0 Hz, OCH_2CH$_2$Si), 3.75 (br s, 4H, ArNCH_2CH$_2$CH$_2$NCH$_3$ and ArNCH_2-CH$_2$NCH$_3$), 3.45 (br s, 2H, ArNCH$_2$CH_2NCH$_3$), 3.31 (br s, 2H, ArNCH$_2$CH$_2$CH_2NCH$_3$), 2.83 (s, 3H, NCH_3), 2.28 (br s, 2H, ArNCH$_2$CH_2CH$_2$NCH$_3$), 0.92 (t, 2H, J = 8.0 Hz, OCH$_2$CH_2Si), −0.04 (s, 9H, Si(CH_3)$_3$); Mass Spec.: Calcd for [$C_{24}H_{37}N_3O_5Si$ + H]$^+$ Theor. m/z = 476; Obs. = 476.

4.3.3. 6-Methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (15). To a light brown solution of **14** (1.00 g, 2.10 mmol) in 18 mL 3:1:1 tetrahydrofuran/methanol/water was added lithium hydroxide monohydrate (0.267 g, 6.35 mmol). The reaction mixture was stirred at room temperature for 5 h, acidified to pH 4 with 1 N HCl, and stirred an additional 20 min. The reaction mixture was concentrated and dried under high vacuum to afford an orange solid (0.97 g, quantitative yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.06 (s, 1H, NH), 7.53 (s, 1H, C=CH), 7.00 (d, 1H, J_m = 2.4 Hz, ArH_5), 6.70 (d, 1H, J_m = 2.4 Hz, ArH_7), 4.05–3.99 (m, 2H, ArNCH_2 CH$_2$CH$_2$NCH$_3$), 3.87 (s, 3H, OCH_3), 3.68–3.60 (m, 2H, ArNCH_2CH$_2$NCH$_3$), 3.54–3.47 (m, 2H, ArNCH$_2$ CH_2NCH$_3$), 3.41–3.26 (m, 2H, ArNCH$_2$CH$_2$CH_2NCH$_3$), 2.82 (d, 3H, J = 4.8 Hz, NCH_3), 2.46-2.41 (m, 1H, ArNCH$_2$CH_2CH$_2$NCH$_3$), 2.30–2.25 (m, 1H ArNCH$_2$-CH_2CH$_2$NCH$_3$); Mass Spec.: Calcd for [$C_{17}H_{21}$ N_3O_4 + H]$^+$ Theor. m/z = 332; Obs. = 332.

4.3.4. 6-Methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-morpho-lin-4-yl-phenyl)amide (7a). To a solution of **15** (2.10 mmol) and DIEA (1.4 mL, 8.6 mmol) in DMF (34 mL) were added TBTU (1.40 g, 4.36 mmol) and HOBt (0.588 g, 4.35 mmol) followed by the addition of 4-morpholinoaniline (0.463 g, 2.60 mmol). The resulting dark brown solution was stirred at room temperature under nitrogen for 19 h. The reaction mixture was concentrated in vacuo and the crude product was taken up in methylene chloride/methanol. Filtration of the resulting mixture afforded some product as a yellow solid. The filtrates were concentrated and partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The organic layer was washed with saturated sodium bicarbonate, dried over $MgSO_4$, filtered, and concentrated under vacuum to afford a brown solid. This was suspended in methanol and filtered to afford the desired product as a yellow solid (0.714 g, 69%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.97 (br s, 1H, NH), 7.67 (d, 2H, J_o = 8.8 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.47 (br s, 1H, ArH_5), 7.00 (s, 1H, C=CH), 6.99 (d, 2H, J_o = 8.8 Hz, Ar$H_{3'}$ and $H_{5'}$), 6.71 (br s, 1H, ArH_7), 3.85 (s, 3H, OCH_3), 3.75 (t, 4H, J = 4.6 Hz, OCH_2CH$_2$N), 3.70 (br s, 2H, ArNCH_2CH$_2$CH$_2$NCH$_3$), 3.55 (br s, 2H, ArNCH_2CH$_2$-NCH$_3$), 3.09 (t, 4H, J = 4.6 Hz, OCH$_2$CH_2N), 2.95 (br s, 2H, ArNCH$_2$CH_2NCH$_3$), 2.73 (br s, 2H, ArNCH$_2$CH$_2$ CH_2NCH$_3$), 2.36 (s, 3H, NCH_3), 2.07 (br s, 2H, ArNCH$_2$CH_2CH$_2$NCH$_3$); Mass Spec.: Calcd for [$C_{27}H_{33}N_5O_4$ + H]$^+$ Theor. m/z = 492; Obs. = 492.

4.3.5. 8-[(3-Dimethylamino-propyl)-methyl-amino]-6-methoxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (7b). The title compound was prepared from **5** in the same manner as described for **7a** using *N*,*N*,*N*′-trimethyl-1,3-propanediamine for the Buchwald–Hartwig coupling except that the SEM deprotection was carried out using 1.0 M HCl in ether (30 mL). The product precipitated from the reaction mixture and was isolated by filtration and washed with ether to afford the title compound as a cream colored solid (0.264 g, 62% yield from **5**). ^{1}H NMR (300 MHz, DMSO-d_6/CF_3CO_2D) 8.26 (d, 2H, J_o = 8.9 Hz, Ar$H_{2'}$ and $H_{6'}$), 8.19 (s, 1H, ArH_5), 7.85 (s, 1H, C=CH), 7.67 (s, 1H, ArH_7), 7.59 (d, 2H, J_o = 8.9 Hz, Ar$H_{3'}$ and $H_{5'}$), 4.03 (s, 3H, OCH_3), 3.97 (br s, 4H, OCH_2CH$_2$N), 3.89 (t, 2H, J = 7.2 Hz, ArNCH_2CH$_2$), 3.54 (br s, 4H, OCH$_2$CH_2N), 3.46 (s, 3H, ArNCH_3), 3.15 (t, 2H, J = 7.2 Hz, CH$_2$CH_2N(CH$_3$)$_2$), 2.69 (s, 6H, CH$_2$N(CH_3)$_2$), 1.91 (br s, 2H, ArNCH$_2$ CH_2CH$_2$ N(CH$_3$)$_2$); Mass Spec.: Calcd for [$C_{27}H_{35}$ N_5O_4 + H]$^+$ Theor. m/z = 494; Obs. = 494. Analysis for

$C_{27}H_{35}$-N_5O_4·3.1HCl·2.15H_2O: Calculated C, 50.25; H, 6.62; N, 10.82. Found C, 50.28; H, 6.67; N, 10.79.

4.3.6. 6-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (7c). The title compound was prepared from **2** as described in the alternate synthesis for **7a** (see above). The desired product was obtained as a yellow solid (0.144 g, 43% yield from **15**). ^{1}H NMR (300 MHz, DMSO-d_6/CF_3CO_2D) 7.90 (d, 2H, J_o = 8.9 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.59 (s, 1H, C=CH), 7.36 (d, 2H, J_o = 8.9 Hz, Ar$H_{3'}$ and $H_{5'}$), 7.19 (d, 1H, J_m = 2.4 Hz, ArH_5), 6.95 (d, 1H, J_m = 2.4 Hz, ArH_7), 4.09 (t, 2H, J = 11.6 Hz, ArNCH_2CH_2N), 3.91 (s, 3H, OCH_3), 3.89 (t, 4H, d, 1H, J = 5.4 Hz, OCH_2CH_2N), 3.66 (t, 2H, J = 11.6 Hz, ArNCH_2CH_2N), 3.52 (t, 2H, J = 11.6 Hz, ArNCH_2CH_2N), 3.38 (t, 4H, J = 5.4 Hz OCH_2CH_2N), 3.18 (t, 2H, J = 11.6 Hz, ArNCH_2CH_2N), 2.97 (s, 3H, NCH_3); Mass Spec.: Calcd for [$C_{26}H_{31}N_5O_4$ + H]$^+$ Theor. m/z = 478.2449; Obs. = 478.2440. Analysis for $C_{26}H_{31}N_5O_4$·0.2HCl: Calculated C, 64.41H 6.49; N, 14.44. Found C, 64.49; H, 6.29; N, 14.42.

4.3.7. 8-[(2-Dimethylamino-ethyl)-methyl-amino]-6-methoxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (7d). The title compound was prepared from **5** in the same manner as described for **7b** using *N*,*N*,*N*′-trimethyl ethylene diamine for the Buchwald–Hartwig coupling. The desired product was obtained as a light yellow solid (0.269 g, 77% yield from **5**). ^{1}H NMR (300 MHz, DMSO-d_6/CF_3CO_2D) 8.10 (d, 2H, J_o = 8.4 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.69 (s, 1H, ArH_5), 7.61 (s, 1H, C=CH), 7.55 (d, 2H, J_o = 8.4 Hz, Ar$H_{3'}$ and $H_{5'}$), 7.44 (s, 1H, ArH_7), 4.01 (t, 2H, J = 6.6 Hz, ArNCH_2CH_2N), 3.98 (br s, 4H, OCH_2CH_2N), 3.98 (s, 3H, OCH_3), 3.51 (br s, 4H, OCH_2CH_2N), 3.43 (t, 2H, J = 6.6 Hz, ArNCH_2CH_2N), 3.24 (s, 3H, ArNCH_3), 2.83 (s, 6H, CH_2N(CH_3)$_2$); Mass Spec.: Calcd for [$C_{26}H_{33}N_5O_4$ + H]$^+$ Theor. m/z = 480; Obs. = 480. Analysis for $C_{26}H_{33}N_5O_4$·3.15HCl·1.7H_2O: Calculated C, 49.96; H, 6.38; N, 11.20. Found C, 49.94; H, 6.39; N, 11.17.

4.3.8. 8-((3R)-(+)-3-Dimethylamino-pyrrolidin-1-yl)-6-methoxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (7e). The title compound was prepared from **5** in the same manner as described for **7b** using (3*R*)-(+)-3-(dimethylamino)pyrrolidine for the Buchwald–Hartwig coupling. A final trituration in methylene chloride containing a small amount of methanol followed by filtration and washing with methylene chloride afforded the desired product as a yellow solid (0.190 g, 59% yield from **5**). ^{1}H NMR (300 MHz, DMSO-d_6/CF_3CO_2D) 10.72 (br s, <1H, CH=CNH), 10.33 (br s, <1H, C(O)NH), 8.07 (d, 2H, J_o = 9.0 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.69 (d, 2H, J_o = 9.0 Hz, Ar$H_{3'}$ and $H_{5'}$), 7.61 (s, 1H, C=CH), 7.03 (d, 1H, J_m = 2.4 Hz, ArH_5), 6.71 (br s, 1H, ArH_7), 4.28-3.91 (m, 6H, ArNCH_2CH(N)CH_2CH_2), 4.03 (t, 4H, J = 4.4 Hz, OCH_2CH_2N), 3.91 (s, 3H, OCH_3), 3.57 (t, 4H, J = 4.4 Hz, OCH_2CH_2N), 2.92 (d, 6H, J = 5.7 Hz, NCH_3)$_2$), 2.42–2.32 (m, 1H, CHN(CH_3)$_2$); Mass Spec.: Calcd for [$C_{27}H_{33}N_5O_4$ + H]$^+$ Theor. m/z = 492.2605; Obs. = 492.2608. Analysis for $C_{27}H_{33}N_5O_4$·3.6HCl·0.01-H_2O: Calculated C, 51.92; H, 5.94; N, 11.21. Found C, 51.99; H, 5.88; N, 11.15.

4.3.9. 8-((3*S*)-(−)-3-Dimethylamino-pyrrolidin-1-yl)-6-methoxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (7f). The title compound was prepared from **5** in the same manner as described for **7e** using (3*S*)-(−)-3-(dimethylamino)-pyrrolidine for the Buchwald–Hartwig coupling. The desired product was obtained as a yellow solid (0.178 g, 56% yield from **5**). ^{1}H NMR (300 MHz, DMSO-d_6/CF_3CO_2D) 8.03 (d, 2H, J_o = 9.0 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.63 (d, 2H, J_o = 9.0 Hz, Ar$H_{3'}$ and $H_{5'}$), 7.59 (s, 1H, C=CH), 7.00 (s, 1H, ArH_5), 6.65 (s, 1H, ArH_7), 4.24-3.91 (m, 6H, ArNCH_2CH(N)CH_2CH_2), 4.00 (br s, 4H, OCH_2CH_2N), 3.91 (s, 3H, OCH_3), 3.55 (br s, 4H, OCH_2CH_2N), 2.93 (d, 6H, J = 3.9 Hz, NCH_3)$_2$), 2.35-2.29 (m, 1H, CHN(CH_3)$_2$); Mass Spec.: Calcd for [$C_{27}H_{33}N_5O_4$ + H]$^+$ Theor. m/z = 492.2605; Obs. = 492.2616. Analysis for $C_{27}H_{33}N_5O_4$·3.0HCl·0.3H_2O: Calculated C, 53.48; H, 6.08; N, 11.55. Found C, 53.52; H, 6.11; N, 11.51.

4.3.10. 8-[Ethyl-(1-ethyl-pyrrolidin-3-yl)-amino]-6-methoxy-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (7g). The title compound was prepared from **5** in the same manner as described for **7b** using 3-diethylaminopyrrolidine for the Buchwald–Hartwig coupling. A final trituration in diethyl ether containing a small amount of methanol followed by filtration and washing with ether afforded the desired product as a beige solid (0.163 g, 37% yield from **5**). ^{1}H NMR (300 MHz, DMSO-d_6/CF_3CO_2D) 8.03 (d, 2H, J_o = 9.0 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.65 (d, 2H, J_o = 9.0 Hz, Ar$H_{3'}$ and $H_{5'}$), 7.58 (s, 1H, C=CH), 6.99 (s, 1H, ArH_5), 6.23 (s, 1H, ArH_7), 4.23–4.05 (m, 3H, ArNCHCH_2 & ArNCHCH_2N), 4.01 (br s, 4H, OCH_2CH_2N), 3.91 (s, 3H, OCH_3), 3.90 (br s, 2H, ArNCHCH_2CH_2N), 3.58 (br s, 4H, OCH_2CH_2N), 3.46–3.40 (m, 2H, ArNCH_2CH_3), 3.27–3.22 (m, 2H, NCH_2CH_3), 2.31 (br s, 2H, ArNCHCH_2CH_2N), 1.28 (t, 3H, J = 7.2 Hz, ArNCH_2CH_3), 1.24 (t, 3H, J = 7.2 Hz, NCH_2CH_3); Mass Spec.: Calcd for [$C_{29}H_{37}N_5O_4$ + H]$^+$ Theor. m/z = 520.2918; Obs. = 520.2907. Analysis for $C_{29}H_{37}N_5O_4$·4.00HCl·0.35Et_2O: Calculated C, 52.81; H, 6.49; N, 10.13. Found C, 52.81; H, 6.24; N, 9.89.

4.3.11. 6-Methoxy-8-[methyl-(1-methyl-pyrrolidin-3-yl)-amino]-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (7h). The title compound was prepared from **5** in the same manner as described for **7g** using *N*,*N*′-dimethyl-3-aminopyrrolidine for the Buchwald–Hartwig coupling except that the hydroscopic material was dissolved in methanol, stirred in the presence of potassium carbonate, filtered, and concentrated to dryness prior to the trituration in diethyl ether. This yielded a brown solid which was purified on silica gel using a gradient of 100:0 to 80:20 methylene chloride:methanol as an eluent. After a final trituration in

methanol, the desired product was obtained as a yellow solid (0.024 g, 13% yield from **5**). ^{1}H NMR (300 MHz, DMSO-d_6/CF_3CO_2D) 7.95 (d, 2H, J_o = 9.0 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.57 (s, 1H, C=CH), 7.47 (d, 2H, J_o = 9.0 Hz, Ar$H_{3'}$ and $H_{5'}$), 7.39 (s, 1H, ArH_5), 7.36 (s, 1H, ArH_7), 4.90–4.70 (m, 1H, ArNCHCH$_2$), 3.95 (s, 3H, OCH_3), 3.95–3.50 (m, 6H, OCH_2CH$_2$N and ArNCHCH_2N), 3.46 (br s, 4H, OCH$_2$CH_2N), 3.44–3.18 (m, 2H, ArNCHCH$_2$CH_2N), 3.07 (m, 3H, ArNCH_3), 2.77 (m, 3H, CH$_2$NCH_3), 2.34-2.22 (m, 2H, NCHCH_2CH$_2$N); Mass Spec.: Calcd for $[C_{27}H_{33}N_5O_4 + H]^+$ Theor. m/z = 492.2605; Obs. = 492.2603.

4.4. Synthesis of Quinoline 7i

4.4.1. 2-(2-Bromo-4-fluoro-phenylamino)-but-2-enedioic acid dimethyl ester (8). A 150 mL round-bottomed flask equipped with a reflux condenser, nitrogen inlet and magnetic stir bar was charged with 2-bromo-4-fluoroaniline (9.85 g, 51.8 mmol). The material was then dissolved in methanol (85 mL). To this solution was added dimethylacetylenedicarboxylate (7.37 g, 6.37 mL, 51.8 mmol). The reaction mixture was heated at reflux for 18 h. The reaction mixture was cooled to room temperature and then placed in a freezer to allow crystals to form. The product was isolated as yellow plates by filtration, followed by washing with cold methanol. The material was dried in a vacuum oven to yield the product as a single diastereomer as determined by NMR (14.1 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (br s, 1H, NH), 7.33 (dd, 1H, J = 8.0 Hz, J_m = 2.9 Hz, ArH_3), 6.94 (dt, 1H, J = 8.1 Hz, J_m = 2.9 Hz, ArH_5), 6.79 (dd, 1H, J = 8.9 Hz, J = 5.3 Hz, ArH_6), 5.55 (s, 1H, C=CH), 3.76 (s, 3H, CO_2CH_3), 3.70 (s, 3H, CO_2CH_3); Mass Spec.: Calcd for $[C_{12}H_{11}BrFNO_4 + H]^+$ Theor. m/z = 332, 334; Obs. = 332, 334.

4.4.2. 8-Bromo-6-fluoro-4-oxo-1,4-dihydroquinoline-2-carboxylic acid methyl ester (9). A 500 mL, 3-necked round-bottomed flask equipped with a reflux condenser, thermocouple adapter, nitrogen inlet, and magnetic stirrer was charged with Dowtherm® A (150 mL). The solvent was carefully preheated to 250 °C by applying heat with a heating mantle. After the solvent reached temperature, **8** (14.1 g, 42.5 mmol) was carefully added as a solid portionwise over 20 min. The mixture was allowed to react at 250 °C for an additional hour. After cooling to room temperature, 250 mL of hexane were added. Collection of the resultant solids by filtration, followed by a hexane wash, yielded 9.9 g (78%) of the pure product. A second crop (0.85 g) contained not additional pure product but rather a mixture dominated by the decarboxylated side product as identified by LC/MS. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (br s, 1H, NH), 7.98 (dd, 1H, J = 8.4 Hz, J_m = 2.7 Hz, ArH_7), 7.08 (dd, 1H, J = 7.2 Hz, J_m = 2.7 Hz, ArH_5), 6.94 (d, 1H, J = 1.8 Hz, C=CH), 4.07 (s, 3H, CO_2CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 178.6, 163.2, 160.6, 157.3, 136.8, 134.0, 128.5, 128.4, 125.7, 125.3, 113.2, 113.1, 111.5, 111.2, 54.2; Mass Spec.: Calcd for $[C_{11}H_7BrFNO_3 + H]^+$ Theor. m/z = 300, 302; Obs. = 300, 302. Analysis for $C_{11}H_7BrFNO_3$: Calculated C 44.03; H, 2.35; N, 4.67. Found C, 44.14; H, 2.14; N, 4.70.

4.4.3. 8-Bromo-6-fluoro-4-(2-trimethylsilanyl-ethoxymethoxy)-quinoline-2-carboxylic acid methyl ester (10). A 250 mL, 3-necked round-bottomed flask equipped with a reflux condenser, nitrogen inlet, and magnetic stirrer was charged with **9** (1.25 g, 4.17 mmol) and NMP (75 mL). To this solution was cautiously added sodium hydride (60% dispersion in oil, 183 mg, 4.58 mmol). Since no reaction occured when the reaction mixture was cooled in an ice bath, the anion was allowed to form at room temperature for 1 h. The solution turned a yellow color when the anion had formed. When this process was complete, 2-(trimethylsilyl)ethoxymethyl chloride (764 mg, 810 μL, 4.58 mmol) was added to the reaction. The yellow color then disappeared and the reaction turned a milky white. This mixture was allowed to stir for an additional 1 h. At the end of this time, the reaction was cautiously quenched with 100 mL of water and then the entire mixture was poured into 500 mL of water. The resultant solids were collected by filtration and washed with water. The solids were dried and the material further purified by silica gel chromatography using 20% ethyl acetate in methylene chloride as eluent. The pure product was recovered as a colorless solid (1.4 g, 78%). The structural assignment of the O alkylation product versus the possible N alkylation was made based upon NMR data. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, 1H, J = 7.8 Hz, J_m = 3.0 Hz, ArH_7), 7.83 (dd, 1H, J = 7.8 Hz, J_m = 3.0 Hz, ArH_5), 7.84 (s, 1H, ArH_3), 5.53 (s, 2H, OCH_2O), 4.04 (s, 3H, CO_2CH_3), 3.82 (t, 2H, J = 8.3 Hz, OCH_2CH$_2$Si), 0.96 (t, 2H, J = 8.3 Hz, OCH$_2$CH_2Si), −0.03 (s, 9 H, Si(CH_3)$_3$); Mass Spec.: Calcd for $[C_{17}H_{21}BrFNO_4Si + H]^+$ Theor. m/z = 430, 432; Obs. = 430, 432.

4.4.4. 6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-(2-trimethylsilanylethoxymethoxy)-quinoline-2-carboxylic acid methyl ester (11). A 250 mL, 3-necked round-bottomed flask equipped with a reflux condenser, nitrogen inlet, and magnetic stirrer was charged with **10** (715 mg, 1.66 mmol), $Pd_2(dba)_3$ (30 mg, 0.033 mmol), BINAP (123 mg, 0.20 mmol), 4 Å molecular sieves (1 g), and anhydrous toluene (100 mL). To the stirred suspension was then added 1-methylpiperazine (183 mg, 203 μL, 1.82 mmol), followed by cesium carbonate (757 mg, 2.32 mmol). The mixture was heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature and filtered through a plug of Celite with toluene washing to remove solid byproducts. Purification by flash chromatography using a gradient of 5–20% methanol in methylene chloride as eluent yielded 560 mg (75%) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H, ArH_3), 7.29 (dd, 1H, J = 9.3 Hz, J_m = 2.7 Hz, ArH_7), 6.77 (dd, 1H, J = 11.1 Hz, J_m = 2.7 Hz, ArH_5), 5.41 (s, 2H, OCH_2O), 3.90 (s, 3H, CO_2CH_3), 3.73 (t, 2H, J = 8.3 Hz, OCH_2CH$_2$Si), 3.44 (br s, 4H, ArNCH_2CH$_2$N), 2.69 (br s, 4H, ArNCH$_2$CH_2N), 2.33 (s, 3H, NCH_3), 0.87 (t, 2H, J = 8.3 Hz, OCH$_2$CH_2Si), −0.10 (s, 9H, Si(CH_3)$_3$); Mass

Spec.: Calcd for $[C_{22}H_{32}FN_3O_4Si + H]^+$ Theor. m/z = 450; Obs. = 450.

4.4.5. 6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (12). Into a 125 mL Erlenmeyer flask containing tetrahydrofuran (30 mL) and methanol (30 mL) was placed **11** (560 mg, 1.24 mmol). To this was added with stirring a solution of lithium hydroxide monohydrate (104 mg, 2.48 mmol) in water (30 mL). The reaction mixture was stirred for 1 h and then quenched with 2 N HCl (10 mL). The solution was filtered and the solids washed with 0.5 N HCl (10 mL). The combined filtrates were concentrated to give the solid yellow product as the hydrochloride salt (400 mg, 95%). Mass Spec.: Calcd for $[C_{15}H_{16}FN_3O_3 + H]^+$ Theor. m/z = 306; Obs. = 306.

4.4.6. 6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (7i). To a 100 mL round-bottomed flask equipped with a nitrogen inlet and magnetic stirrer was added **12** (200 mg, 0.59 mmol). The material was dissolved in DMF (20 mL) and then treated with 4-morpholinoaniline (125 mg, 0.70 mmol). To the stirred solution were quickly added simultaneously TBTU (379 mg, 1.18 mmol) and HOBt (160 mg, 1.18 mmol). At this point DIEA (305 mg, 385 μL, 2.36 mmol) was added via syringe over 5 min. The reaction mixture was stirred at room temperature for 18 h and then concentrated on a rotary evaporator under high vacuum to remove the DMF. The residue was triturated with methanol and the crude solids were isolated by filtration. The material was then dissolved in methylene chloride and extracted with 10% sodium bicarbonate solution. The organic layer was dried and concentrated. These residues were then purified by flash chromatography using a gradient of 5–10% methanol in methylene chloride as eluent. The material was then crystallized from methanol to give the pure product as a yellow solid (150 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.28 (s, 1H, CH=CN*H*), 10.24 (s, 1H, C(O)N*H*), 7.94 (d, 2H, J_o = 9.0 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.76 (dd, 1H, J = 8.7 Hz, J_m = 2.6 Hz, ArH_7), 7.56 (s, 1H, C=C*H*), 7.22 (dd, 1H, J = 9.3 Hz, J_m = 2.6 Hz, ArH_5), 7.01 (d, 2H, J_o = 9.0 Hz, Ar$H_{3'}$ and $H_{5'}$), 3.90 (t, 4H, J = 4.8 Hz, ArNCH_2CH_2N), 3.21 (t, 4H, J = 4.8 Hz, ArNCH$_2$CH_2N), 3.08 (br s, 4H, OCH_2CH$_2$N), 2.78 (br s, 4H, OCH$_2$CH_2N), 2.45 (br s, 3H, NCH_3); Mass Spec.: Calcd for $[C_{25}H_{28}FN_5O_3 + H]^+$ Theor. m/z = 466.2249; Obs. = 466.2262. Analysis for $C_{25}H_{28}FN_5O_3 \cdot 0.25HCl$: Calculated C, 63.26; H, 6.00; N, 14.76. Found C, 63.38; H, 5.90; N, 14.70.

4.5. Synthesis of quinolines 18a–b

4.5.1. 8-Bromo-4-chloro-6-methoxy-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (16). A suspension of **3**, (0.52 g, 1.75 mmol) in methylene chloride (20 mL) was treated with oxalyl chloride (1.5 mL, 17.2 mmol) and catalytic DMF (3 drops). The reaction mixture bubbled vigorously and became clearer. The reaction was heated at reflux for 2 h. LCMS of a sample quenched in methanol confirmed complete consumption of starting material. The reaction mixture was cooled to room temperature and concentrated in vacuo to afford a pale yellow solid which was kept under nitrogen and used as quickly as possible.

To a yellow solution of the acid chloride in methylene chloride (20 mL) were added 4-morpholinoaniline (0.347 g, 1.94 mmol) and DIEA (1.0 mL, 6.1 mmol). The solution became orange and gas evolution was observed. Within 30 min, solids began to precipitate from the solution. The reaction mixture was stirred at room temperature for 1 h. The solids were isolated by filtration and dried under high vacuum to afford the desired product (0.406 g, 49%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.15 (s, 1H, C(O)N*H*), 8.33 (s, 1H, ArH_3), 8.10 (d, 1H, J_m = 2.7 Hz, ArH_7), 7.70 (d, 2H, J_o = 9.0 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.56 (d, 1H, J_m = 2.7 Hz, ArH_5), 7.01 (d, 2H, J_o = 9.0 Hz, Ar$H_{3'}$ and $H_{5'}$), 4.06 (s, 3H, OCH_3), 3.75 (t, 4H, J = 4.8 Hz, OCH_2CH$_2$N), 3.11 (t, 4H, J = 4.8 Hz, OCH$_2$CH_2N); Mass Spec.: Calcd for $[C_{21}H_{19}BrClN_3O_3 + H]^+$ Theor. m/z = 476, 478; Obs. = 476, 478.

4.5.2. 8-Bromo-4-dimethylamino-6-methoxy-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (17a). A solution of **16** (0.1512 g, 0.317 mmol) in 2.0 M dimethyl amine in THF (100 mL) was heated at 100 °C in a Parr bomb. The pressure was initially at 75–80 psi and then remained at approximately 60 psi. After 18 h, the reaction mixture was cooled to room temperature, concentrated, and dried to afford the crude product as a brown solid. Purification on silica gel using a gradient of 100:0 to 95:5 methylene chloride/methanol afforded the clean product (0.142 g, 92%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.20 (s, 1H, C(O)N*H*), 7.90 (d, 1H, J_m = 2.7 Hz, ArH_5), 7.69 (d, 2H, J_o = 9.0 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.60 (s, 1H, ArH_3), 7.41 (d, 1H, J_m = 2.7 Hz, ArH_7), 7.01 (d, 2H, J_o = 9.0 Hz, Ar$H_{3'}$ and $H_{5'}$), 3.96 (s, 3H, OCH_3), 3.75 (t, 4H, J = 4.8 Hz, OCH_2CH$_2$N), 3.10 (t, 4H, J = 4.8 Hz, OCH$_2$CH_2N), 3.08 (s, 6H, N(CH_3)$_2$); Mass Spec.: Calcd for $[C_{21}H_{19}BrClN_3O_3 + H]^+$ Theor. m/z = 485, 487; Obs. = 485, 487.

4.5.3. 4-Dimethylamino-6-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (18a). To a suspension of **17a** (139.9 mg, 0.288 mmol), *N*-methylpiperazine (48 μL, 0.43 mmol), and 4 Å molecular sieves in anhydrous toluene (15 mL) were added $Pd_2(dba)_3$ (15.3 mg, 16.7 μmol), BINAP (63.0 mg, 0.101 mmol), and cesium carbonate (0.436 g, 1.345 mmol). The resulting wine colored mixture was heated at reflux under nitrogen for 20 h. The reaction mixture was cooled to room temperature and concentrated. The crude mixture was purified by flash chromatography on silica gel using a gradient of 100:0 to 95:5 methylene chloride/methanol to afford the desired product as a yellow solid (96.9 mg, 67%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.06 (s, 1H, C(O)N*H*), 7.69 (d, 2H, J_o = 9.0 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.58 (s, 1H, ArH_3), 7.58 (d, 2H, J_o = 9.0 Hz, Ar$H_{3'}$ and $H_{5'}$), 6.95 (d, 1H, J_m = 2.7 Hz, ArH_5), 6.76 (d, 1H, J_m = 2.7 Hz, ArH_7), 3.90 (s, 3H, OCH_3), 3.75 (t, 4H, J = 4.8 Hz, OCH_2CH$_2$N), 3.37 (br s, 4H, ArNCH_2CH$_2$N), 3.10

(t, 4H, J = 4.8 Hz, OCH_2CH_2N), 3.01 (s, 6H, $N(CH_3)_2$), 2.71 (br s, 4H, $ArNCH_2CH_2N$), 2.35 (s, 3H, $ArNCH_2CH_2NCH_3$); Mass Spec.: Calcd for $[C_{28}H_{36}N_6O_3 + H]^+$ Theor. m/z = 505.2921; Obs. = 505.2923. Analysis for $C_{28}H_{36}N_6O_3 \cdot 0.05H_2O$: Calculated C, 66.53; H, 7.20; N, 16.62. Found C, 66.63; H, 7.06; N, 16.52.

4.5.4. 6-Methoxy-4-methylamino-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (18b). The title compound was prepared from **16** (0.151 g, 0.31 mmol) according to the method described for **18a** using *N*-methyl amine to prepare 8-bromo-4-methylamino-6-methoxy-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (**17b**) (pale yellow solid, 0.131 g, 87%). Following the Buchwald–Hartwig coupling, the title compound was obtained as a yellow solid (76.7 mg, 57%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, 1H, C(O)NH), 7.65 (d, 2H, J_o = 9.0 Hz, Ar$H_{2'}$ and $H_{6'}$), 7.33 (d, 1H, J = 4.7 Hz, ArNH) 7.17 (d, 1H, J_m = 2.1 Hz, ArH_7), 7.10 (s, 1H, ArH_3), 7.02 (d, 2H, J_o = 9.0 Hz, Ar$H_{3'}$ and $H_{5'}$), 6.72 (d, 1H, J_m = 2.1 Hz, ArH_5), 3.88 (s, 3H, OCH_3), 3.75 (t, 4H, J = 4.8 Hz, OCH_2CH_2N), 3.31 (br s, 4H, $ArNCH_2CH_2N$, under H_2O peak), 3.10 (t, 4H, J = 4.8 Hz, OCH_2CH_2N), 2.98 (d, 3H, J = 4.7 Hz, $NHCH_3$), 2.69 (br s, 4H, $ArNCH_2CH_2N$), 2.33 (s, 3H, $ArNCH_2CH_2NCH_3$); Mass Spec.: Calcd for $[C_{27}H_{34}N_6O_3 + H]^+$ Theor. m/z = 491.2765; Obs. = 491.2770. Analysis for $C_{27}H_{34}N_6O_3 \cdot 0.25CH_2Cl_2 \cdot 0.05CH_3OH$: Calculated C, 63.86; H, 6.81; N, 16.37. Found C, 64.13; H, 6.56; N, 16.04.

4.6. Synthesis of quinolines 18c

4.6.1. 8-Bromo-6-fluoro-4-methoxy-quinoline-2-carboxylic acid methyl ester (19). A 150 mL, 3-necked round-bottomed flask equipped with a reflux condenser, magnetic stirrer, and nitrogen inlet was charged with **9** (2.0 g, 6.76 mmol, 1.0 equiv) in NMP (50 mL). Sodium hydride (60% dispersion in oil, 300 mg, 7.44 mmol) was cautiously added portionwise to the solution at room temperature. A yellow color developed, indicating that formation of the anion had occurred, with hydrogen evolution. Stirring of the anion solution was continued for 1 h, followed by addition of iodomethane (1.14 g, 500 μL, 8.04 mmol) via syringe. The mixture was allowed to react for an additional 2 h and was then cautiously quenched with 20 mL of water. The solids, which precipitated upon dilution in 1 L of water, were collected by filtration, washed with water, and dried to give the pure O-methylated material as of a colorless solid (2.1 g, 98%).

Alternatively, a 100 mL, 3-necked round-bottomed flask equipped with a reflux condenser, nitrogen inlet, and magnetic stirrer was charged with **9** (350 mg, 1.17 mmol) and K_2CO_3 (242 mg, 1.75 mmol). This material was suspended in DMSO (20 mL) and then heated to 70 °C for 1 h. Formation of the anion was apparent when the mixture became cloudy. The mixture was cooled to 35 °C. Methyl iodide (331 mg, 145 μL, 2.33 mmol, 2.0 equiv) was added and stirring continued for 2 h. The mixture was poured into water (200 mL) and the resulting solids were collected by filtration and washed with water to give the O-methylated product after drying (340 mg, 93%).

Additional 2D NMR data were used to confirm regioselectivity. HMBC experiments confirmed the proton and carbon assignments and the presence of proton–carbon coupling between the methyl protons of the methoxy group and the C4 of the quinoline ring system which can only be present with O-alkylation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, 1H, J = 7.8 Hz, J_m = 2.7 Hz, ArH_7), 7.84 (dd, 1H, J = 8.9 Hz, J_m = 2.7 Hz, ArH_5), 7.64 (s, 1H, ArH_3), 4.14 (s, 3H, Ar-OCH_3), 4.08 (s, 3H, CO_2CH_3); Mass Spec.: Calcd for $[C_{12}H_9BrFNO_3 + H]^+$ Theor. m/z = 314, 316; Obs. = 314, 316. Analysis for $C_{12}H_9BrFNO_3$: Calculated C 45.89; H, 2.89; N, 4.46. Found C, 45.64; H, 2.68; N, 4.52.

4.6.2. 6-Fluoro-4-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid methyl ester (20). To a 250 mL, 3-necked round-bottomed flask equipped with a reflux condenser, magnetic stirrer, and nitrogen inlet were added **19** (2.1 g, 6.68 mmol), $Pd_2(dba)_3$ (122 mg, 0.134 mmol), BINAP (499 mg, 0.802 mmol), 4 Å molecular sieves (1 g), and anhydrous toluene (80 mL). To the stirred suspension was added 1-methylpiperazine (736 mg, 815 μL, 7.35 mmol), followed by cesium carbonate (3.05 g, 9.35 mmol). The mixture was heated to 80 °C for 36 h. When the reaction was determined to be complete, it was cooled to room temperature and filtered through a plug of Celite, with toluene washing to remove solid byproducts. Purification by flash chromatography, using a gradient of 5–20% methanol in methylene chloride as eluent, yielded the desired product (2.0 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 1H, ArH_3), 7.37 (dd, 1H, J = 9.0 Hz, J_m = 2.7 Hz, ArH_7), 6.87 (dd, 1H, J = 11.0 Hz, J_m = 2.7 Hz, ArH_5), 4.12 (s, 3H, Ar-OCH_3), 4.09 (s, 3H, CO_2CH_3), 3.53 (br s, 4H, $ArNCH_2CH_2N$), 2.78 (t, 4H, J = 4.7 Hz, $ArNCH_2CH_2N$), 2.42 (s, 3H, NCH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.2, 163.7, 163.2, 160.4, 152.6, 152.4, 145.2 (2 peaks), 139.6, 124.5, 124.3, 107.0, 106.6, 100.3, 98.2, 97.9, 56.1, 55.0, 52.8, 51.9, 46.2; Mass Spec.: Calcd for $[C_{17}H_{20}FN_3O_3 + H]^+$ Theor. m/z = 334; Obs. = 334.

4.6.3. 6-Fluoro-4-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (21). To a 125 mL Erlenmeyer flask containing THF (30 mL) and methanol (30 mL) was added **20** (2.1 g, 6.3 mmol). To this solution was added with stirring a solution of lithium hydroxide monohydrate (291 mg, 6.9 mmol) in water (30 mL). This solution was allowed to react for 1 h and then quenched with 2 N HCl (10 mL). The solution was then filtered and the solids washed with 0.5 N HCl (10 mL). The combined filtrates were concentrated to give the solid yellow product as the hydrochloride salt (2.15 g, 95%). Mass Spec.: Calcd for $[C_{16}H_{18}FN_3O_3 + H]^+$ Theor. m/z = 320; Obs. = 320.

4.6.4. 6-Fluoro-4-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amide (18c). To a 250 mL, round-bottomed flask equipped with a nitrogen inlet and magnetic stirrer was added **21** (2.01 g, 6.3 mmol). The material was dissolved in DMF (20 mL) and then 4-morpholinoaniline (1.35 g, 7.56 mmol) was added. To the stirred solution were quickly added simultaneously TBTU (4.05 g, 12.6 mmol) and HOBt (1.7 g, 12.6 mmol). At this point, DIEA (3.25 g, 4.11 mL, 25.2 mmol) was added via syringe over 5 min. The reaction mixture was allowed to stir at room temperature for 18 h. The DMF was removed by concentration on a rotary evaporator under high vacuum. The residue was triturated with methanol and the crude solids were isolated by filtration. The material was then dissolved in methylene chloride and extracted with 10% sodium bicarbonate solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residues were purified by flash chromatography using a gradient of 5–10% methanol in methylene chloride as eluent. The obtained material was crystallized from methanol to give the pure product as a yellow solid (2.83 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (s, 1H, C(O)N*H*), 7.77 (s, 1H, ArH_3), 7.71 (dd, 2H, $J_o = 7.0$ Hz, $J_m = 2.0$ Hz, Ar$H_{2'}$ and $H_{6'}$), 7.45 (dd, 1H, $J = 9.3$ Hz, $J_m = 2.7$ Hz ArH_7), 6.99 (d, 2H, $J_o = 7.0$ Hz, Ar$H_{3'}$ and $H_{5'}$), 6.94 (dd, 1H, $J = 10.8$ Hz, $J_m = 2.7$ Hz, ArH_5), 4.13 (s, 3H, ArOCH_3), 3.88 (t, 4H, $J = 4.8$ Hz, OCH_2CH$_2$N), 3.51 (br s, 4H, ArNCH_2CH$_2$N), 3.17 (t, 4H, $J = 4.8$ Hz, OCH$_2$CH_2N), 2.83 (t, 4H, $J = 4.7$ Hz, ArNCH$_2$CH_2N), 2.47 (s, 3H, NCH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 164.0, 163.9, 163.1, 161.9, 159.8, 151.5, 151.4, 148.2, 148.1, 138.6, 130.8, 124.3, 124.1, 120.5, 116.5, 107.9, 107.5, 99.2, 98.9, 98.2, 66.9, 56.3, 55.4, 52.1, 49.8, 46.3; Mass Spec.: Calcd for $[C_{26}H_{30}FN_5O_3 + H]^+$ Theor. $m/z = 480.2405$; Obs. = 480.2419. Analysis for $C_{26}H_{30}FN_5O_3 \cdot 0.45HCl$: Calculated C, 62.97; H, 6.19; N, 14.12. Found C, 63.24; H, 5.88; N, 14.20.

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References and notes

1. (a) Childers, W. E., Jr.; Robichaud, A. J. *Annu. Rep. Med. Chem.* **2005**, *40*, 17–33; (b) Robichaud, A. J.; Largent, B. L. *Annu. Rep. Med. Chem.* **2000**, *35*, 11–20, Chap. 2; (c) Roth, B. L.; Chuang, D.-M. *Life Sci.* **1987**, *41*, 1051–1064.
2. (a) Barnes, N. M.; Sharp, T. *Neuropharmacology* **1999**, *38*, 1083–1152; (b) Blier, P.; de Montigny, C. *Trends Pharmacol. Sci.* **1994**, *15*, 220–226.
3. (a) Halazy, S.; Lamothe, M.; Jorand-Lebrun, C. *Exp. Opin. Ther. Patents* **1997**, *7*, 339–352; (b) Huang, Y.; Oquendo, M. A.; Harkavy Friedman, J. M.; Greenhill, L. L.; Brodsky, B.; Malone, K. M.; Khait, V.; Mann, J. J. *Neuropsychopharmacology* **2003**, *28*, 163–169; (c) Quist, J. F.; Barr, C. L.; Schachar, R.; Roberts, W.; Malone, M.; Tannock, R.; Basile, V. S.; Beitchman, J.; Kennedy, J. L. *Mol. Psychiatry* **2003**, *8*, 98–102; (d) Smoller, J. W.; Biederman, J.; Arbeitman, L.; Doyle, A. E.; Fagerness, J.; Perlis, R. H.; Sklar, P.; Faraone, S. V. *Biol. Psychiatry* **2006**, *59*, 460–467.
4. (a) Briley, M.; Moret, C. *Clin. Neuropharmacology* **1993**, *16*, 387–400; (b) Chenu, F.; Dailly, E.; Bourin, M. *Drug Dev. Res.* **2005**, *65*, 141–146; (c) Mitchell, S. N.; Greenslade, R. G.; Cooper, J. *Eur. J. Pharmacol.* **2001**, *432*, 19–27.
5. (a) Berg, S.; Larsson, L.-G.; Renyi, L.; Ross, S. B.; Thorberg, S.-O.; Thorell-Svantesson, G. *J. Med. Chem.* **1998**, *41*, 1934–1942; (b) Selkirk, J. V.; Scott, C.; Ho, M.; Burton, M. J.; Watson, J.; Gaster, L. M.; Collin, L.; Jones, B. J.; Middlemiss, D. N.; Price, G. W. *Br. J. Pharmacol.* **1998**, *125*, 202–208; (c) Jorand-Lebrun, C.; Pauwels, P. J.; Palmier, C.; Moret, C.; Chopin, P.; Perez, M.; Marien, M.; Halazy, S. *J. Med. Chem.* **1997**, *40*, 3974–3978; (d) Gaster, L. M.; Blaney, F. E.; Davies, S.; Duckworth, D. M.; Ham, P.; Jenkins, S.; Jennings, A.; Joiner, G.; King, F.; Mulholland, K.; Wyman, P.; Hagan, J.; Hatcher, J.; Jones, B.; Middlemiss, D.; Price, G.; Riley, G.; Roberts, C.; Routledge, C.; Selkirk, J.; Slade, P. *J. Med. Chem.* **1998**, *41*, 1218–1235.
6. (a) Hudzik, T. J.; Yanek, M.; Porrey, T.; Evenden, J.; Paronis, C.; Mastrangelo, M.; Ryan, C.; Ross, S.; Stenfors, C. *J. Pharmacol. Exp. Ther.* **2003**, *304*, 1072–1084; (b) Dawson, L. A.; Hughes, Z. A.; Starr, K. R.; Storey, J. D.; Bettelini, L.; Bacchi, F.; Arban, R.; Poffe, A.; Melotto, S.; Hagan, J. J.; Price, G. W. *Neuropharmacology* **2006**, *50*, 975–983.
7. (a) Ahlgren, C.; Eriksson, A.; Tellefors, P.; Ross, S. B.; Stenfors, C.; Malmberg, A. *Eur. J. Pharmacol.* **2004**, *499*, 67–75; (b) Stenfors, C.; Hallerback, T.; Larsson, L.-G.; Wallsten, C.; Ross, S. B. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2004**, *369*, 330–337.
8. Tidwell, T. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797–11810.
9. Heindel, N. D.; Bechara, I. S.; Lemke, T. F.; Fish, V. B. *J. Org. Chem.* **1967**, 4155–4157.
10. (a) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067; (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157.
11. De la Cruz, A.; Elguero, J.; Goya, P.; Martínez, A. *Tetrahedron* **1992**, *48*, 6135–6150.
12. Glennon, R. A.; Westkaemper, R. B. *Drug News & Perspect.* **1993**, *6*, 390–405.
13. Chapdelaine, M.; Davenport, T.; Haeberlein, M.; Horchler, C.; McCauley, J.; Pierson, Ed.; Sohn, D.; WO 2003037872 A1, 2003.
14. Lazareno, S. In *Methods in Molecular Biology*; Walker, J. M., Keen, M., Eds.; Humana Press: Totowa, New Jersey, 1999; pp 231–245, Vol. 106.
15. Hagan, J. J.; Slade, P. D.; Gaster, L.; Jeffrey, P.; Hatcher, J. P.; Middlemiss, D. N. *Eur. J. Pharmacol.* **1997**, *331*, 169–174.
16. Polar surface areas were calculated according to Ertl, P.; Rohde, B.; Selzer, P. *J. Med. Chem.* **2000**, *43*, 3714–3717, Calculated PSA values were as follows: **7a–h** 86.4 Å^2, **7i** 77.2 Å^2, **10a** 73.4 Å^2, **10b** 82.2 Å^2, **10c** 64.2 Å^2..
17. Girault, G.; Coustal, S.; Rumpf, P. *Bull. Soc. Chim. Fr.* **1972**, *7*, 2787–2798.
18. Berthelot, M.; Laurence, C.; Safar, M.; Besseau, F. *J. Chem. Soc. Perkin Trans. 2* **1998**, 283–290.