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The Synthesis and Biological Evaluation of Quinolyl-piperazinyl Piperidines as Potent Serotonin 5-HT$_{1A}$ Antagonists

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As part of an effort to identify 5-HT$_{1A}$ antagonists that did not possess typical arylalkylamine or keto/amido-alkyl aryl piperazine scaffolds, prototype compound **10a** was identified from earlier work in a combined 5-HT$_{1A}$ antagonist/SSRI program. This quinolyl-piperazinyl piperidine analogue displayed potent, selective 5-HT$_{1A}$ antagonism but suffered from poor oxidative metabolic stability, resulting in low exposure following oral administration. SAR studies, driven primarily by in vitro liver microsomal stability assessment, identified compound **10b**, which displayed improved oral bioavailability and lower intrinsic clearance. Further changes to the scaffold (e.g., **10r**) resulted in a loss in potency. Compound **10b** displayed cognitive enhancing effects in a number of animal models of learning and memory, enhanced the antidepressant-like effects of the SSRI fluoxetine, and reversed the sexual dysfunction induced by chronic fluoxetine treatment.

Introduction

The 5-HT$_{1A}$[a] receptor is arguably the most thoroughly studied of all the serotonin receptor subtypes. A plethora of information on this receptor has been generated since its discovery in 1981[1] and subsequent cloning in 1988.[2] The receptor possesses a tertiary structure typical of 7-transmembrane G-protein coupled receptors (GPCRs), with multiple sites for glycosylation and phosphorylation. It is located both presynaptically, where it functions as an inhibitory somatodendritic autoreceptor and postsynaptically, where it also functions as an inhibitory receptor. The rat 5-HT$_{1A}$ receptor is 89% homologous to the human protein and resembles its human counterpart both pharmacologically and in terms of anatomical localization. The 5-HT$_{1A}$ receptor has been an important drug discovery target in the brain for nearly two decades and continues to attract attention.[3]

Several lines of evidence suggest that 5-HT$_{1A}$ receptors are involved in learning and memory.[4,5] The 5-HT$_{1A}$ receptor is expressed in abundance in several brain regions thought to be associated with learning and memory, such as the hippocampus, frontal cortex, and septum.[6] These receptors are poised to modulate cholinergic neurotransmission via both direct and indirect signaling. Postsynaptic 5-HT$_{1A}$ receptors provide inhibitory tone to the cholinergic projections from the nucleus basalis of Maynert to the frontal cortex and hippocampus. Presynaptic 5-HT$_{1A}$ receptors in the dorsal raphe modulate serotonergic neurotransmission to the prefrontal cortex (where they control excitatory glutamatergic signals) and the locus cerruleus (where they control adrenergic signaling). A 5-HT$_{1A}$ antagonist would be expected to directly block inhibitory tone in the nucleus basalis while, at the same time, indirectly stimulate excitatory tone from the prefrontal cortex and locus ceruleus via blockade of autoreceptors in the dorsal raphe. The net result would be an increase in cholinergic signaling from the nucleus basalis to the frontal cortex. Consistent with this hypothesis, administration of 5-HT$_{1A}$ antagonists enhanced glutamate and acetylcholine release.[7−9] This enhancement on cholinergic neurotransmission correlated with improvement in animal models of cognition.

5-HT$_{1A}$ antagonists have also been explored as potential adjunctive therapies for selective serotonin reuptake inhibitor (SSRI) antidepressants. SSRIs are extensively used to treat depression. However, as a class, they suffer from a delayed onset of antidepressant action[10] and a number of side effects, including sexual dysfunction.[11] The delay in onset of clinical

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[a] Abbreviations: 5-HT, 5-hydroxytryptamine; 8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino)-tetralin; Aβ, beta-amyloid; AMP, adeonosine monophosphate; APP, amyloid precursor protrein; BINAP, tetrakis-(triphenylphosphino)-1,1-binapthyl; B/P, brain to plasma; CHO, Chinese hamster ovary; CYMAP, dicyclohexylphosphine-2′-(*N*,*N*-dimethylamino)-biphenyl; E_{max}, maximum enhancing effect level; GPCR, G-protein coupled receptor; GTPγS, guanosine 5′-*O*-[γ-thio]triphosphate; HPLC, high pressure liquid chromatography; I_{max}, maximum inhibitory effect level; MED, minimal effective dose; NADPH, nicotinamide adenine dinucleotide phosphate; OB, olfactory bulbectomy; PK, pharmacokinetic; SAR, structure−activity relationship; SSRI, selective serotonin reuptake inhibitor.

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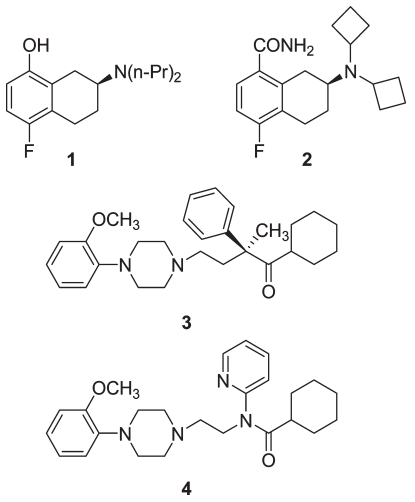


Figure 1. Representative 5-HT_{1A} antagonists.

efficacy is thought to occur because the high density of inhibitory 5-HT_{1A} autoreceptors in the target forebrain regions compensates for the elevations in synaptic 5-HT induced by acute SSRI treatment.[12] Chronic SSRI treatment is required to see positive effects and the 2−4 week delay in onset of action is thought to represent the time needed for desensitization of the autoreceptors to occur. Clinical evidence with pindolol suggests that coadministration of a 5-HT_{1A} antagonist may shorten this delay,[13] although the data with pindolol may be confounded by the compound's β-adrenergic antagonist activity.[14] There is conflicting clinical evidence regarding whether 5-HT_{1A} antagonists may be useful adjuctive therapies for ameliorating SSRI-induced sexual dysfunction, but encouraging data from animal models is beginning to emerge.[15]

Selective 5-HT_{1A} antagonists reported to date generally fall into two structural classes. The first class (Figure 1) is the aryl alkyl amines, exemplified by compounds like (S)-U-301 (**1**) and robalzotan (**2**). The second structural class is the aryl piperazines (Figure 1), represented by compounds like LY-426965 (**3**) and WAY-100635 (**4**). We recently reported on two potent, selective orally active 5-HT_{1A} antagonists possessing this moiety (Figure 2), lecozotan (**5**)[16] and WAY-101405 (**6**).[7] Similar aryl piperazine analogues (Figure 2), such as adatanserin (**7**)[17] and BMY 7378 (**8**),[18] display partial agonist activity, especially in the dorsal raphe where the high degree of receptor reserve seen for presynaptic 5-HT_{1A} autoreceptors amplifies small levels of intrinsic activity. One of the structural features that may promote potent, full antagonist activity in compounds **3**−**6** is the presence of a pendent aryl or heteroaryl group located in proximity to the carbonyl moiety. The carboxamide grouping of compounds like **5**−**8** represents a potential site for metabolic hydrolysis and/or chemical instability. In our continuing search for 5-HT_{1A} antagonists, we explored structural scaffolds that did not possess a carboxamide moiety.

More recently, compounds prepared as dual-acting 5-HT_{1A} antagonists/SSRIs have been reported.[19] These compounds, which often consist of combinations of 5-HT_{1A} pharmacophores and SSRI pharmacophores (see, for example, Hatzenbuhler et al.[20,21]), do not possess all three structural features inherent in selective 5-HT_{1A} antagonists like **3**−**6** (i.e., the aryl piperazine, the substituted amide/ketone, and the pendent aryl/heteroaryl grouping). We recently disclosed our work on a series of quinolylpiperazines as mixed SSRI-5-HT_{1A} antagonists.[22] These compounds, exemplified by **9** (Figure 3), displayed potent affinity for both the human serotonin transporter (measured as displacement of [^{3}H]-paroxetine) and the human 5-HT_{1A} receptor and a variety of intrinsic activities in an in vitro functional model (inhibition of GTPγS binding to the human 5-HT_{1A}/G-protein complex). In the course of prosecuting this series, we synthesized the previously undisclosed quinolyl-piperazinyl piperidine analogue **10a** (Figure 3). Compound **10a** was surprisingly devoid of serotonin transporter affinity yet maintained potent affinity and full antagonist activity at the 5-HT_{1A} receptor. To our knowledge, this compound represents one of the first potent, selective aryl piperazine-based 5-HT_{1A} antagonists that does not possess an amide/ketone moiety. Previous work[22] had shown that substitution in the 6-position of the quinolylpiperazinyl ring system was particularly favorable for producing compounds that profiled in vitro as potent, full 5-HT_{1A} antagonists, so we kept the 6-methoxy group constant for the purposes of the SAR studies that are the subject of this manuscript.

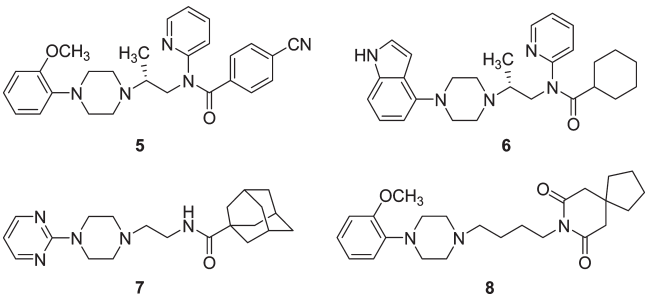


Figure 2. Aryl-piperazine 5-HT_{1A} antagonists and partial agonists.

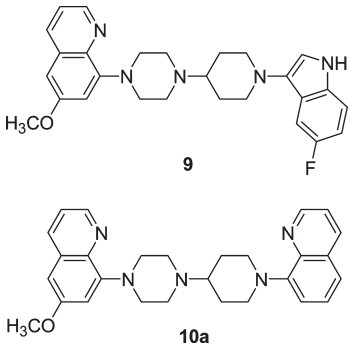


Figure 3. Recently identified 5-HT_{1A} antagonists.

Chemistry

Target compounds **10a**−**r** were prepared by condensation of 5-methoxy-7-(1-piperazinyl)quinoline **15** and appropriate quinolinylpiperidinones **18a**−**r** under reductive amination conditions (Scheme 1).[23]

Compound **15** was synthesized in four steps (Scheme 2) from 3-chloro-4-aminophenol (**11**) in a sequence that involved a Skraup reaction[24] to give **12**, followed by methylation of the phenol to provide **13**. Treatment of **13** with a monoprotected piperazine derivative under modified Buchwald−Hartwig conditions[25,26] afforded **14**, which was deprotected to give **15**. Required quinolinylpiperidones **18a**−**r** were prepared by deprotecting ketals **17a**−**r**. Intermediates **17a**−**d** and **17f**−**r** were obtained from 8-haloquinolines **16a**−**d** and **16f**−**r**, respectively, by treatment with 1,4-dioxa-8-azaspiro[4,5]decane

under modified Buchwald−Hartwig conditions (Scheme 3). When the halogen leaving group was bromine, tetrakis-(triphenylphosphino)-1,1-binapthyl (BINAP) was used as a catalyst, whereas dicyclohexylphosphine-2′-(*N*,*N*-dimethylamino)-biphenyl (CYMAP) was preferred when the leaving group was chlorine. Compound **17e** was obtained by condensation of 7,8-difluoroquinoline **16e** with 1,4-dioxa-8-azaspiro-[4,5]decane to give a mixture of protected piperidinones which was separated by chromatography to yield the desired 7-fluoro isomer (Scheme 4). The required haloquinolines **16a−r** were obtained from commercial sources or were prepared via a variety of published methods from appropriately substituted commercially available haloanilines.

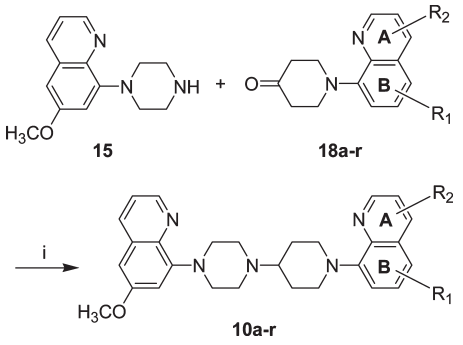
In Vitro Metabolism/Metabolite ID. Microsomal stability was determined by incubating test compounds with rat or human liver microsomes at 37 °C for 20 min in the presence of NADPH or a NADPH regenerating system. Structural identification of microsomal metabolites was accomplished by incubating test compounds with rat or human liver microsomes at 37 °C for 15 min in the presence of NADPH. Concentrated supernatants were subjected to LC/MS/MS analysis. Major components were isolated by HPLC, and their structures were confirmed by NMR analysis.

Receptor Occupancy. In vivo receptor occupancy was determined by measuring the displacement of [^{3}H]-WAY-100635 from rat hippocampus and cortex by test compounds.[7] The cerebellum was used as a reference tissue for nonspecific binding of [^{3}H]-WAY-100635 which, under the present conditions, accounted for 15% to 18% of the total binding.

Pharmacokinetics. The pharmacokinetic profile of test compounds was asssessed in rats following a 1 mg/kg iv or 3 mg/kg po dose. Plasma or brain homogenate concentrations were determined following protein precipitation with acetonitrile by LC/MS/MS using an internal standard.

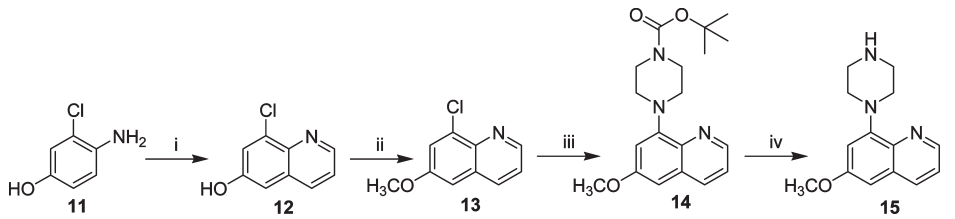
In Vitro. 5-HT$_{1A}$ data were generated using membranes from CHO cells stably transfected with the human 5-HT$_{1A}$ receptor as previously described.[7,27] Affinity for the human 5-HT$_{1A}$ receptor was assessed as the test compound's ability to inhibit binding of [^{3}H]-8-OH DPAT. In vitro 5-HT$_{1A}$ intrinsic activity was measured as the test compound's ability to block 8-OH DPAT-induced inhibition of forskolin-stimulated increases in cyclic AMP. Data are expressed in nM as IC_{50} values, with the maximum percent inhibition of the 8-OH DPAT effect expressed as an I_{max} value. Compounds with I_{max} values of 95−100 are considered to be full

Scheme 1[a]



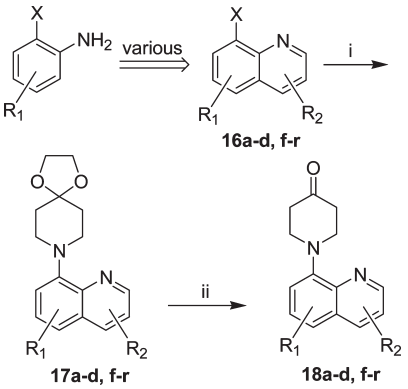
[a] Reagents and conditions: (i) $NaBH_3CN$, room temperature, overnight.

Scheme 2[a]



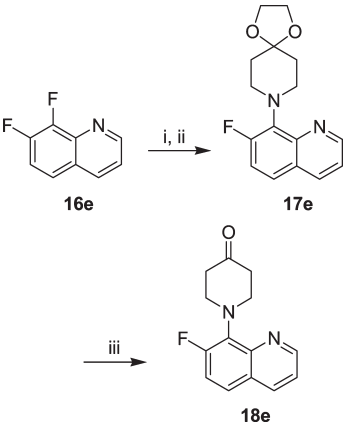
[a] Reagents and conditions: (i) $Fe_2(SO_4)_3$, glycerol, H_3BO_3, H_2SO_4, 150 °C; (ii) CH_3I, K_2CO_3; (iii) *tert*-butoxycarbonylpiperazine, sodium *tert*-butoxide, CYMAP, $Pd_2(dba)_3$; (iv) 4N HCl/dioxane.

Scheme 3[a]



[a] Reagents and conditions: (i) for X = Cl, 1,4-dioxa-8-azaspiro-4,5-decane, *tert*-butoxide, CYMAP, $Pd_2(dba)_3$; For X = Br, 1,4-dioxo-8-azaspiro-4,5-decane, *tert*-butoxide, BINAP, $Pd_2(dba)_3$; (ii) 2N NCl/diethyl ether.

Scheme 4[a]



[a] Reagents and conditions: (i) 1,4-dioxa-8-azaspiro-4,5-decane, 120 °C; (ii) separation of 7- and 8-fluororegioisomers by flash chromatography; (iii) 2N HCl/diethyl ether.

antagonists, while compounds with I_{max} values significantly less than 100 are considered to be partial agonists.

In Vivo. In vivo microdialysis was used to confirm the 5-HT_{1A} antagonist activity of test compounds by measuring their effect on 5-HT release in the frontal cortex. The technique was also used to assess the effect of test compounds on acetylcholine release in the hippocampus. The pro-cognitive effects of test compounds were examined in a number of animal models of learning and memory. The ability of test compounds to enhance recognition memory was assessed using a novel object recognition model. The Atlantis water maze model was used to examine compound effects on hippocampal-based spatial memory. Test compounds were also evaluated for their ability to enhance contextual memory in transgenic Tg2576 mice overexpressing a mutated form of human amyloid precursor protein (APP) using a contextual fear conditioning model.

In addition to assessment in a battery of cognitive tests, compounds were examined for their ability to enhance the antidepressant-like effects or inhibit the sexual dysfunction side effects of the SSRI fluoxetine. In vivo microdialysis was used to examine the effect of test compounds on fluoxetine-induced 5-HT release in the rat frontal cortex. The ability of compounds were evaluated for their ability to enhance antidepressant-like behavioral effects induced by fluoxetine was assessed using a rat olfactory bulbectomy model and schedule-induced polydipsia, a model of obsessive/compulsive behavior. Finally, test compounds were examined for their ability to inhibit the decrease in rat penile erections caused by fluoxetine.

Results and Discussion

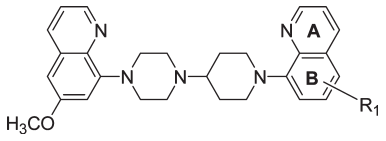
Compound **10a** displayed a desirable in vitro pharmacological profile (Table 1). The compound displayed similar potency for the 5-HT_{1A} receptor as that seen with the standard 5-HT_{1A} antagonist **4** and showed no intrinsic activity in the functional cyclic AMP-based assay. However, stability data from rat and human microsomal preparations predicted that the compound might not possess optimal pharmacokinetic parameters. A rat PK study (Table 2) confirmed this assessment. Administration of **10a** was characterized by high clearance and a short half-life. The peak plasma concentration following a 3 mg/kg oral dose was moderate (in the range of 200−300 nM), although significant brain penetration was seen following a 3 mg/kg intravenous dose (B/P = 2.8). A study was undertaken to identify the potential sites of oxidative metabolism. Compound **10a** was incubated with rat and human liver microsomes, and the major metabolites were identified by LC/MS/MS and NMR. The results are summarized in Figure 4. Minor metabolites in both species included the des-methyl metabolite **19** and metabolites **20** and **21**, where hydroxylation had occurred on the piperidinyl group. The major metabolite in both species was the 5-hydroxyquinolyl derivative **22**.

SAR studies were initiated to block metabolism on the 5-position of the quinoline appended to the piperidine group (Table 1). Substituting the 5-position with a fluorine group (to give compound **10b**) retained potent 5-HT_{1A} full antagonist activity but resulted in only a marginal increase in stability in the human microsomal assay. Substitutions in the 6- and 7-positions of the quinoline ring induced some degree of intrinsic activity in the in vitro cAMP assay, suggesting that these compounds were partial agonists. Surprisingly, even a fluoro substituent in the 7-position resulted in a significant loss in 5-HT_{1A} affinity, suggesting the possibility of electronic or torsional requirements for that region of the scaffold. As with compound **10a**, none of the analogues showed significant 5-HT uptake inhibitory activity.

Another metabolite identification study was performed to determine the sites of metabolism for **10b**. The results are summarized in Figure 5. Once again, des-methylation of the methoxy group to give the metabolite **23** was a minor pathway in rat and human microsomes. The major pathway involved the formation of the 3-hydroxy derivative **26** via the 2,3-dihydroxy metabolite **25**. The formation of **25** was hypothesized to occur through a proposed 2,3-epoxy intermediate **24**. The structure of **24** was tentatively assigned by LC/MS/MS, but the metabolite was too unstable to be fully characterized by NMR.

An effort was then undertaken to block this alternate metabolic pathway. An initial SAR study examining the effects of substitution on the "A"-ring of the quinoline in the absence of the 5-fluoro substitutient was performed. The results are summarized in Table 3. Compounds containing typical leaving groups in the 2- and 4-position of the quinoline ring were excluded to avoid potential side reactions. Substitution in the 2-position (e.g., compounds **10f** and **10g**) maintained good 5-HT_{1A} potency and antagonist activity,

Table 1. SAR of the Quinoline "B"-Ring



		5-HT_{1A}	cAMP		microsomal $t_{1/2}$ (min)	
compd	R_1	K_i (nM)[a]	IC_{50} (nM)[a]	I_{max} (%)[a]	RLM[b]	HLM[c]
4[d]		0.9	7.1	100	> 1	> 1
10a	H	0.40	3.9	100	2	3
10b	5-F	0.40	2.7	100	2	6
10c	6-F	3.4	46.5	82	2	4
10d	6-Br	0.61	10	73	2	2
10e	7-F	276	331	61	3	3

[a] Data are the results of at least three repetitions. [b] RLM = rat liver microsomes. [c] HLM = human liver microsomes. [d] Data taken from Childers, W. E., et al.[53]

Table 2. PK Parameters of Compounds **10a**, **10b**, and **10r**[a]

	1 mg/kg (iv)		3 mg/kg (po)					
	CL (mL/min/kg)	V_{ss} (L/kg)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC (h·ng/mL)	F (%)	B/P
10a	38.7	2.8	130	1.0	1.2	360	27	2.8
10b	15.0	2.6	247	0.8	1.1	472	33	1.3
10r	9.0	2.5	417	2.0	4.8	3758	60	0.2

[a] CL = intrinsic clearance; V_{ss} = volume of distribution. AUC = calculated area under the curve from $t = 0$ to $t = \infty$; F(%) = percent bioavailability following oral administration. B/P = brain to plasma ratio.

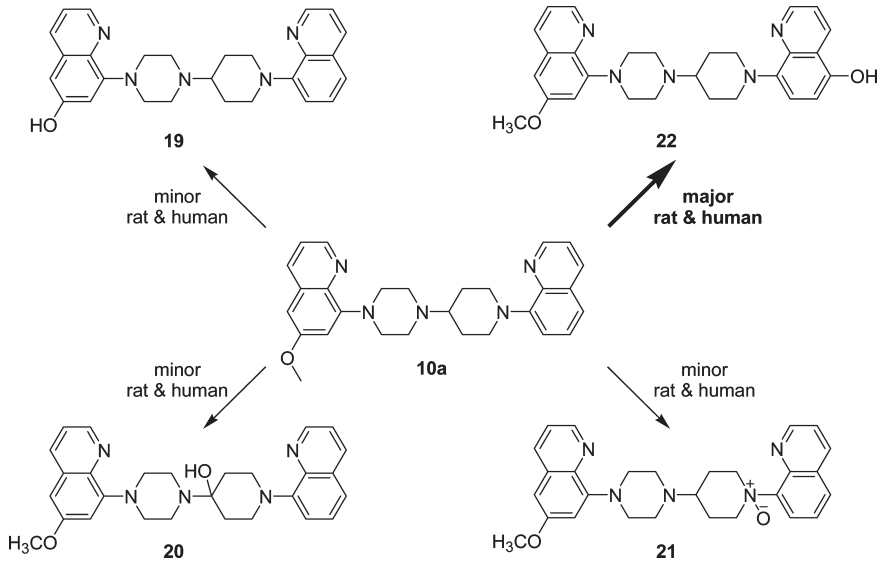


Figure 4. Microsomal metabolism of compound **10a**.

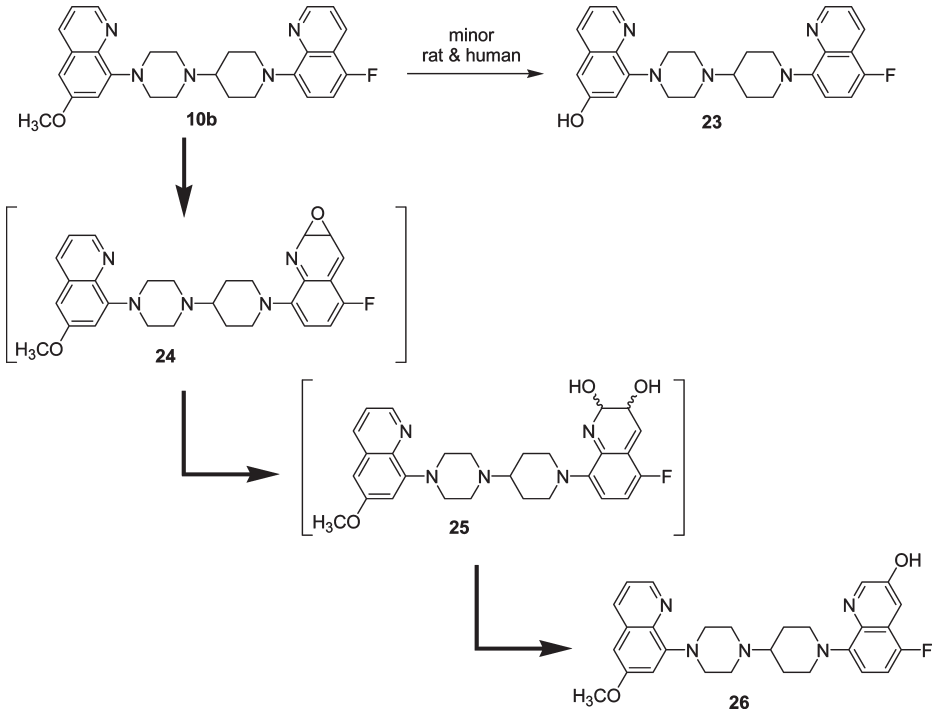


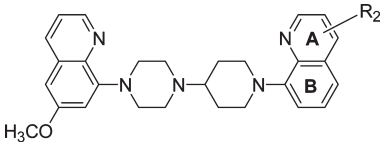
Figure 5. Microsomal metabolism of compound **10b**.

although the potency in the functional assay was around 10-fold lower that that seen with the unsubstituted analogue **10a**. Substitution of fluorine in the 3-position of the "A"-ring retained antagonist activity, but larger groups in the 3- and 4- positions of the "A"-ring (compounds **10i**−**k**) imparted partial agonist activity. Results with 2,4-bis substitution were variable, with the dimethyl analogue **10l** profiling as a full antagonist and the 2-trifluoromethyl-4-methoxy derivative **10m** showing partial agonist activity. It was not expected that "A"-ring substitution would dramatically increase metabolic stability, given likelihood of hydroxylation on the 5-position. Nevertheless, some encouraging results were obtained with 3- and 2,4-bis substitution (compounds **10j** and **10m**, respectively) where increases in stability were seen in human microsomal preparations.

Finally, the effects of "A"-ring substitution in the presence of the 5-fluoro group were examined (Table 4). Substitution in the 2-position did little to improve metabolic stability. Substitution in the 3-position could enhance stability in both rat and human microsomes, although the size of the substituent influenced its impact. The 3-trifluoromethyl derivative **10o** showed an increase in stability while the 3-fluoro analogue **10p** was not particularly stable. Unfortunately, as with the des-fluoro compounds **10i** and **10j**, the 3-substituted 5-fluoro analogues profiled as partial agonists. Compounds with substituents in the 2- and 4-positions profiled as antagonists, and an appropriate choice of metabolically stable substituents (such as those seen in **10r**) led to a compound with enhanced stability in both rat and human microsomal

preparations. As with the B-ring substituted analogues, A-ring substituted derivatives showed no inhibitory activity on 5-HT uptake.

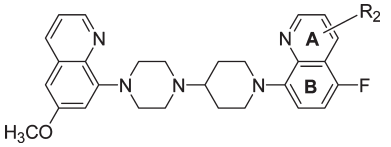
Table 3. SAR of the Quinoline "A"-Ring



		5-HT$_{1A}$	cAMP		microsomal $t_{1/2}$ (min)	
compd	R_2	K_i (nM)[a]	IC_{50} (nM)[a]	I_{max} (%)[a]	RLM[b]	HLM[c]
4[d]		0.9	7.1	100	< 1	< 1
10f	2-CH_3	0.54	47	100	< 1	3
10g	2-CF_3	1.8	23	100	2	3
10h	3-F	0.79	5.6	100	2	2
10i	3-CH_3	0.46	5.9	78	2	2
10j	3-CF_3	1.2	30	44	4	10
10k	4-CH_3	0.61	1.4	85	2	2
10l	2,4-CH_3	0.63	4.8	98	4	< 1
10m	2-CF_3 4-OCH_3	2.1	30	78	4	13

[a] Data are the results of at least three repetitions. [b] RLM = rat liver microsomes. [c] HLM = human liver microsomes. [d] Data taken from Childers, W. E. et al.[53]

Table 4. SAR of 5-Fluoroquinolylpiperazine Analogues



		5-HT$_{1A}$	cAMP		microsomal $t_{1/2}$ (min)	
compd	R_2	K_i (nM)[a]	IC_{50} (nM)[a]	I_{max} (%)[a]	RLM[b]	HLM[c]
4[d]		0.9	7.1	100	> 1	> 1
10n	2-CF_3	3.6	7.0	100	3	3
10o	3-CF_3	0.87	15	34	9	27
10p	3-F	0.47	20	54	< 1	5
10q	2,4-CH_3	177	2.8	100	3	3
10r	2-CF_3 4-OCH_3	2.0	9.1	94	12	15

[a] Data are the results of at least three repetitions. [b] RLM = rat liver microsomes. [c] HLM = human liver microsomes. [d] Data taken from Childers, W. E., et al.[53]

To assess intrinsic activity in vivo, compounds **10b** and **10r** were examined for their effects on rat cortical serotonin release in a series of microdialysis studies (Figure 6). Previous studies have shown that this assay is sensitive to small degrees of 5-HT$_{1A}$ intrinsic activity.[28] In this assay, the full 5-HT$_{1A}$ agonist 8-OH-DPAT induced a significant decrease in extracellular 5-HT levels through its action on presynaptic 5-HT$_{1A}$ autoreceptors. When doses were at 10 mg/kg po, compounds **10b** and **10r** had no effect on extracellular 5-HT levels on their own. However, pretreatment with **10b** (P = 0.049) or **10r** (P = 0.048) completely blocked the effect of 8-OH-DPAT. These data are indicative of full antagonist activity, and the results are similar to those obtained with other 5-HT$_{1A}$ antagonists.[7,16]

Animal Models of Cognition

A 5-HT$_{1A}$ antagonist would be expected to enhance learning and memory by enhancing cholinergic (and glutamatergic) neurotransmission.[29] We have previously shown that systemic administration of 5-HT$_{1A}$ antagonists can enhance the release of both glutamate[9] and acetylcholine[7,9] in brain regions known to degenerate in Alzheimer's disease. As a representative of the series, compound **10b** was examined for its effects on modulating acetylcholine levels using in vivo microdialysis. The results are presented in Figure 7. A 10 mg/kg oral dose of **10b** caused a significant increase in the level of acetylchloine in the rat dorsal hippocampus. The pharmacodynamic effect of **10b** correlated with its plasma PK profile, achieving maximum effect at around 40 min postadministration and lasting for approximately 2−3 h. These data suggest that the brain PK profile for **10b** tracks closely with that seen in the plasma.

Compounds **10b** and **10r** were considered for more detailed profiling. The lower potency of **10r** relative to **10b**, coupled

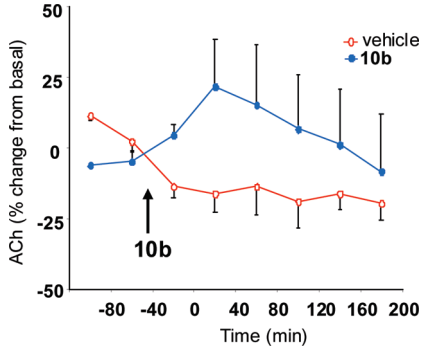


Figure 7. Effect of compound **10b** (10 mg/kg po) on rat hippocampal acetylcholine levels.

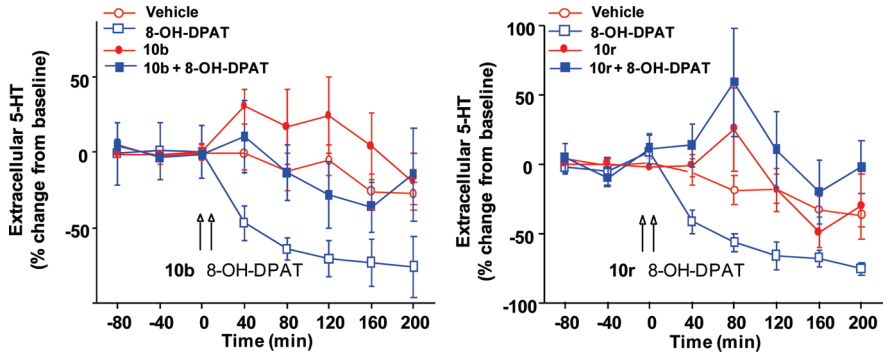


Figure 6. Effect of compounds **10b** and **10r** (10 mg/kg po) on rat cortical 5-HT levels.

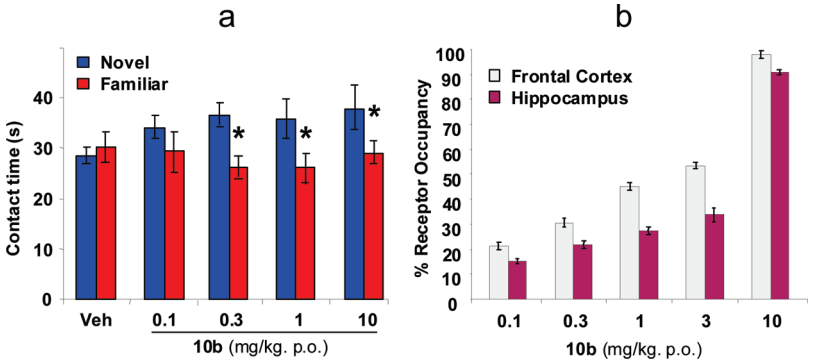


Figure 8. (a) Effect of **10b** novel object recognition; (b) receptor occupancy of **10b** in rat cortex and hippocampus.

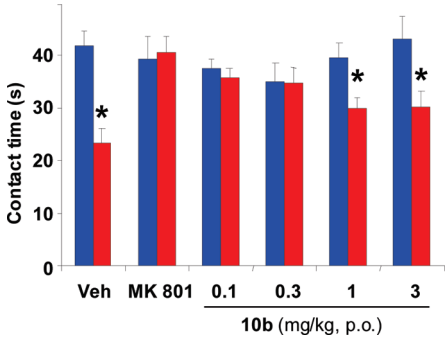


Figure 9. Reversal of MK-801-induced deficit in novel object recognition by **10b**.

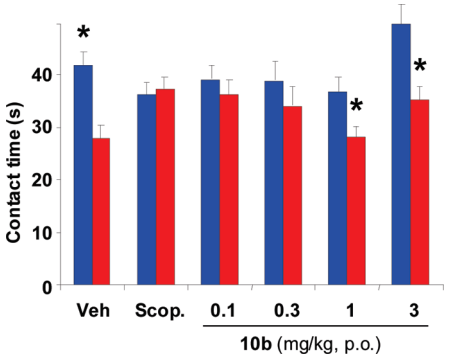


Figure 10. Reversal of scopolamine-induced deficit in novel object recognition by **10b**.

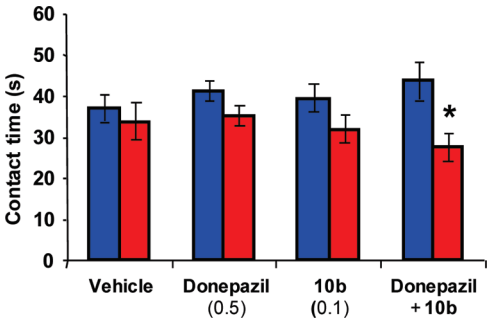


Figure 11. Cognitive-enhancing synergy of **10b** and donepazil in novel object recognition.

with solubility issues and lower CNS penetration (likely due to the compound's increased lipophilicity, data not shown), led us to deprioritize **10r**. Compounds **10b** was therefore profiled for its effect in the novel object recognition test, a memory test based on exploratory activity.[30] Animals are allowed to explore a pair of identical objects (training) and then returned to their home cages. After a period of time, the animals are presented with one previously explored "familiar" object and an unexplored "novel"object". The animal will spontaneously explore the novel object more than the familiar one. Memory for the familiar object is recorded as greater time spent exploring the novel object. When the time between training and the trial is increased to 48 h, the animal no longer remembers the familiar object and will spend equal amounts of time exploring both objects during the trial. Compounds **10b** was able to reverse the time-induced cognitive deficit, with the MED (minimal effective dose) for **10b** being 0.3 mg/kg po (Figure 8). Compound **10b** was effective in this model when receptor occupancy was in the 20−30% range. A selectivity profile (NovaScreen) for compound **10b** (data not shown) revealed that the compound had no significant affinity for 55 receptors, ion channels transporters, and enzyme binding sites at concentrations up to 1 uM, supporting the assertion that the compound's pro-cognitive efficacy in this model, even at relatively low receptor occupancy, was due to its 5-HT_{1A} antagonist activity.

Memory deficits in the novel object recognition model can also be induced by treatment with a glutamatergic antagonist like MK-801 (dizocilpine) or a cholinergic antagonist like scopolamine prior to training. Compound **10b** was able to reverse both the MK-801-induced deficit (Figure 9) and the scopolamine-induced deficit (Figure 10), with MED values of 1.0 mg/kg po ($P < 0.05$) and 0.3 mg/kg po ($P < 0.05$), respectively. In addition, a subeffective dose of compound **10b** coadministered with a subeffective dose of the clinically used acetylcholinesterase inhibitor donepazil reversed the 48 h delay-induced deficit (Figure 11), suggesting a possible synergy between the two mechanisms.

The impressive in vivo potency of compound **10b** in the novel object recognition model encouraged us to test the compound in additional cognition models. **10b** was evaluated in the Atlantis water maze, a hippocampal-dependent spatial memory task (Figure 12).[31] In this variation of the classic water maze test, animals do not have ready access to the escape platform but must spend a predetermined amount of "dwell time" in a "trigger zone", which encompasses the spot in which a pneumatically activated platform rises from the bottom of the water tank. Increasing dwell times over training sessions is a way to nonpharmacologically increase the difficulty of the task, thus providing for an expanded window to see improvements with test compounds. On the first training day, vehicle- and drug-treated rats (3 and 10 mg/kg po) learned the location of the escape platform, using the extra-maze

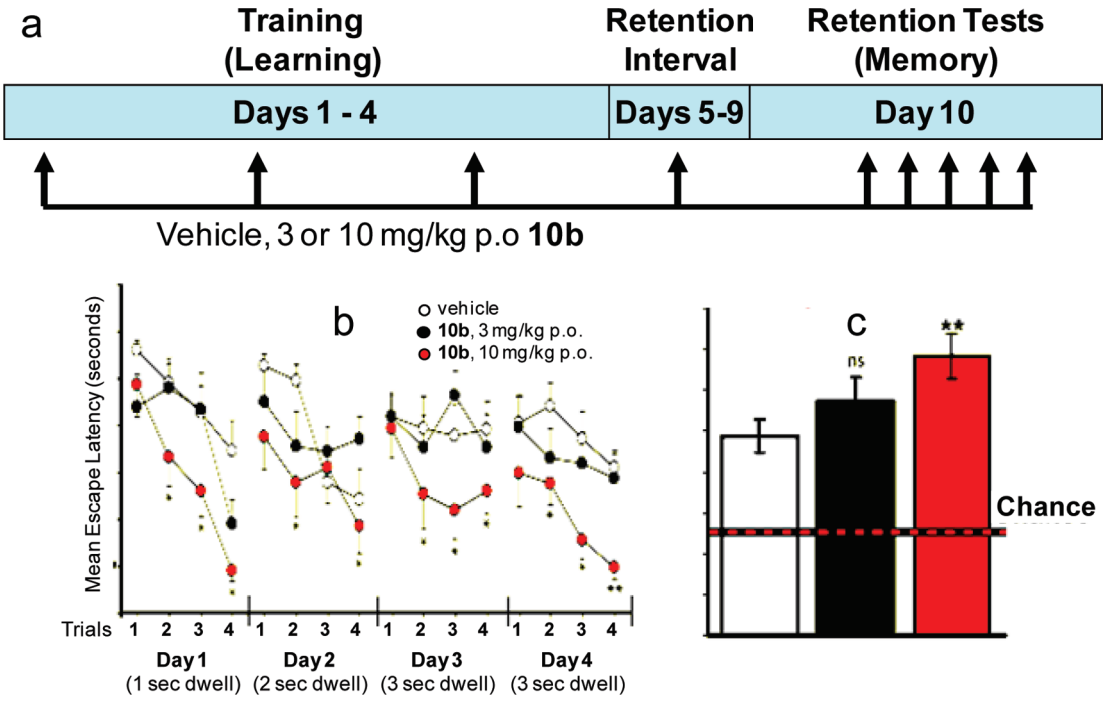


Figure 12. Cognitive enhancing effects of **10b** in the Atlantis water maze model: (a) training/dosing schedule; (b) training phase; (c) memory trials.

cues, from trial 1 to trial 4, as reflected by the progressive decrease in the mean escape latency (Figure 12b). As the task became progressively more demanding on the subsequent days, when the dwell time over the trigger zone increased to 2 s and then to 3 s, the vehicle and 3 mg/kg groups found it harder to locate the platform. In contrast, the 10 mg/kg po group demonstrated an improvement by trial 4 (P's = 0.009−0.015), or earlier, demonstrating a positive effect on the encoding of spatial memory. There was not significant effect of drug treatment on swim speed (data not shown). The retention of this memory was assessed in a drug-free probe test conducted 5 days after the conclusion of acquisition training. Animals were placed back in the water maze without the platform. As can be seen in Figure 12c, the group treated with 10 mg/kg po of compound **10b** spent significantly greater percentage of time in the previously targeted zone than vehicle- or 3 mg/kg-treated animals ($P = 0.0003$).

Our next goal was to assess the potential efficacy of compound **10b** in a cognition model with at least some of the hallmarks of Alzheimer's disease present. Tg2576 mice overexpress a mutated form of APP and show increased $A\beta_{40}$ and $A\beta_{42/43}$ and plaque deposition at 9−12 months of age.[32] These animals display behavioral deficits that correlate with soluble β-amyloid species, which may be one of the contributing factors to cognitive decline and neurodegeneration in Alzheimer's patients. Dineley and co-workers reported that Tg2576 mice show hippocampal-dependent conditioning deficits beginning at 20 weeks of age.[33] These deficits can be monitored using a contextual fear conditioning (CFC) model in which animals are trained to associate a mild foot shock with an auditory cue (the context) and then later display memory for the context by freezing when presented with the auditory cue in the absence of the shock.[34] As can be seen in Figure 13, compound **10b**, when administered 1 h prior to training, was able to improve contextual memory in the CFC model, with an MED of 0.3 mg/kg po ($P < 0.05$).

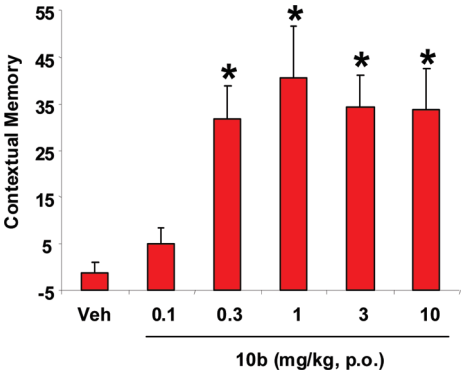


Figure 13. Cognitive enhancing effect of **10b** on contextual memory in Tg2576 mice.

Animal Models of Depression

Although currently available SSRIs like fluoxetine acutely inhibit the 5-HT transporter and elevate 5-HT levels in midbrain regions, there is little or no elevation of 5-HT in desired target forebrain regions until an adaptive desensitization of the inhibitory 5-HT_{1A} autoreceptors has occurred.[35] This delayed effect on forebrain 5-HT is thought to contribute to the delayed onset of clinical efficacy suffered by SSRIs like fluoxetine.[12] It has been hypothesized that cotherapy of a 5-HT_{1A} antagonist with an SSRI might maximize serotonergic function by inhibiting feedback inhibition of neuronal firing and immediately increasing synaptic levels of 5-HT in the forebrain regions. In support of this hypothesis, acute treatment with fluoxetine had no significant effect on cortical 5-HT levels.[36] Chronic fluoxetine treatment was required to increase forebrain 5-HT, and these increases correlated with desensitization of 5-HT1A autoreceptors in the dorsal raphe.[37,38] However, cotreatment with the 5-HT_{1A} antagonist **4** accelerated the fluoxetine-induced increases in cortical 5-HT. These neurochemical effects seem to correlate behaviorally, at least

in some models. For example, cotreatment with **4** accelerated the antidepressant-like effect of the SSRI paroxetine in the rat olfactory bulbectomy model.[39]

We therefore examined the effects of compound **10b** on fluoxetine-induced 5-HT release in the rat frontal cortex using in vivo microdialysis (Figure 14). Treatment with **10b** alone had no effect on cortical 5-HT levels. As expected, acute fluoxetine treatment had no significant effect on cortical 5-HT levels. However, coadministration of **10b** (10 mg/kg po) together with fluoxetine resulted in an immediate, significant increase in cortical 5-HT, which peaked at around 120% over baseline ($P = 0.02$).

Schedule-induced polydipsia has been used as a model of obsessive compulsive behavior and is responsive to treatment with SSRIs like fluoxetine.[40] When food pellets are delivered to rats on a schedule of one every two minutes for a period of two hours, the animals will develop a repetitive drinking behavior resulting in consumption of water that is 5−10-fold greater than baseline levels. Chronic treatment with fluoxetine prior to the trial inhibits this obsessive drinking behavior, and it has been shown that cotreatment with **4** can accelerate this activity.[41] To examine the potential enhancing effects of **10b** on fluoxetine in this model, an initial dose−response study was performed with fluoxetine (Figure 15a). A 5.6 mg/kg ip dose of fluoxetine was shown to have no significant effect. A dose−response with compound **10b** in combination with a 5.6 mg/kg ip dose of fluoxetine was then performed. As can been seen from Figure 15b, a 10 mg/kg po dose of compound **10b** had no effect on drinking alone. However, compound **10b** dose-dependently inhibited adjunctive water intake when coadministered with the subefffective dose of fluoxetine, with an MED value of 3 mg/kg po in this study ($P < 0.001$).

The rat olfactory bulbectomy (OB) model has been widely used to profile potential antidepressant agents.[42] In this model, bilateral removal of the olfactory bulbs results in a characteristic increase in locomotor activity. Many of the neurochemical, endocrine, and immunological changes induced in this model correspond with those seen in clinical depression. Treatment with many classes of antidepressant agents, including SSRIs, result in a reduction in OB-induced hyperlocomotor activity. However, chronic treatment with the antidepressant agent is required for efficacy, which correlates with the typical delayed onset of action seen in the clinical setting. For example, 14 days of treatment is required to see efficacy in this model with fluoxetine. Co-treatment with **4** has been shown to accelerate the antihyperlocomotor effect seen with the SSRI paroxetine in the OB model.

Compound **10b** was assessed for its enhancing effects on a subeffective dose of fluoxetine in the OB model (Figure 16). Bulbectomy resulted in an approximately 25% significant increase in locomotor activity compared to sham-surgery control animals when evaluated beginning at 14 days postsurgery.

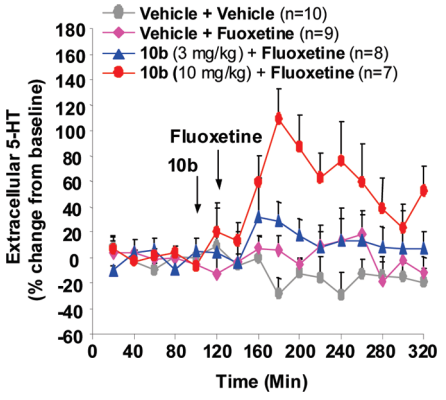


Figure 14. **10b** enhances the acute effect of fluoxetine on rat cortical 5-HT levels.

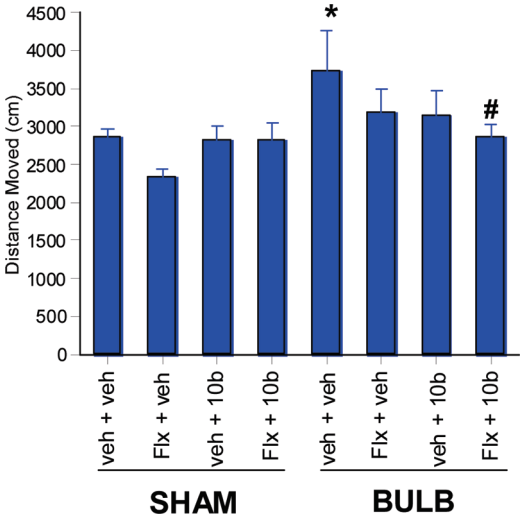


Figure 16. **10b** (10 mg/kg po) enhances the antidepressant-like effect of fluoxetine on olfactory bulbectomized rats.

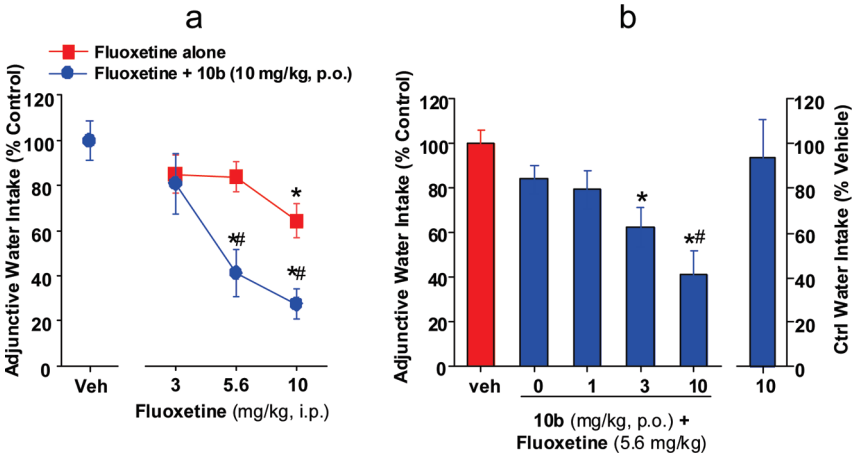


Figure 15. **10b** enhances the effect of fluoxetine on adjuvant drinking in schedule-induced polydipsia: (a) fluoxetine dose−response; (b) effect of **10b**/fluoxetine combination on SIP.

A dose−response curve (data not shown) identified a 5.6 mg/kg ip dose given once daily for 7 days as a subeffective dose of fluoxetine. This dose produced a small, nonsignificant decrease in locomotor activity compared to treatment with vehicle in bulbectomized rats. A 7-day cotreatment with fluoxetine (5.6 mg/kg ip) and **10b** (10 mg/kg po) provided a significant reduction in locomotor activity, returning the total distance moved back to sham control levels ($P < 0.05$).

Sexual dysfunction is one of the leading causes of antidepressant discontinuation.[11] The role of 5-HT_{1A} receptors in sexual function is still poorly understood, but a small number of clinical trials have demonstrated an improvement in SSRI-induced sexual dysfunction by treatment with the 5-HT_{1A} partial agonist buspirone.[43,44] That data, coupled with the recent clinical report of failure of the 5-HT_{1A} agonist VML-670 to ameliorate SSRI-induced sexual dysfunction,[45] suggest that the 5-HT_{1A} antagonist-like properties of buspirone may contribute to the compound's beneficial effects on SSRI-induced sexual dysfunction.

We recently reported on a rat noncontact penile erection model of sexual dysfunction[46] and demonstrated that either chronic or acute cotreatment with 5-HT_{1A} antagonists ameliorate the fluoxetine-induced decrease in erections seen in that model.[47] Compound **10b** was examined in this model (see Supporting Information). Following 14 day treatment, fluoxetine (10 mg/kg ip, once daily) produced a 54% decrease in the number of noncontact penile erections relative to vehicle treated controls. Compound **10b** (10 mg/kg po), when administered either acutely on day 14 or chronically with fluoxetine on days 1−14, reversed the SSRI-induced decrease in noncontact penile erections, returning them essentially to sham control levels. By itself, compound **10b** had no effect on noncontact penile erections.

Conclusion

SAR around prototype compound **10a** led to the identification of a series of quinolyl-piperazinyl piperidines that displayed potent 5-HT_{1A} antagonist activity. Stability in rat and human liver microsomes was used as a predictive screen to help guide the SAR directed at enhancing metabolic stability. Identification of the primary paths of oxidative metabolism was crucial to the success of this effort. Unfortunately, structural changes that significantly improved metabolic stability also decreased in vitro affinity and potency and led to a reduction in CNS penetration. Compound **10b** displayed potent 5-HT_{1A} antagonist activity both in vitro and in vivo and was selected for detailed profiling. The compound stimulated acetylcholine release in the rat frontal cortex and displayed cognitive enhancing activity in a number of animal models of learning and memory, including a contextual fear conditioning model in transgenic Tg2576 mice. In addition, compound **10b** was able to accelerate the antidepressant-like neurochemical and behavioral effects of fluoxetine and to reverse the sexual dysfunction induced by chronic fluoxetine treatment in a rat noncontact penile erection model. Despite the limited metabolic stability seen for **10b**, successful development of sustained release formulations[48,49] has allowed us to advance the compound to phase 1 clinical trials.

Experimental Section

Melting points were recorded on a Thomas−Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Unity Plus 400 or a Varian 500 Unity INOVA spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) downfield from zero relative to the residual chloroform signal (7.26 ppm) or DMSO signal (2.49 ppm). Coupling constants are reported in hertz (Hz), and the exchangeable protons from HCl are not reported. Mass spectra were recorded on either a Hewlett−Packard 5995A, a Finnigan Trace MS, or a Micromass LCT spectrometer. Purity of tested compounds was assessed by reversed-phase high pressure liquid chromatography on a C18 column using two separate solvent systems: (1) A, 10 mM ammonium bicarbonate in water (pH 9.5), B, 50:50 acetonitrile:methanol, gradient of 85/15 A/B to 5/95 A/B over 2 min; (2) A, 10 mM ammonium formate in water (pH 3.5), B, 50:50 acetonitrile:methanol, gradient of 85/15 A/B to 5/95 A/B over 2 min. Detection was performed by UV analysis at both 215 and 254 nm. All compounds were shown to be >95% pure. Structures were confirmed by high resolution mass spectrometry on an Agilent TOF instrument. Unless otherwise noted below, reagents were obtained from commercial sources and were used without further purification. Chromatographic purifications were performed by flash chromatography using Baker 40 μm silica gel. Some of the procedures described below were originally presented in the patent literature.[23]

General Chemical Procedures. The synthesis of **10a** illustrates the general procedure used to prepare compounds **10a**−**r**.

6-Methoxy-8-{4-[1-(8-quinolinyl)-4-piperidinyl]-1-piperazinyl}-quinoline Trihydrochloride (10a). To a solution of **15** (0.250 g, 1.03 mmol) in methanol (15 mL) was added **18a** (0.279 g, 1.023 mmol) followed by sodium cyanoborohydride (0.126 g, 2.00 mmol). The resulting reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated on a rotary evaporator and the residue taken up in ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The resulting residue was purified by flash chromatography on silica gel (5% methanol/ethyl acetate) to give the desired product, which was dissolved in methanol and treated with excess 2N HCl in diethyl ether to afford the trihydrochloride salt (0.229 g, 40% yield) as a yellow solid: mp = 241−243 °C. ^{1}H NMR (DMSO-d_6) δ 9.15 (d, J = 4.2 Hz, 1H), 8.95 (d, J = 4.0 Hz, 1H), 8.88 (d, J = 6.6 Hz, 1H), 8.85−8.93 (m, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.88−7.95 (m, 2H), 7.82−7.93 (m, 2H), 7.78 (d, J = 7.9 Hz, 1H), 7.60 (s, 1H), 3.92 (s, 3H), 3.70−3.98 (m, 2H), 3.39−3.78 (m, 9H), 3.12 (t, J = 13.7 Hz, 2H), 2.40−2.52 (m, 2H), 2.25−2.90 (m, 2H). MS (ESI+) (m/z) 454 ([M + H]$^+$).

The following compounds were prepared using a similar procedure.

5-Fluoro-8-{4-[4-(6-methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl} Quinoline Trihydrochloride (10b). Prepared from **15** and **18b** in 56% overall yield and obtained as a yellow solid: mp = 226−230 °C. ^{1}H NMR (DMSO-d_6) δ 9.04 (dd, J_1 = 4.3 Hz, J_2 = 1.6 Hz, 1H), 8.92 (d, J = 3.7 Hz, 1H), 8.65−8.78 (m, 1H), 8.54 (dd, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H), 7.76−7.88 (m, 1H), 7.66−7.74 (m, 1H), 7.35−7.50 (m, 2H), 7.30−7.43 (m, 1H), 7.16−7.26 (m, 1H), 3.91 (s, 3H), 3.84−3.95 (m, 2H), 3.57−3.88 (m, 6H), 3.43−3.58 (m, 1H), 3.42 (t, J = 12.1 Hz, 2H), 2.96−3.13 (m, 2H), 2.30−2.42 (m, 2H), 2.18−2.32 (m, 2H). MS (ESI+) (m/z) 472 ([M + H]$^+$).

6-Fluoro-8-{4-[4-(6-methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl} Quinoline Trihydrochloride (10c). Prepared from **15** and **18c** in 41% overall yield and obtained as a yellow solid: mp = 222−225 °C. ^{1}H NMR (DMSO-d_6) δ 8.85−8.98 (m, 2H), 8.60−8.73 (m, 1H), 8.38 (d, J = 8.3 Hz, 1H), 7.74−7.85 (m, 1H), 7.59 (dd, J_1 = 8.4 Hz, J_2 = 4.4 Hz, 1H), 7.25−7.42 (m, 2H), 7.06−7.24 (m, 2H), 4.09 (d, J = 11.3 Hz, 2H), 3.91 (s, 3H), 3.54−3.80 (m, 5H), 3.28−3.52 (m, 4H), 2.84 (t, J = 11.6 Hz, 2H), 2.25−2.37 (m, 2H), 2.07−2.21 (m, 2H). MS (ESI+) (m/z) 472 ([M + H]$^+$).

6-Bromo-8-{4-[4-(6-methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl} Quinoline Trihydrochloride (10d). Prepared from **15**

and **18d** in 47% overall yield and obtained as a yellow solid: mp = 230−234 °C. ^{1}H NMR (DMSO-d_6) δ 8.83−8.94 (m, 2H), 8.62−8.74 (m, 1H), 8.35 (dd, J_1 = 8.4 Hz, J_2 = 1.3 Hz, 1H), 7.84 (d, J = 1.8 Hz, 1H), 7.73−7.84 (m, 1H), 7.58 (dd, J_1 = 8.3 Hz, J_2 = 4.3 Hz, 1H), 7.25−7.37 (m, 1H), 7.27 (m, 1H), 7.03−7.12 (m, 1H), 4.07 (d, J = 11.1 Hz, 2H), 3.90 (s, 3H), 3.58−3.82 (m, 6H), 3.39−3.53 (m, 1H), 3.30−3.42 (m, 2H), 2.85 (t, J = 11.6 Hz, 2H), 2.25−2.35 (m, 2H), 2.05−2.19 (m, 2H). MS (ESI+) (m/z) 533 ([M + H]$^+$).

7-Fluoro-8-{4-[4-(6-methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl} Quinoline Trihydrochloride (10e). Prepared from **15** and **18e** in 50% overall yield and obtained as a yellow solid: mp = 214−217 °C. ^{1}H NMR (DMSO-d_6) δ 9.03−9.12 (m, 1H), 8.87−8.96 (m, 1H), 8.42−8.54 (m, 1H), 7.90−8.02 (m, 1H), 7.65−7.80 (m, 1H), 7.54−7.72 (m, 3H), 7.12−7.23 (m, 1H), 6.95−7.045 (m, 1H), 3.88 (s, 3H), 3.40−4.03 (m, 10H), 3.36−3.52 (m, 1H), 3.26−3.41 (m, 2H), 2.40−2.57 (m, 2H), 2.15−2.25 (m, 2H). MS (ESI+) (m/z) 472 ([M + H]$^+$).

8-{4-[4-(6-Methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl}-2-methylquinoline Trihydrochloride (10f). Prepared from **15** and **18f** in 58% overall yield and obtained as a yellow solid: mp = 235−237 °C. ^{1}H NMR (DMSO-d_6) δ 8.87 (d, J = 2.2 Hz, 1H), 8.61−8.75 (m, 2H), 7.90 (d, J = 8.3 Hz, 1H), 7.65−7.83 (m, 4H), 7.37 (D, J = 2.0 Hz, 1H), 7.22 (d, J = 1.9 Hz, 1H), 3.92 (s, 3H), 3.72−3.83 (m, 2H), 3.42−3.76 (m, 7H), 3.33 (t, J = 10.9 Hz, 2H), 3.07−3.19 (m, 2H), 2.58−2.79 (m, 4H). MS (ESI+) (m/z) 468 ([M + H]$^+$).

8-{4-[4-(6-Methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl}-2-(trifluoromethyl) Quinoline Trihydrochloride (10g). Prepared from **15** and **18g** in 39% overall yield and obtained as a yellow solid: mp = 245−248 °C. ^{1}H NMR (DMSO-d_6) δ 8.81−8.85 (m, 1H), 8.53−8.63 (m, 2H), 7.92 (d, J = 8.5 Hz, 1H), 7.67−7.74 (m, 1H), 7.60−7.66 (m, 2H), 7.30 (dd, J_1 = 8.2 Hz, J_2 = 4.1 Hz, 1H), 7.25−7.29 (m, 1H), 7.07−7.11 (m, 1H), 4.12 (d, J = 11.2 Hz, 2H), 3.89 (s, 3H), 3.70−3.81 (m 2H), 3.41−3.79 (m, 5H), 3.25−3.38 (m, 2H), 2.35 (t, J = 1.2 Hz, 2H), 2.30−2.39 (m, 2H), 2.04−2.10 (m, 2H). MS (ESI+) (m/z) 522 ([M + H]$^+$).

3-Fluoro-8-{4-[4-(6-methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl} Quinoline Trihydrochloride (10h). Prepared from **15** and **18h** in 20% overall yield and obtained as a yellow solid: mp = 234−236 °C. ^{1}H NMR (DMSO-d_6) δ 8.87−8.94 (m, 2H), 8.63−8.73 (M, 1H), 8.20 (dd, J_1 = 9.6 Hz, J_2 = 2.9 Hz, 1H), 7.74−7.86 (m, 1H), 7.53−7.62 (m, 2H), 7.25−7.40 (m, 2H), 7.15−7.23 (m, 1H), 4.03 (d, J = 12.2 Hz, 2H), 3.90 (s, 3H), 3.58−3.79 (m, 6H), 3.45−3.57 (m, 1H), 3.33−3.44 (m, 2H), 3.39 (t, J = 12.4 Hz, 2H), 2.30−2.40 (m, 2H), 2.06−2.22 (m, 2H). MS (ESI+) (m/z) 472 ([M + H]$^+$).

8-{4-[4-(6-Methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl}-3-methylquinoline Trihydrochloride (10i). Prepared from **15** and **18i** in 44% overall yield and obtained as a yellow solid: mp = 232−235 °C. ^{1}H NMR (DMSO-d_6) δ 8.93 (s, 1H), 8.81−8.87 (m, 1H), 8.45−8.57 (m, 2H), 7.60−7.72 (m, 2H), 7.60−7.68 (m, 1H), 7.52−7.63 (m, 1H), 7.19−7.27 (m, 1H), 7.02−7.13 (m, 1H), 3.89 (s, 3H), 3.80−3.95 (m, 2H), 3.69−3.81 (m, 2H), 3.53−3.72 (m, 4H), 3.45−3.58 (m, 1H), 3.30−3.44 (m, 2H), 2.53 (s, 3H), 2.93−3.06 (m, 2H), 2.25−2.40 (m, 4H). MS (ESI+) (m/z) 468 ([M + H]$^+$).

8-{4-[4-(6-Methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl}-3-(trifluoromethyl) Quinoline Trihydrochloride (10j). Prepared from **15** and **18j** in 33% overall yield and obtained as a yellow solid: mp = 244−247 °C. ^{1}H NMR (DMSO-d_6) δ 9.16 (d, J = 2.3 Hz, 1H), 8.83−8.95 (m, 2H), 8.53−8.67 (m, 1H), 7.70−7.83 (m, 2H), 7.65 (t, J = 7.8 Hz, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7,23−7,32 (m, 1H), 7.06−7.16 (m, 1H), 4.10 (d, J = 1.5 Hz, 2H), 3.91 (s, 3H), 3.79−4.05 (m, 2H), 3.64−3.75 (m, 3H), 3.45−3.73 (m, 2H), 3.30−3,42 (m, 2H), 2.87 (t, J = 11.3 Hz, 2H), 2.30−2.42 (m, 2H), 2.05−2.18 (m, 2H). MS (ESI+) (m/z) 522 ([M + H]$^+$).

8-{4-[4-(6-Methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl}-4-methylquinoline Trihydrochloride (10k). Prepared from **15** and **18k** in 37% overall yield and obtained as a yellow solid: mp = 230−234 °C. ^{1}H NMR (DMSO-d_6) δ 8.69−8.80 (m, 2H), 8.00 (dd, J_1 = 8.2 Hz, J_2 = 1.7 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.25−7.38 (m, 1H), 7.1−7.24 (m, 2H), 6.82 (s, 1H), 6.70−6.78 (m, 1H), 4.09 (d, J = 11.7 Hz, 2H), 3.90 (s, 3H), 3.40−3.61 (m, 5H), 3.08−3.20 (m, 4H), 2.82 (t, J = 11.5 Hz, 2H), 2.68 (s, 3H), 2.02−2.19 (m, 4H). MS (ESI+) (m/z) 468 ([M + H]$^+$).

8-{4-[4-(6-Methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl}-2,4-dimethylquinoline Trihydrochloride (10l). Prepared from **15** and **18l** in 52% overall yield and obtained as a yellow solid: mp = 240−244 °C. ^{1}H NMR (DMSO-d_6) δ 8.83 (d, J = 4.4 Hz, 1H), 8.58 (d, J = 8.2 Hz, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.81−7.90 (m, 2H), 7.78 (s, 1H), 7.70−7.77 (m, 1H), 7.26 (d, J = 1.7 Hz, 1H), 7.15 (d, J = 2.1 Hz, 1H), 3.89 (s, 3H), 3.85 (d, J = 11.5 Hz, 2H), 3.55−3.78 (m, 6H), 3.40−3.50 (m, 2H), 3.28−3.37 (m, 1H), 3.04 (t, J = 11.6 Hz, 2H), 2.95 (s, 3H), 2.84 (s, 3H), 2.20−2.43 (m, 4H). MS (ESI+) (m/z) 482 ([M + H]$^+$).

4-Methoxy-8-{4-[4-(6-methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl}-2-(trifluoromethyl)-quinoline Trihydrochloride (10m). Prepared from **15** and **18m** in 37% overall yield and obtained as a yellow solid: mp = 244−248 °C. ^{1}H NMR (DMSO-d_6) δ 8.81−8.86 (m, 1H), 8.50−8.62 (m, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.56 (t, J = 7.9, 1H), 7.36 (s, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.20−7.29 (m, 1H), 7.06−7.13 (m, 1H), 4.10 (s, 3H), 3.75−4.15 (m, 5H), 3.89 (s, 3H), 3.70 (d, J = 11.2 Hz, 2H), 3.42−3.62 (m, 2H), 3.24−3.38 (m, 2H), 2.82 (t, J = 11.8 Hz, 2H), 2.27−2.38 (m, 2H), 1.98−2.12 (m, 2H). MS (ESI+) (m/z) 552 ([M + H]$^+$).

5-Fluoro-8-{4-[4-(6-methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl}-2-(trifluoromethyl)-quinoline Trihydrochloride (10n). Prepared from **15** and **18n** in 46% overall yield and obtained as a yellow solid: mp = 239−241 °C. ^{1}H NMR (DMSO-d_6) δ 8.92 (d, J = 4.5 Hz, 1H), 8.67−8.80 (m, 1H), 8.71 (d, J = 7.9 Hz, 1H), 8.02 (d, J = 8.7 Hz, 1H), 7.80−7.91 (m, 1H), 7.50 (t, J = 8.8 Hz, 1H), 7.37 (s, 1H), 7.16−7.30 (m, H), 4.00 (d, J = 12.1 Hz, 2H), 3.91 (s, 3H), 3.57−3.73 (m, 6H), 3.40−3.55 (m, 1H), 3.33−3.43 (m, 2H), 2.84 (t, J = 11.5 Hz, 2H), 2.30−2.40 (m, 2H), 2.00−2.14 (m, 2H). MS (ESI+) (m/z) 540 ([M + H]$^+$).

5-Fluoro-8-{4-[4-(6-methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl}-3-(trifluoromethyl)-quinoline Trihydrochloride (10o). Prepared from **15** and **18o** in 40% overall yield and obtained as a yellow solid: mp = 239−243 °C. ^{1}H NMR (DMSO-d_6) δ 9.26 (d, J = 2.1 Hz, 1H), 8.85−8.93 (m, 1H), 8.79 (s, 1H), 8.86−8.71 (m, 1H), 7.70−7.85 (m, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.36 (dd, J_1 = 8.5 Hz, J_2 = 5.3 Hz, 1H), 7.25−7.33 (m, 1H), 7.10−7.20 (m, 1H), 3.93 (d, J = 11.8 Hz, 2H), 3.90 (s, 3H), 3.52−3.88 (m, 6H), 3.38−3.54 (m, 1H), 3.30−3.42 (m, 2H), 2.83 (t, J = 11.7 Hz, 2H), 2.25−2.41 (m, 2H), 2.04−2.18 (m, 2H). MS (ESI+) (m/z) 540 ([M + H]$^+$).

3,5-Difluoro-8-{4-[4-(6-methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl}quinoline Trihydrochloride (10p). Prepared from **15** and **18p** in 51% overall yield and obtained as a yellow solid: mp = 232−234 °C. ^{1}H NMR (DMSO-d_6) δ 8.99 (d, J = 2.9 Hz, 1H), 8.80−8.86 (m, 1H), 8.49−8.61 (m, 1H), 8.23 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 7.64−7.74 (m, 1H), 7.40 (t, J = 8.9 Hz, 1H), 7.19−7.27 (m, 1H), 7.15 (dd, J_1 = 8.7 Hz, J_2 = 5.4 Hz, 1H), 7.03−7.13 (m, 1H), 3.94 (d, J = 11.7 Hz, 2H), 3.89 (s, 3H), 3.39−3.89 (m, 6H), 3.25−3.38 (m, 2H), 3.20−3.34 (m, 1H), 2.81 (t, J = 11.5 Hz, 2H), 2.25−2.39 (m, 2H), 2.04−2.15 (m, 2H). MS (ESI+) (m/z) 490 ([M + H]$^+$).

5-Fluoro-8-{4-[4-(6-methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl}-2,4-dimethylquinoline Trihydrochloride (10q). Prepared from **15** and **18q** in 36% overall yield and obtained as a yellow solid: mp = 236−240 °C. ^{1}H NMR (DMSO-d_6) δ 8.82−8.90 (m, 1H), 8.53−8.65 (m, 1H), 7.64−7.78 (m, 1H), 7.42−7.60 (m, 2H), 7.29−7.41 (m, 1H), 7.20−7.31 (m, 1H), 7.06−7.16 (m, 1H), 3.89 (s, 3H), 3.70−3.94 (m, 4H), 3.48−3.74 (m, 5H), 3.30−3.45 (m, 2H), 2.77 (s, 3H), 2.73−2.82 (m, 2H), 2.72 (s, 3H), 2.23−2.45 (m, 4H). MS (ESI+) (m/z) 500 ([M + H]$^+$).

5-Fluoro-4-methoxy-8-{4-[4-(6-methoxyquinolin-8-yl)piperazin-1-yl]piperidin-1-yl}-2-(trifluoromethyl)quinoline Trihydrochloride (10r). Prepared from **15** and **18r** in 22% overall yield and

obtained as a yellow solid: mp = 251−254 °C. ^{1}H NMR (DMSO-d_6) δ 8.77−8.85 (m, 1H), 8.42−8.58 (m, 1H), 7.63−7.712 (m, 1H), 7.42 (s, 1H), 7.30−7.46 (m, 1H), 7.15−7.29 (m, 2H), 7.0−7.09 (m, 1H), 4.08 (s, 3H), 3.90−3.96 (m, 2H), 3.90 (s, 3H), 3.53−3.81 (m, 6H), 3.40−3.53 (m, 1H), 3.25−3.29 (m, 2H), 2.79 (t, J = 11.7, 2H), 2.24−2.38 (m, 2H), 1.95−2.11 (m, 2H). MS (ESI+) (m/z) 560 ([M + H]$^+$).

Synthesis of 6-Methoxy-8-piperazinoquinoline (15). 8-Chloro-6-hydroxyquinoline (12). To a 500 mL 3-neck round-bottom flask was added, in order, iron(II) sulfate (2.0 g, 13.2 mmol), 4-amino-3-chlorophenol hydrochloride (6.4 g, 35.5 mmol), nitrobenzene (2.9 mL), and a solution of boric acid (3.0 g, 48.5 mmol) in glycerol (16 mL). The stirred mixture was cooled in an ice bath, and concentrated sulfuric acid (9.0 mL) was added dropwise. The ice bath was then removed and the stirred mixture cautiously heated to 120 °C for 2 h, then at 150 °C for 20 h. The reaction mixture was cooled to room temperature and then poured onto ice. The resulting aqueous mixture was neutralized with solid potassium carbonate, and the desired product precipitated as a light-brown solid. The solid was collected by vacuum filtration, washed with water and hexane, and dried in vacuo to provide the desired product as a tan solid (7.0 g, 77% yield). ^{1}H NMR (DMSO-d_6) δ 10.37 (s, 1H), 8.77 (d, J = 4.3 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.35−7.52 (m, 2H), 7.17 (s, 1H). MS (ESI−) (m/z) 178 ([M − H]$^-$).

8-Chloro-6-methoxyquinoline (13). To a solution of **12** (3.3 g, 18.4 mmol) in dimethylformamide (30 mL) was added anhydrous potassium carbonate (3.8 g, 27.5 mmol), followed by iodomethane (5.2 g, 36.6 mmol). The mixture was stirred at room temperature overnight. Water 200 mL) was added, and the resulting mixture was extracted three times with dichloromethane (75 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The resulting residue was purified by flash chromatography on silica gel (100% dichloromethane) to afford the desired product (2.2 g, 62% yield) as a beige solid: mp = 74−75 °C. ^{1}H NMR (chloroform-d) δ 8.89 (dd, J_1 = 4.3 Hz, J_2 = 1.8 Hz, 1H), 8.07 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.54 (d, J = 2.8 Hz, 1H), 7.36−7.49 (m, 1H), 7.02 (d, J = 2.8 Hz, 1H), 3.93 (s, 3H). MS (ESI+) (m/z) 180 ([M + H]$^+$).

6-Methoxy-8-[1-(*tert*-butoxycarbonyl)-4-piperazino]quinoline (14). To a mixture of **13** (2.7 g, 14.0 mmol) in anhydrous tetrahydrofuran (50 mL) under a nitrogen atmosphere was added tris(dibenzylideneacetone)dipalladium (0) ($Pd_2(dba)_3$, 0.064 g, 0.07 mmol), sodium *tert*-butoxide (1.9 g, 5.21 mmol), 2-dicylcohexylphosphine-2′-(*N*,*N*-dimethylamino)biphenyl (CYMAP, 0.08 g, 0.20 mmol), and *tert*-butoxycarbonylpiperazine (3.4 g, 15.3 mmol). The resulting mixture was stirred at reflux for 5 h and then cooled to room temperature. The reaction mixture was diluted with diethyl ether, filtered through a pad of celite, and concentrated on a rotary evaporator. The resulting residue was purified by flash chromatography on silica gel (100% dichloromethane) to afford the desired product (4.4 g, % yield) as a beige solid: mp = 92−93 °C. ^{1}H NMR (chloroform-d) δ 8.72 (dd, J_1 = 4.2 Hz, J_2 = 1.9 Hz, 1H), 8.00 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.33 (dd, J_1 = 8.2 Hz, J_2 = 4.2 Hz, 1H), 6.78 (d, J = 2.7 Hz, 1H), 6.72 (d, J = 2.5 Hz, 1H), 3.91 (s, 3H), 3.73−3.84 (m, 4H), 3.28−3.40 (M, 4H), 1.50 (s, 9H). MS (ESI+) (m/z) 344 ([M + H]$^+$).

6-Methoxy-8-piperazinoquinoline (15). To a solution of **14** (4.0 g, 11.7 mmol) in 1,4-dioxane (20 mL) was added 4N HCl/dioxane (10 mL). The resulting mixture was stirred at room temperature overnight, during which time a white precipitate formed. The precipitate was collected by vacuum filtration, dissolved in water, and neutralized with 2.5 N aqueous sodium hydroxide. The resulting aqueous mixture was extracted three times with dichloromethane (50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator to give the desired product (2.8 g, 98% yield) as a tan solid which was used without further purification: mp = 105−107 °C. ^{1}H NMR (chloroform-d) δ 8.71 (dd, J_1 = 4.2 Hz, J_2 = 2.4 Hz, 1H), 7.98 (dd, J_1 = 8.4 Hz, J_2 = 1.7 Hz, 1H), 7.25−7.35 (m, 1H), 6.78 (d, J = 2.7 Hz, 1H), 6.69 (d, J = 2.7 Hz, 1H), 3.90 (s, 3H), 3.35−3.48 (m, 4H), 3.15−3.24 (m, 4H), (2.05 (br s, 1H). MS (ESI+) (m/z) 224 ([M + H]$^+$).

8-Chloro-5-fluoroquinoline (16b). To a stirred mixture of 2-chloro-5-fluoroaniline (5.0 g, 34.3 mmol) and *m*-nitrobenzene sulfonic acid sodium salt (11.0 g, 48.9 mmol) and glycerol (6.0 g, 65.2 mmol) was added dropwise 70% sulfuric acid (20 mL). The reaction temperature was then raised to 140 °C and stirred at that temperature for 2 h. The reaction mixture was cooled to room temperature, poured into water, filtered through a bed of celite, made slightly basic (pH = 8−9) with 50% aqueous sodium hydroxide, and extracted three times with dichloromethane (75 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel (100% dichloromethane) to afford the desired product (3.70 g, 59% yield) as a white solid. ^{1}H NMR (DMSO-d_6) δ 9.04 (dd, J_1 = 4.3 Hz, J_2 = 1.7 Hz, 1H), 8.47 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.84−7.934 (m, 1H), 7.65−7.71 (m, 1H), 7.40 (t, J = 8.5 Hz, 1H). MS (ESI+) (m/z) 182 ([M + H]$^+$).

8-Bromo-6-fluoroquinoline (16c). To a mixture of 2-bromo-4-fluoroaniline (6.8 g, 35.8 mmol), glycerol (6.8 g, 73.8 mmol), and *m*-nitrobenzene sulfonic acid sodium salt (12.8 g, 56.8 mmol) was added 70% sulfuric acid (30 mL) dropwise. The reaction temperature was raised to 150 °C for 4 h. The mixture then was cooled to room temperature, poured into ice water, and was neutralized with 50% aqueous sodium hydroxide solution. The mixture was then extracted three times with dichloromethane (100 mL). The combined organics were washed with brine and dried over anhydrous magnesium sulfate to yield 3.1 g (37%) of the desired product as an off-white solid, which was used without further purification: ^{1}H NMR (DMSO-d_6) δ 8.99 (dd, J_1 = 4.2 Hz, J_2 = 1.2 Hz, 1H), 8.43 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 8.20 (dd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, 1H), 7.90 (dd, J_1 = 9.1 Hz, J_2 = 2.8 Hz, 1H), 7.67 (dd, J_1 = 8.4 Hz, J_2 = 4.2 Hz, 1H). MS (ESI+) (m/z) 226, 228 ([M + H]$^+$).

8-Fluoro-6-Bromoquinoline (16d). To a mixture of 4-bromo-2-fluoroaniline (6.8 g, 35.8 mmol), glycerol (6.8 g, 73.8 mmol), and *m*-nitrobenzene sulfonic acid sodium salt (12.8 g, 56.8 mmol) was added 70% sulfuric acid (30 mL) dropwise. The reaction temperature was raised to 150 °C for 4 h. The mixture then was cooled to room temperature, poured into ice water, and was neutralized with 50% aqueous sodium hydroxide solution. The mixture was then extracted three times with dichloromethane (100 mL). The combined organics were washed with brine and dried over anhydrous magnesium sulfate to yield 4.1 g (50%) of the desired product as a tan solid, which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 8.98 (dd, J_1 = 4.3 Hz, J_2 = 1.5 Hz, 1H), 8.38−8.43 (m, 1H), 8.15 (d, J = 1.8 Hz, 1H), 7.87 (dd, J_1 = 10.4 Hz, J_2 = 2.1 Hz, 1H), 7.68 (dd, J_1 = 8.4 Hz, J_2 = 4.1 Hz, 1H). MS (ESI+) (m/z) 226, 228 ([M + H]$^+$)

7,8-Difluoroqinoline (16e). To a stirred mixture of 2,3-difluoroaniline (3.57 g, 27.7 mmol), glycerol (5.55 g, 60.3 mmol), and *m*-nitrobenzene sulfonic acid sodium salt (10.12 g, 45.0 mmol) was added dropwise 70% sulfuric acid (20 mL). The resulting mixture was heated to 135 °C and then stirred at that temperature for 3.5 h. The reaction was cooled to room temperature, poured onto ice, and made slightly basic (pH = 8−9) with 50% aqueous sodium hydroxide. The aqueous mixture was extracted three times with diethyl ether (75 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The desired compound (4.13 g, 90% yield) was obtained as a light-brown solid and was pure enough to use in subsequent reactions without further purification. ^{1}H NMR (DMSO-d_6) δ 9.00 (dd, J_1 = 4.3 Hz, J_2 = 1.5 Hz, 1H), 8.49 (dd, J_1 = 8.5 Hz, J_2 = 1.4 Hz, 1H), 7.85−7.95 (m, 1H), 7.71−7.79 (m, 1H), 7.60−7.71 (m, 1H). MS (ESI+) (m/z) 166 ([M + H]$^+$).

8-Bromo-2-methylquinoline (16f). A mixture of 2-bromoaniline (4.27 g, 24.8 mmol) and crotonaldehyde (2.20 g, 25.0 mmol) in 6N aqueous HCl (12.4 mL) was stirred at reflux overnight. The reaction mixture was cooled to room temperature, made basic (pH = 10) by addition of 2.5 N aqueous sodium hydroxide, and extracted four times with dichloromethane (50 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel (30% ethyl acetate/hexane) to afford the desired product 2.10 g, 39% yield) as a yellow oil. ^{1}H NMR (chloroform-*d*) δ 7.98−8.06 (m, 2H), 7.73 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H), 7.28−7.37 (m, 2H), 2.81 (s, 3H). MS (ESI+) (*m*/*z*) 222, 224 ([M + H]$^+$).

8-Bromo-2-(trifluoromethyl)quinoline (16g). Compound **16g** was prepared using the sequence described by Cottet, et al.[50] The compound was isolated as a white solid by recrystallization from hexane. ^{1}H NMR (chloroform-*d*) δ 8.42 (d, *J* = 8.4 Hz, 1H), 8.22 (dd, J_1 = 7.6 Hz, J_2 = 1.4 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H),7.55−7.63 (m, 1H). MS (ESI+) (*m*/*z*) 276, 278 ([M + H]$^+$).

8-Bromo-3-fluoroquinoline (16h). To a solution of 3-aminoquinoline (1.00 g, 6.94 mmol) in 48% fluoroboric acid (10 mL) at 0 °C was added sodium nitrate (0.60 g, 14.49 mmol) dissolved in water (2 mL). The reaction was stirred at 0 °C for 1 h. The reaction was cooled to room temperature, and the resulting yellow precipitate was collected by vacuum filtration, washed with cold ethanol and cold diethylethyl ether, and dried in vacuo. The dried yellow precipitate was suspended in toluene (10 mL) and heated at 110 °C for 1 h. The cooled reaction mixture was poured into ice water. The mixture was treated with diethyl ether to dissolve the resulting brown precipitate, and the layers were separated. The aqueous was made basic with 2.5 N aqueous sodium hydroxide solution and extracted three times with ethyl acetate (50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel (5% ethyl acetate/hexane) to give 0.64 g (63%) of 3-fluoroquinoline as clear oil. ^{1}H NMR (DMSO-d_6) δ 8.90 (d, *J* = 2.9 Hz, 1H), 8.22 (dd, J_1 = 9.6 Hz, J_2 = 2.8 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 1H), 7.96 (dd, J_1 = 8.1 Hz, J_2 = 1.4 Hz, 1H), 7.72 (t, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H). MS (ESI+) (*m*/*z*) 148 ([M + H]$^+$).

A solution of 3-fluoroquinoline (0.64 g, 4.35 mmol) in concentrated sulfuric acid (3.75 mL) was cooled to 0 °C. Fuming nitric acid was added dropwise. The reaction was warmed to room temperature and stirred for 1 h, then poured onto ice. The resulting mixture was made basic with 50% aqueous sodium hydroxide solution and extracted three times with ethyl acetate (50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator to give 0.81 g (97% yield) of a 1:3 mixture of 3-fluoro-8-nitroquinoline and 3-fluoro-5-nitroquinoline as a clear oil, which was used in the next step without further purification: MS (ESI+) (*m*/*z*) 193 ([M + H]$^+$).

To the mixture of 3-fluoro-8-nitroquinoline and 3-fluoro-5-nitroquinoline (0.81 g, 4.23 mmol) in ethyl acetate (20 mL) was added 10% Pd/C (0.3 g). The mixture was hydrogenated at 55 psi in a Parr reactor for 1 h. The suspension was filtered through celite to remove the catalyst, concentrated on a rotary evaporator, and purified by flash chromatography on silica gel (30% EtOAc/hexane) to give 8-amino-3-fluoroquinoline (0.12 g, 17% yield) as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.70 (d, *J* = 2.9 Hz, 1H), 8.00 (dd, J_1 = 10.1 Hz, J_2 = 2.8 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 5.98 (br s, 2H). MS (ESI+) (*m*/*z*) 163 ([M + H]$^+$).

A mixture of copper(II) bromide (0.123 g, 0.57 mmol) and *tert*-butyl nitrite (0.09 g, 0.86 mmol) in dry acetonitrile (5 mL) was stirred and heated to 65 °C. To that mixture was added a solution of 3-fluoroquinolin-8-amine (0.09 g, 0.57 mmol) in dry acetonitrile (3 mL) dropwise over 5 min. The resulting reaction mixture was stirred at 65 °C for 15 min and then cooled to room temperature. The reaction was poured into cold 20% aqueous sodium hydroxide solution and extracted three times with diethyl ether (30 mL). The organic layer was concentrated on a rotary evaporator and purified by flash chromatography on silica (5% EtOAc/hexane) to give 0.027 g (17%) of the desired 8-bromo-5-fluoroquinoline as a light-yellow solid. ^{1}H NMR (DMSO-d_6) δ 9.05 (d, *J* = 3.4 Hz, 1H), 8.37 (dd, J_1 = 5.5 Hz, J_2 = 2.6 Hz, 1H), 8.13 (d, *J* = 7.5 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H). MS (ESI+) (*m*/*z*) 226, 228 ([M + H]$^+$).

8-Bromo-3-methylquinoline (16i). A mixture of 2-bromoaniline (4.56 g, 26.5 mmol) and methacrolein (3.10 g, 39.8 mmol) in 6N aqueous HCl (13 mL) was stirred at reflux overnight. The reaction mixture was cooled to room temperature, made basic (pH = 10) by addition of 50% aqueous sodium hydroxide, and extracted three times with dichloromethane (50 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel (15% ethyl acetate/hexane) to afford the desired product 2.15 g, 46% yield) as a yellow oil. ^{1}H NMR (chloroform-*d*) δ 8.76 (s, 1H), 7.85 (d, *J* = 7.4 Hz, 1H), 7.76 (s, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 2.41 (s, 3H). MS (ESI+) (*m*/*z*) 222, 224 ([M + H]$^+$).

8-Bromo-3-(trifluoromethyl)quinoline (16j). To a solution of 8-bromoquinoline (1.0 g, 4.81 mmol) in glacial acetic acid (6 mL) was added, portionwise, *N*-iodosuccinimide (1.08 g, 4.81 mmol). The resulting mixture was stirred at 70 °C overnight, cooled to room temperature, and concentrated on a rotary evaporator. The residue was taken up in dichloromethane and washed with saturated aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel (5% ethyl acetate/hexane) to afford the intermediate 8-bromo-3-iodoquinoline (0.79 g, 49% yield) as a white solid. ^{1}H NMR (chloroform-*d*) δ 9.12 (d, *J* = 2.0 Hz, 1H), 8.52 (d, *J* = 2.1 Hz, 1H), 8.03 (dd, J_1 = 7.5 Hz, J_2 = 1.3 Hz, 1H), 7.66 (dd, J_1 = −8.1 Hz, J_2 = 2.1 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H). MS (ESI+) (*m*/*z*) 334, 336 ([M + H]$^+$).

A mixture of copper(I) iodide (0.25 g, 1.32 mmol) and potassium fluoride (0.077 g, 1.32 mmol) was placed under a high vacuum and heated until the solid assumed a slightly green color. The cooled solid mass was suspended in anhydrous *N*-methylpyrrolidinone (5 mL) and then treated with the previously described 8-bromo-3-iodoquinoline (0.40 g, 1.20 mmol), followed by trifluoromethyltrimethylsilane (0.17 g, 1.20 mmol). The resulting mixture was stirred under a nitrogen atmosphere at 50 °C overnight. The mixture was then cooled to room temperature and poured into 15% aqueous ammonium hydroxide. The aqueous mixture was extracted four times with diethyl ether (25 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel (4:1 hexane/ethyl acetate) to afford the desired product **16j** (0.27 g, 33% yield) as a brown oil. ^{1}H NMR (chloroform-*d*) δ 9.18 (d, *J* = 2.0 Hz, 1H), 8.43 (s, 1H), 8.17 (dd, J_1 = 7.5 Hz, J_2 = 1.1 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 1H). MS (ESI+) (*m*/*z*) 276, 278 ([M + H]$^+$).

8-Bromo-4-methylquinoline (16k). To a mixture of 2-bromoaniline (7.00 g, 40.7 mmol) and methyl vinyl ketone (4.00 mL g, 48.8 mmol) in ethanol/water (37 mL/7 mL) was added zinc chloride (1.35 g, 10.1 mmol) and iron(III) chloride (1.10 g, 6.5 mmol). The resulting mixture was stirred at reflux overnight. The reaction mixture was cooled and treated with ethanol (50 mL), followed by 12% aqueous sodium hydroxide (50 mL). The resulting inorganic white precipitate was removed by vacuum filtration, and the filtrate was extracted twice with dichloromethane (100 mL). The combined organic extracts were

washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel (15% ethyl acetate/hexane) to afford the desired product (3.45 g, 38% yield) as an off-white solid. ^{1}H NMR (chloroform-*d*) δ 8.87 (d, J = 4.3 Hz, 1H), 8.03 (d, J = 7.4 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1 H), 7.27 (d, J = 4.4 Hz, 1H), 2.70 (s, 3H). MS (ESI+) (*m*/*z*) 222, 224 ([M + H]$^+$).

8-Bromo-2,4-dimethylquinoline (16l). A mixture of 2-bromoaniline (4.00 g, 23.3 mmol) and 3-penten-2-one (65%, 4.18 mL, 27.9 mmol) in concentrated HCl (50 mL) was stirred at reflux for 12 h. The reaction mixture was cooled to room temperature and then cooled in an ice bath and made basic (pH = 10) by addition of 5 N aqueous sodium hydroxide. The resulting aqueous mixture was extracted three times with dichloromethane (75 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel (10% ethyl acetate/hexane) to afford the desired product 2.15 g, 46% yield) as a white solid. ^{1}H NMR (chloroform-*d*) δ 7.97 (d, J = 7.3 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.29(t, J = 7.8 Hz, 1H), 7.15 (s, 1H), 2.73 (s, 3H), 2.63 (s, 3H). MS (ESI+) (*m*/*z*) 236, 238 ([M + H]$^+$).

8-Bromo-4-methoxy-2-(trifluoromethyl)quinoline (16m). A solution of ethyl 4,4,4-trifluoroacetoacetate (4.0 mL, 27.3 mmol) in polyphosphoric acid (22) was heated to 100 °C. 2-Bromoaniline (4.47 g, 26.0 mmol) was added slowly to the stirred reaction. The resulting mixture was heated to 150 °C and then stirred at that temperature overnight. The reaction was then cooled to room temperature, and water was added carefully. The resulting tan precipitate was collected by vacuum filtration, washed with water, and dissolved in ethyl acetate. The ethyl acetate solution was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The crude product was purified by flash chromatography on silica gel (4:1 hexane/ethyl acetate) to give 8-bromo-2-(trifluoromethyl)-quinolin-4-ol (4.76 g, 63% yield) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 12.60 (s, 1H), 8.16−8.22 (m, 2H), 7.52 (t, J = 8.2 Hz, 1H), 7.19 (s, 1H). MS (ESI+) (*m*/*z*) 291, 293 ([M − H]$^-$).

To a solution of 8-bromo-2-(trifluoromethyl)quinolin-4-ol (0.50 g, 1.71 mmol) in acetone (15 mL) was added anhydrous potassium carbonate (0.50 g, 3.60 mmol), followed by iodomethane (0.53 g, 3.76 mmol). The resulting mixture was stirred at reflux for 1.5 h. An additional aliquot of iodomethane (0.53 g, 3.76 mmol) was added, and reflux was continued for an additional hour. The reaction was cooled to room temperature, poured onto ice, and extracted three times with ethyl acetate (50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator to give **16m** (0.42 g, 79% yield) as a beige solid, which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 8.18−8.27 (m, 2H), 7.58 (t, J = 8.0 Hz, 1H), 7.47 (s, 1H), 4.15 (s, 3H). MS (ESI+) (*m*/*z*) 305, 307 ([M + H]$^+$).

8-Chloro-5-fluoro-2-(trifluoromethyl)quinoline (16n). A solution of 4,4,4-trifluoroacetoacetate (4 mL, 27.3 mmol) in polyphosphoric acid (22 mL) was heated to 100 °C. 2-Chloro-5-fluoroaniline (3.78 g, 26.0 mmol) was added portionwise to the stirred solution. The resulting reaction mixture was heated to 150 °C and then stirred at that temperature overnight. The reaction was cooled to room temperature, and water was added carefully. The resulting light-brown precipitate was collected by vacuum filtration, washed with water, and dissolved in ethyl acetate. The ethyl acetate solution was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel (4:1 ethyl acetate/hexane) to afford 8-chloro-5-fluoro-2-(trifluoromethyl)quinolin-4-ol (3.54 g, 51% yield) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 12.74 (br s, 1H), 7.94−8.01 (m, 1H), 7.37 (7.34−7.43 (m, 1H), 7.23 (s, 1H). MS (ESI+) (*m*/*z*) 264 ([M − H]$^-$).

To phosphorus oxybromide (6.4 g, 23.00 mmol)) heated at 75 °C was slowly added 8-chloro-5-fluoro-2-(trifluoromethyl)-quinolin-4-ol (3.04 g, 11.45 mmol) and the temperature was raised to 150 °C for 2 h. After cooling to room temperature, the reaction was poured over ice and three times extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The crude product was purified by flash chromatography on silica gel (10% ethyl acetate in hexane) using hexane/ethyl acetate to give 4-bromo-8-chloro-5-fluoro-2-(trifluoromethyl)quinoline (3.13 g, 83% yield) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 8.50 (s, 1H), 8.12−8.18 (m, 1H), 7.67−7.75 (m, 1H). MS (ESI+) (*m*/*z*) 328, 330 ([M + H]$^+$).

A stirred mixture of 1.6 *n*-butyl lithium/hexane (6.8 mL, 10.8 mmol) in dry tetrahydrofuran (10 mL) under a nitrogen atmosphere was cooled to −78 °C with a dry ice/acetone bath. A solution of 4-bromo-8-chloro-5-fluoro-2-(trifluoromethyl)quinoline (2.9 g, 8.8 mmol) in dry tetrahydrofuran (15 mL) was added dropwise over 15 min. The resulting reaction mixture was stirred at −78 °C for 20 min and then quenched by addition of methanol (2 mL). The reaction was warmed to room temperature, poured into brine, and partially concentrated on a rotary evaporator to remove the tetrahydrofuran. The resulting aqueous mixture was extracted twice with ethyl acetate (75 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The crude residue was purified by flash chromatography on silica gel (20% dichloromethane in hexane) to provide **16n** (1.1 g, 50% yield) as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.83 (d, J = 8.7 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.05−8.15 (m, 1H), 7.62 (t, J = 8.7 Hz, 1H). MS (ESI+) (*m*/*z*) 250 ([M + H]$^+$).

8-Chloro-5-fluoro-3-(trifluoromethyl)quinoline (16o). To a stirred mixture of 2-chloro-5-fluoroaniline (5.00 g, 34.3 mmol), glycerol (6.00 g, 65.2 mmol), and *m*-nitrobenzene sulfonic acid sodium salt (11.0 g, 48.9 mmol) was added dropwise 70% sulfuric acid. The reaction was then heated to 140 °C and stirred at that temperature for 2 h. The mixture was cooled to room temperature and then poured into water, filtered through a bed or celite, made slightly basic (pH = 8−9) with 50% aqueous sodium hydroxide, and extracted three times with dichloromethane (75 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel (100% dichloromethane) to afford the desired product (3.70 g, 59% yield) as a white solid. ^{1}H NMR (DMSO-d_6) δ 9.04 (dd, J_1 = 4.3 Hz, J_2 = 1.7 Hz, 1H), 8.47 (dd, J_1 = 8.4 Hz, J_2 = 1. Hz, 1H), 7.84−7.92 (m, 1H), 7.65−7.71 (m, 1H), 7.40 (t, J = 8.5 Hz, 1H). MS (ESI+) (*m*/*z*) 182 ([M + H]$^+$).

To a solution of 8-chloro-5-fluoroquinoline (3.50 g, 19.3 mmol) in glacial acetic acid (50 mL) was added, portionwise, *N*-iodosuccinimide (4.34 g, 19.3 mmol). The resulting mixture was stirred at 70 °C overnight, cooled to room temperature, and concentrated on a rotary evaporator. The residue was taken up in dichloromethane and washed with saturated aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel (5% ethyl acetate/hexane) to afford the intermediate 8-bromo-5-fluoro-3-iodoquinoline (1.68 g, 28% yield) as an off-white solid. ^{1}H NMR (chloroform-*d*) δ 9.16 (d, J = 2.1 Hz, 1H), 8.79 (d, J = 2.1 Hz, 1H), 7.70−7.77 (m, 1H), 7.317 (t, J = 8.8 Hz, 1H). MS (ESI+) (*m*/*z*) 308 ([M + H]$^+$).

A mixture of copper(I) iodide (2.07 g, 10.9 mmol) and potassium fluoride (0.63 g, 10.9 mmol) was placed under a high vacuum and heated until the solid assumed a slightly green color. The cooled solid mass was suspended in anhydrous *N*-methylpyrrolidinone (20 mL) and then treated with the previously described 8-bromo-5-fluoro-3-iodoquinoline (1.68 g,

5.47 mmol), followed by trifluoromethyltrimethylsilane (2.33 g, 16.4 mmol). The resulting mixture was stirred under a nitrogen atmosphere at 50 °C overnight. The mixture was then cooled to room temperature and poured into 15% aqueous ammonium hydroxide. The aqueous mixture was extracted four times with diethyl ether (50 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel (5% ethyl acetate/hexane) to afford the desired product **16o** (0.56 g, 41% yield) as an off-white solid. ^{1}H NMR (chloroform-*d*) δ 9.23 (s, 1H), 8.73 (s, 1H), 7.84−7.94 (m, 1 h), 7.29 (t, J = 8.6 Hz, 1H). MS (ESI+) (m/z) 250 ([M + H]$^+$).

8-Bromo-3,5-difluoroquinoline (16p). Flash chromatography of the mixture of 5-amino-8-fluoroquinoline and 8-amino-3-fluoroquinoline obtained in the synthesis of **16h** on silica gel (30% ethyl acetate/hexane) afforded 5-amino-3-fluoroquinoline as a light-brown solid in 53% yield. ^{1}H NMR (DMSO-d_6) δ 8.79 (d, J = 2.8 Hz, 1H), 8.35 (dd, J_1 = 10.9 Hz, J_2 = 2.8 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 7.5 Hz 1H), 5.94 (br s, 2H). MS (ESI+) (m/z) 163 ([M + H]$^+$).

3,5-Difluoroquinoline was obtained as a tan solid in 63% yield by treatment of 5-amino-3-fluoroquinoline with 48% fluoroboric acid using the procedure described for preparing 3-fluoroquinoline in the synthesis of **16h**. The crude reaction residue was purified by flash chromatography on silica using 5% ethyl acetate/hexane: ^{1}H NMR (chloroform-*d*) δ 8.86 (d, J = 8.5 Hz, 1H), 8.02 (dd, J_1 = 8.5 Hz, J_2 = 2.6 Hz, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.60−7.71 (m, 1H), 7.26−7.35 (m, 1H). MS (ESI+) (m/z) 166 ([M + H]$^+$).

3,5-Difluoro-8-nitroquinoline was obtained as a yellow solid in 48% yield from 3,5-difluoroquinoline by treatment with fuming nitric acid in concentrated sulfuric acid using the procedure described for preparing 3-fluoro-8-nitroquinoline in the synthesis of **16h**. The product was obtained by vacuum filtration of the aqueous mixture and was pure enough to use in subsequent reactions. ^{1}H NMR (DMSO-d_6) δ 9.16 (d, J = 2.4 Hz, 1H), 8.52 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 8.30−8.38 (m, 1H), 7.68 (t, J = 8.7). MS (ESI+) (m/z) 211 ([M + H]$^+$).

8-Amino-3,5-difluoroquinoline was obtained as a white solid in 83% yield by hydrogenation of 3,5-difluoro-8-nitroquinoline over 10% Pd/C at 55 psi. The crude reaction residue was purified by flash chromatography on silica gel using 30% ethyl acetate/hexane. ^{1}H NMR (DMSO-d_6) δ 8.77 (d, J = 2.8 Hz, 1H), 8.06 (dd, J_1 = 9.6 Hz, J_2 = 2.8 Hz, 1H), 7.19 (t, J = 9.2 Hz, 1H), 6.67−6.73 (m, 1H), 5.82 (br s, 2H). MS (ESI+) (m/z) 181 ([M + H]$^+$).

To a solution of 8-amino-3,5-difluoroquinoline (0.05 g, 0.28 mmol) in water (2 mL) was added concentrated hydrobromic acid (5 mL) and cooled to 0 °C. To the reaction was added sodium nitrite (0.038 g, 0.55 mmol) in water (1 mL). The resulting mixture was poured into a solution of copper(I) bromide (0.12 g, 0.84 mmol) in concentrated hydrobromic acid (5 mL). The reaction was stirred at room temperature overnight. The reaction was poured into cold 20% aqueous sodium hydroxide solution and extracted three times with diethyl ether (20 mL). The combined organic layers were concentrated on a rotary evaporator to give 0.061 g (89%) of 8-bromo-3,5-difluoroquinoline as a yellow oil, which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 9.10 (d, J = 2.8 Hz, 1H), 8.38 (dd, J_1 = 8.9 Hz, J_2 = 2.8 Hz, 1H), 8.05−8.12 (m, 1H), 7.46 (t, J = 8.8 Hz, 1H). MS (ESI+) (m/z) 244, 246 ([M + H]$^+$).

8-Bromo-5-fluoro-2,4-dimethylquinoline (16q). A mixture of 2-bromo-5-fluoroaniline (3.0 g, 15.8 mmol) and 3-penten-2-one (65%, 2.44 g, 18.9 mmol) in concentrated HCl (30 mL), was stirred at reflux overnight. The reaction mixture was cooled to room temperature and then cooled in an ice bath. The pH was adjusted to 10 with 2.5 N aqueous sodium hydroxide, and the resulting aqueous mixture was extracted three times with dichloromethane (50 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel (60% ethyl acetate/hexane) to afford the desired product (2.42 g, 60% yield) as a light-yellow solid. ^{1}H NMR (chloroform-*d*) δ 7.84−7.91 (m, 1H), 7.12 (s, 1H), 6.95−7.04 (m, 1H), 2.77 (d, J = 7.1 Hz (fluorine coupling), 3H), 2.71 (s, 3H). MS (ESI+) (m/z) 254, 256 ([M + H]$^+$).

8-Chloro-5-fluoro-4-methoxy-2-(trifluoromethyl)quinoline (16r). A solution of 4,4,4-trifluoroacetoacetate (4 mL, 27.3 mmol) in polyphosphoric acid (22 mL) was heated to 100 °C. 2-Chloro-5-fluoroaniline (3.78 g, 26.0 mmol) was added portionwise to the stirred solution. The resulting reaction mixture was heated to 150 °C and then stirred at that temperature overnight. The reaction was cooled to room temperature, and water was added carefully. The resulting light-brown precipitate was collected by vacuum filtration, washed with water, and dissolved in ethyl acetate. The ethyl acetate solution was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel (4:1 hexane/ethyl acetate) to afford 8-chloro-5-fluoro-2-(trifluoromethyl)quinolin-4-ol (3.54 g, 51% yield) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 12.74 (br s, 1H), 7.94−8.01 (m, 1H), 7.37 (7.34−7.43 (m, 1H), 7.23 (s, 1H). MS (ESI+) (m/z) 264 ([M − H]$^-$).

To a solution of 8-chloro-5-fluoro-2-(trifluoromethyl)quinolin-4-ol (3.54 g, 13.3 mmol, preparation described in the synthesis of **16n**) in acetone (75 mL) was added anhydrous potassium carbonate (3.88 g, 28.0 mmol), followed by iodomethane (1.8 mL, 28.9 mmol). The resulting mixture was stirred at reflux for 1.5 h. An additional aliquot of iodomethane (1.8 mL, 28.9 mmol) was added, and reflux was continued for an additional 1 h. The reaction was cooled to room temperature, poured onto ice, and extracted three times with ethyl acetate (50 mL). The combined organic layers were dired over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The desired **16r** (3.72 g, 100% yield) was isolated as a yellow solid and was pure enough to use in subsequent reactions without further purification. ^{1}H NMR (DMSO-d_6) δ 8.00−8.05 (m, 1H), 7.53 (s, 1H), 7.43−7.50 (m, 1H), 4.12 (s, 3H). MS (ESI+) (m/z) 280 ([M + H]$^+$).

The synthesis of 8-(1,4-dioxa-8-azaspiro[4,5]dec-8-yl)quinoline (**17a**) illustrates the general sequence used to prepare compounds **17a**, **17c**−**d**, **17f**−**m** and **17p**−**q**.

8-(1,4-Dioxa-8-azaspiro[4,5]dec-8-yl)quinoline (17a). A solution of commercially available 8-bromoquinoline (**16a**) (4.0 g, 19.2 mmol) in anhydrous tetrahydrofuran (20 mL) was purged with nitrogen for 10 min and then placed under a nitrogen atmosphere. To the stirred solution was added tris-(dibenzylideneacetone)dipalladium (0) ($Pd_2(dba)_3$, 0.2 g, 0.02 mmol), sodium *tert*-butoxide (2.6 g, 27.1 mmol), tetrakis-(triphenylphosphino)-1,1-binapthyl (BINAP, 0.1 g, 0.16 mmol), and 1,4-dioxa-8-azaspiro-4,5-decane (3.3 g, 23.1 mmol). The resulting mixture was stirred at reflux for 3 h and then cooled to room temperature. The reaction mixture was diluted with diethyl ether, filtered through a pad of celite, and concentrated on a rotary evaporator. The resulting residue was purified by flash chromatography on silica gel (4:1 hexane/ethyl acetate) afforded the desired product (3.0 g, 58% yield) as a brown oil. ^{1}H NMR (DMSO-d_6) δ 8.83 (d, J = 4.2 Hz, 1H), 8.26 (d, J = 5.5 Hz, 1H), 7.40−7.51 (m, 3H), 7.15 (d, J = 7.2 Hz, 1H), 3.89 (s, 4H), 3.36 (t, J = 5.4 Hz, 4H), 1.83 (t, J = 5.4 Hz, 4H). MS (ESI+) (m/z) 244 ([M + H]$^+$).

The following compounds were prepared using a similar procedure:

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-6-fluoroquinoline (17c). Prepared from **16c** in 36% overall yield and obtained as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 8.80 (dd, J_1 = 4.1 Hz, J_2 = 1.7 Hz, 1H), 8.25 (dd, J_1 = 8.3 Hz, J_2 = 1.7 Hz, 1H), 7.45−7.58 (m, 1H), 7.20−7.31 (m, 1H), 6.98 (dd, J_1 = 11.8 Hz, J_2 = 2.7 Hz, 1H),

3.93 (s, 4H), 3.46 (t, J = 5.6 Hz, 4H), 1.84 (t, J = 5.6 Hz, 4H). MS (ESI+) (m/z) 289 ([M + H]$^+$).

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-6-bromoquinoline (17d). Prepared from **16d** in 94% overall yield and obtained as a brown oil. ^{1}H NMR (DMSO-d_6) δ 8.86 (d, J = 4.1 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.50−7.55 (m, 1H), 7.15 (s, J = 2.1 Hz, 1H), 3.93 (s, 4H), 3.44 (t, J = 5.2 Hz, 4H), 1.84 (t, J = 5.4 Hz, 4H). MS (ESI+) (m/z) 348, 350 ([M + H]$^+$).

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-2-methylquinoline (17f). Prepared from **16f** in 52% overall yield and obtained as a brown oil. ^{1}H NMR (chloroform-d) δ 7.95 (d, J = 8.5 Hz, 1H), 7.28−7.46 (m, 2H), 7.15 (d, J = 7.1 Hz, 1H), 7.05−7.11 (m, 1H), 4.00 (s, 4H), 3.47 (t, J = 5.6 Hz, 4H), 2.71 (s, 3H), 2.04 (t, J = 5.6 HZ, 4H). MS (ESI+) (m/z) 285 ([M + H]$^+$).

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-2-(trifluoromethyl)quinoline (17g). Prepared from **16g** in 63% overall yield and obtained as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 8.86 (d, J = 8.6 Hz, 1H),7.91 (d, J = 8.4 Hz, 1H), 7.55−7.68 (m, 2H), 7.17−7.32 (m, 1H), 3.93 (s, 4H), 3.44 (t, J = 5.5 Hz, 4H), 1.83 (t, J = 5.5 Hz, 4H). MS (ESI+) (m/z) 339 ([M + H]$^+$).

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-3-fluoroquinoline (17h). Prepared from **16h** in 82% overall yield and obtained as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 8.85 (d, J = 3.0 Hz, 1H), 8.14 (dd, J_1 = 9.7 Hz, J_2 = 2.9 Hz, 1H), 7.44−7.52 (m, 2H), 7.12 (t, J = 4.6 Hz, 1H), 3.91 (s, 4H), 3.36 (t, J = 5.2 Hz, 4H), 1.84 (t, J = 5.2 Hz, 4H). MS (ESI+) (m/z) 289 ([M + H]$^+$).

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-3-methylquinoline (17i). Prepared from **16i** in 67% overall yield and obtained as a brown oil. ^{1}H NMR (chloroform-d) δ 8.73 (d, J = 2.2 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H), 7.28−7.42 (m, 2H), 7.08 (dd, J_1 = 7.3 Hz, J_2 = 1.5 Hz, 1H), 4.00 (s, 4H), 3.46 (t, J = 5.8 Hz, 4H), 2.05 (t, J = 5.8 Hz, 4H). MS (ESI+) (m/z) 285 ([M + H]$^+$).

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-3-(trifluoromethyl)quinoline (17j). Prepared from **16j** in 78% overall yield and obtained as a beige solid. ^{1}H NMR (chloroform-d) δ 9.07 (d, J = 2.3 Hz, 1H), 8.38 (s, 1H), 7.45−7.58 (m, 2H), 7.28 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 4.03 (s, 4H), 3.48 (t, J = 5.5 Hz, 4H), 2.43 (s, 3H), 2.05 (t, J = 5.5 Hz, 4H). MS (ESI+) (m/z) 339 ([M + H]$^+$).

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-4-methylquinoline (17k). Prepared from **16k** in 52% overall yield and obtained as a brown oil. ^{1}H NMR (chloroform-d) δ 8.72 (d, J = 4.3 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.42 (t, J = 7.7 Hz, 1H), 7.05−7.12 (m, 2H), 4.00 (s, 4H), 3.44 (t, J = 4.8 Hz, 4H), 2.65 (s, 3H), 2.04 (t, J = 4.9 Hz, 4H). MS (ESI+) (m/z) 285 ([M + H]$^+$).

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-2,4-dmethylquinoline (17l). Prepared from **16l** in 43% overall yield and obtained as a brown oil. ^{1}H -NMR (chloroform-d) δ 7.55 (d, J_1 = 8.4 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 7.09 (s, 1H), 4.02 (s, 4H), 3.47 (t, J = 5.6 Hz, 4H), 2.68 (S, 3H), 2.62 (s, 3H), 2.05 (t, J = 5.6 Hz, 4H). MS (ESI+) (m/z) 299 ([M + H]$^+$).

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-4-methoxy-2-(trifluoromethyl)quinoline (17m). Prepared from **16m** in 71% overall yield and obtained as a yellow oil. ^{1}H -NMR (DMSO-d_6) δ 7.68 (d, J = 8.3 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.32 (s, 1H), 7.20 (d, J = 7.7 Hz, 1H), 4.08 (s, 3H), 3.89 (s, 4H), 3.37 (t, J = 5.1 Hz, 4H), 1.82 (t, J = 5.1 Hz, 4H). MS (ESI+) (m/z) 369 ([M + H]$^+$).

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-3,5-difluoroquinoline (17p). Prepared from 16 h in 39% overall yield and obtained as a yellow oil. ^{1}H -NMR (DMSO-d_6) δ 8.55 (d, J = 2.9 Hz, 1H), 7.70 (d, J = 2.9 Hz, 1H), 6.98−7.15 (m, 2H), 3.90 (s, 4H), 2.82 (t, J = 5.6 Hz, 4H), 1.82 (t, J = 5.6 Hz, 4H). MS (ESI+) (m/z) 307 ([M + H]$^+$).

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-5-fluoro-2,4-dimethylquinoline (17q). Prepared from **16q** in 30% overall yield and obtained as a brown oil. ^{1}H -NMR (chloroform-d) δ 7.10−7.16 (m, 1H), 6.95−7.05 (m, 2H), 3.99 (s, 4H), 3.34 (t, J = 5.3 Hz, 4H), 2.77 (s, 3H), 2.72 (s, 3H), 2.04 (t, J = 5.3 Hz, 4H). MS (ESI+) (m/z) 317 ([M + H]$^+$).

The synthesis of **17b** illustrates the general method used to prepare compounds **17b**, **17n**−**o** and **17r**.

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-5-fluoro-quinoline (17b). To a solution of **16b** (2.25 g, 12.4 mmol) in anhydrous tetrahydrofuran (40 mL), flushed with nitrogen, and kept under a nitrogen atmosphere, was added tris(dibenzylideneacetone)-dipalladium (0) ($Pd_2(dba)_3$, 0.417 g, 0.02 mmol), sodium *tert*-butoxide (01.66 g, 16.3 mmol), 2-dicyclohexylphosphine-2′-(*N*,*N*-dimethylamino)biphenyl (CYMAP, 0.072 g, 0.02 mmol), and 1,4-dioxa-8-azaspiro-4,5 decane (2.10 mg, 14.7 mmol). The resulting mixture was stirred at 70 °C overnight. The reaction was cooled to room temperature, diluted with diethyl ether, filtered through a plug of silica gel, and concentrated on a rotary evaporator. The resulting residue was purified by flash chromatography on silica gel (40% ethyl acetate/hexane) to afford the desired product (2.10 g, 60% yield) as a beige solid. ^{1}H NMR (DMSO-d_6) δ 8.92 (d, J = 4.1 Hz, 1H), 8.38 (d, J = 8.4 Hz, 1H), 7.55−7.61 (m, 1H), 7.21−7.30 (m, 1H), 7.06−7.14 (m, 1H), 3.89 (s, 4H), 331 (t, J = 5.3 Hz, 4H), 1.82 (t, J = 5.3 Hz, 4H). MS (ESI+) (m/z) 289 ([M + H]$^+$)

The following compounds were prepared using a similar procedure.

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-5-fluoro-2-(trifluoromethyl)-quinoline (17n). Prepared from **16n** in 44% overall yield and obtained as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 8.70 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.48 (t, J = 9.6 Hz, 1H), 7.19−7.27 (m, 1H), 3.92 (s, 4H), 3.35 (t, J = 5.6 Hz, 4H), 1.85 (t, J = 5.6 Hz, 4H). MS (ESI+) (m/z) 357 ([M + H]$^+$).

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-5-fluoro-3-(trifluoromethyl)quinoline (17o). Prepared from **16o** and isolated as a beige solid in 30% yield. ^{1}H NMR (chloroform-d) δ 9.10 (d, J = 2.2 Hz, 1H), 8.64 (d, J = 2.1 Hz, 1H), 7.10−7.25 (m, 2H), 4.00 (s, 4H), 3.39 (t, J = 4.9 Hz, 4H), 2.02 (t, J = 4.9 Hz, 4H). MS (ESI+) (m/z) 357 ([M + H]$^+$).

8-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-5-fluoro-4-methoxy--2-(trifluoromethyl)quinoline (17r). Prepared from **16r** and isolated as a beige solid in 64% yield. ^{1}H NMR (DMSO-d_6) δ 7.38 (s, 1H), 7.25−7.32 (m, 1H), 7.13−7.18 (m, 1H), 4.06 (s, 3H), 3.88 (s, 4H), 3.31 (t, J = 5.5 Hz, 4H), 1.80 (t, J = 5.5 Hz, 4H). MS (ESI+) (m/z) 387 ([M + H]$^+$).

7-(1,4-Dioxa-8-azaspiro[4,5]dec-8-yl)-8-fluoroquinoline (17e). A mixture of **16e** (0.50 g, 3.03 mmol) and dioxa-8-azaspiro-4,5-decane (5 mL, 39.1 mmol) was stirred at 120 °C for 48 h. The reaction was cooled to room temperature, poured into water, and extracted three times with diethyl ether (30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator to give a residue consisting of a mixture of 7- and 8-substituted regioisomers. The residue was subjected to flash chromatography on silica gel. Elution with 30% ethyl acetate/hexane afforded the desired 8-(1,4-dioxa-8-azaspiro[4,5]dec-8-yl)-7-fluoroquinoline (**17e**, 0.39 g,) as a yellow oil. ^{1}H -NMR (DMSO-d_6) δ 8.80 (dd, J_1 = 4.2 Hz, J_2 = 1.5 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.44 (t, J = 8.4 Hz, 1H), 7.34−7.39 (m, 1H), 3.89 (s, 4H), 3.27 (t, J = 5.1 Hz, 4H), 1.77 (t, J = 5.1 Hz, 4H). MS (ESI+) (m/z) 289 ([M + H]$^+$).

The eluent was switched to 50% ethyl acetate/hexane and the undesired 7-(1,4-dioxa-8-azaspiro[4,5]dec-8-yl)-8-fluoroquinoline eluted and was obtained as a white solid (0.23 g). The structures of both regioisomers were assigned by ^{1}H NMR and confirmed with a nuclear Overhauser effect spectroscopy experiment (data not shown).

The synthesis of 1-quinolin-8-yl-pipiridin-4-one (**18a**). illustrates the general sequence used to prepare compounds **18a**−**r**.

1-Quinolin-8-yl-pipiridin-4-one (18a). To a solution of **17a** (4.0 g, 14.8 mmol) in tetrahydrofuran (10 mL) was added 2N HCl/diethyl ether (10 mL). The resulting mixture was stirred at room temperature overnight. The resulting reaction mixture was diluted with water (100 mL), made basic with 2.5 N aqueous sodium hydroxide, and extracted three times with dichloromethane (100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator to give the desired product (3.2 g, 95% yield)

as a yellow oil which was used without further purification. ^{1}H NMR (chloroform-*d*) δ 8.92 (dd, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz, 1H), 8.14 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.35−7.53 (m, 3H), 7.17 (dd, $J_1 = 6.8$ Hz, $J_2 = 1.9$ Hz, 1H), 3.70 (t, $J = 6.2$ Hz, 4H), 2.79 (t, $J = 6.1$ Hz, 4H). MS (ESI+) (*m*/*z*) 227 ([M + H]$^+$).

The following compounds were prepared using a similar procedure.

1-(5-Fluoroquinolin-8-yl)piperidin-4-one (18b). Prepared from **17b** in 91% yield and obtained as a tan solid. ^{1}H NMR (DMSO-d_6) δ 8.95−9.00 (m, 1H), 8.43 (dd, $J_1 = 8.5$ Hz, J2−2.4 Hz, 1H), 7.59−7.65 (m, 1H), 7.32 (t, $J = 9.1$ Hz, 1H), 7.13−7.19 (m, 1H), 3.58 (t, $J = 6.0$ Hz, 4H), 2.58 (t, $J = 6.0$ Hz, 4H). MS (ESI+) (*m*/*z*) 245 ([M + H]$^+$).

1-(6-Fluoroquinolin-8-yl)piperidin-4-one (18c). Prepared from **17c** in 66% yield and obtained as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.79 (dd, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz, 1H), 8.25 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz, 1H), 7.45−7.53 (m, 1H), 7.25 (dd, $J_1 = 9.0$ Hz, $J_2 = 2.8$ Hz, 1H), 7.02 (dd, $J_1 = 11.6$ Hz, $J_2 = 2.8$ Hz, 1H), 3.72 (t, $J = 6.1$ Hz, 4H), 2,56 (t, $J = 6.1$ Hz, 4H). MS (ESI+) (*m*/*z*) 245 ([M + H]$^+$).

1-(6-Bromoquinolin-8-yl)piperidin-4-one (18d). Prepared from **17d** in 79% yield and obtained as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 8.89 (dd, $J_1 = 4.1$ Hz, $J_2 = 1.8$ Hz, 1H), 8.28 (dd, $J_1 = 8.5$ Hz, $J_2 = 1.8$ Hz, 1H), 7.80 (d, $J = 2.1$ Hz, 1H), 7.54−7.58 (m, 1H), 7.22 (d, $J = 2.1$ Hz, 1H), 3.72 (t, $J = 6.0$ Hz, 4H), 2.59 (t, $J = 6.0$ Hz, 4H). MS (ESI+) (*m*/*z*) 305, 307 ([M + H]$^+$).

1-(7-Fluoroquinolin-8-yl)piperidin-4-one (18e). Prepared from **17e** in 80% yield and obtained as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 8.88 (dd, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz, 1H), 8.31 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.8$ Hz, 1H), 7.63−7.69 (m, 1H), 7.42−7.50 (m, 2H), 3.66 (t, $J = 6.0$ Hz, 4H), 2.53 t, $J = 6.0$ Hz, 4H). MS (ESI+) (*m*/*z*) 245 ([M + H]$^+$).

1-(2-Methylquinolin-8-yl)piperidin-4-one (18f). Prepared from **17f** in 95% yield and obtained as a yellow oil. ^{1}H NMR (chloroform-*d*) δ 8.00 (d, $J = 8.4$ Hz, 1H), 7.32−7.41 (m, 1H), 7.25 (d, $J = 8.4$ Hz, 1H), 7.05−7.17 (m, 2H), 3.70 (t, $J = 5.9$ Hz, 4H), 2.76 (t, $J = 5.9$ Hz, 4H), 2.73 (s, 3H). MS (ESI+) (*m*/*z*) 241 ([M + H]$^+$).

1-[2-(Trifluoromethyl)-quinolin-8-yl]piperidin-4-one (18g). Prepared from **17g** in 13% yield and obtained as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 8.64 (d, $J = 8.3$ Hz, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 7.33−7.42 (m, 1H), 7.12−7.20 (m, 1H), 7.04−7.14 (m, 1H), 3.62 (t, $J = 5.8$ Hz, 4H), 2.57 (t, $J = 6.2$ Hz, 4H). MS (ESI+) (*m*/*z*) 295 ([M + H]$^+$).

1-[3-Fluoroquinolin-8-yl]piperidin-4-one (18h). Prepared from **17h** in 48% yield and obtained as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 8.81 (d, $J = 2.6$ Hz, 1H), 8.10 (dd, $J_1 = 9.1$ Hz, $J_2 = 2.5$ Hz, 1H), 7.39−7.47 (m, 2H), 7.08 (t, $J = 5.2$ Hz, 1H), 3.38 (t, $J = 5.6$ Hz, 4H), 1.88 (t, $J = 5.6$ Hz, 4H). MS (ESI+) (*m*/*z*) 245 ([M + H]$^+$).

1-(3-Methylquinolin-8-yl)piperidin-4-one (18i). Prepared from **17i** in 96% yield and obtained as a yellow oil. ^{1}H NMR (chloroform-*d*) δ 8.76 (s, 1H), 7.88 (s, 1H), 7.32−7.42 (m, 2H), 7.05−7.16 (m, 1H), 3.67 (t, $J = 5.9$ Hz, 4H), 2.76 (t, $J = 5.9$ Hz, 4H), 2.49 (s, 3H). MS (ESI+) (*m*/*z*) 241 ([M + H]$^+$).

1-[3-(Trifluoromethyl)-quinolin-8-yl]piperidin-4-one (18j). Prepared from **17j** in 65% yield and obtained as a yellow oil. ^{1}H NMR (chloroform-*d*) δ 9.08 (d, $J = 2.2$ Hz, 1H), 8.40 (s, 1H), 7.53−7.60 (m, 2H), 7.21−7.30 (m, 1H), 3.70 (t, $J = 5.9$ Hz, 4H), 2.76 (t, $J = 5.9$ Hz, 4H). MS (ESI+) (*m*/*z*) 295 ([M + H]$^+$).

1-(4-Methylquinolin-8-yl)piperidin-4-one (18k). Prepared from **17k** in 92% yield and obtained as a brown oil. ^{1}H NMR (chloroform-*d*) δ 8.73 (d, $J = 4.3$ Hz, 1H), 7.63 (d, $J = 8.4$ Hz, 1H), 7.43 (t, $J = 7.7$ Hz,, 1H), 7.15−7.25 (m, 1H), 7.14 (d, $J = 7.7$ Hz, 1H), 3.65 (t, $J = 6.0$ Hz, 4H), 2.75 (t, $J = 6.0$ Hz, 4H), 2.66 (s, 3H). MS (ESI+) (*m*/*z*) 241 ([M + H]$^+$).

1−2,4-Dimethylquinolin-8-yl)piperidin-4-one (18l). Prepared from **17l** in 75% yield and obtained as an off-white solid. ^{1}H NMR (chloroform-*d*) δ 7.62 (d, $J = 8.4$ Hz, 1H), 7.40 (t, $J = 7.9$ Hz, 1H), 7.10−7.18 (m, 2H), 3.69 (t, $J = 6.0$ Hz, 4H), 2.78 (t, $J = 6.0$ Hz, 4H), 2.70 (s, 3H), 2.64 (s, 3H). MS (ESI+) (*m*/*z*) 255 ([M + H]$^+$).

1-[4-Methoxy-2-(trifluoromethyl)quinolin-8-yl]piperidin-4-one (18m). Prepared from **17m** in 65% yield and obtained as an off-white solid. ^{1}H -NMR (DMSO-d_6) δ 7.75 (d, $J = 8.2$ Hz, 1H), 7.57 (t, $J = 8.0$ Hz, 1H), 7.38 (s, 1H), 7.30 (d, $J = 7.7$ Hz, 1H), 4.12 (s, 3H), 3.68 (t, $J = 5.9$ Hz, 4H), 2.59 (t, $J = 5.9$ Hz, 4H). MS (ESI+) (*m*/*z*) 325 ([M + H]$^+$).

1-[5-Fluoro-2-(trifluoromethyl)quinolin-8-yl]piperidin-4-one (18n). Prepared from **17n** in 79% yield and obtained as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 8.71 (d, $J = 8.7$ Hz, 1H), 8.02 (d, $J = 8.8$ Hz, 1H), 7.49 (t, $J = 8.7$ Hz, 1H), 7.24−7.30 (m, 1H), 3.62 (t, $J = 6.0$ Hz, 4H), 2.57 (t, $J = 6.9$ Hz, 4H). MS (ESI+) (*m*/*z*) 313 ([M + H]$^+$).

1-[5-Fluoro-3-(trifluoromethyl)quinolin-8-yl]piperidin-4-one (18o). Prepared from **17o** in 71% yield and obtained as a yellow solid. ^{1}H NMR (chloroform-*d*) δ 9.12 (d, $J = 2.2$ Hz, 1H), 8.66 (d, $J = 2.2$ Hz, 1H), 7.10−7.25 (m, 2H), 3.61 (t, $J = 6.0$ Hz, 4H), 2.74 (t, $J = 6.0$ Hz, 4H). MS (ESI+) (*m*/*z*) 313 ([M + H]$^+$).

1-(3,5-Difluoroquinolin-8-yl)piperidin-4-one (18p). Prepared in 68% yield from **17p** and obtained as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 8.51 (d, $J = 2.8$ Hz, 1H), 7.68 (d, $J = 2.8$ Hz, 1H), 7.13−7.27 (m, 2H), 3.65 (t, $J = 5.8$ Hz, 4H), 2.69 (t, $J = 5.8$ Hz, 4H). MS (ESI+) (*m*/*z*) 263 ([M + H]$^+$).

1-[5-Fluoro-2,4-dimethylquinolin-8-yl]piperidin-4-one (18q). Prepared from **17q** in 65% yield and obtained as a yellow oil. ^{1}H NMR (chloroform-*d*) δ 7.54−7.60 (m, 1H), 7.06−7.15 (m, 1H), 6.99−7.05 (m, 1H), 3.58 (t, $J = 6.0$ Hz, 4H), 2.79 (t, $J = 6.0$ Hz, 4H), 2.77 (s, 3H), 2.69 (s, 3H). MS (ESI+) (*m*/*z*) 244 ([M + H]$^+$).

1-[5-Fluoro-4-methoxy-2-(trifluoromethyl)quinolin-8-yl]piperidin-4-one (18r). Prepared from **17r** in 77% yield and obtained as a light-yellow solid. ^{1}H NMR (DMSO-d_6) δ 7.44 (s, 1H), 7.32−7.40 (m, 1H), 7.22−7.28 (m, 1H), 4.10 (s, 3H), 3.56 (t, $J = 5.8$ Hz, 4H), 2.57 (t, $J = 5.8$ Hz, 4H). MS (ESI+) (*m*/*z*) 343 ([M + H]$^+$).

Radioligand Binding Assays. Affinity for the human 5-HT$_{1A}$ receptor was determined using a previously described method[27] and employing a Chinese hampster ovary (CHO) cell line stably transfected with the human 5-HT$_{1A}$ receptor and [^{3}H]-8-OH-DPAT as the standard radioligand. Results are expressed as K_i values and are the average of at least three repetitions.

cAMP Accumulation Assays. Intrinsic activity at the human 5-HT$_{1A}$ receptor was measured using a cAMP accumulation assay in a CHO cell line stably transfected with the human 5-HT$_{1A}$ receptor.[27] Details for the procedures used in this manuscript are available in the Supporting Information.

Microsomal Stability Studies. Microsomal stability of the compounds was determined by incubating compounds with rat or human liver microsomes at 37 °C for 20 min in the presence of NADPH or a NADPH regenerating system. Details for this procedure area available in the Supporting Information.

Pharmacokinetic Studies. The pharmacokinetics of test compounds were determined in male Sprague−Dawley rats after a single 1 mg/kg iv dose (in 2% Tween 80) or a single 3 mg/kg po dose (in 2% Tween 80/0.5% methylcellulose). Details for these procedures are available in the Supporting Information.

In Vivo Microdialysis. In vivo microdialysis studies were carried out as previously described with some modifications.[7] Details for these procedures used in this manuscript are available in the Supporting Information.

Novel Object Recognition. Compound **10b** was assessed for its ability to improve cognitive function (recognition memory) in a rat novel object recognition model as previously described.[7] Details for this procedures used in this manuscript are available in the Supporting Information.

Atlantis Water Maze. The Atlantis water maze model has been described elsewhere.[7] Details for this procedures used in this manuscript are available in the Supporting Information.

Contextual Fear Conditioning. The contextual fear conditioning (CFC) model using male Tg2576 mice has been described

elsewhere.[51] Details for this procedures used in this manuscript are available in the Supporting Information.

Schedule-Induced Polydipsia. The experimental details of the schedule-induced polydipsia model have been published elsewhere.[52] Details for the procedures used in this manuscript are available in the Supporting Information.

Olfactory Bulbectomy. Test compounds were examined for their effects on olfactory bulbectomy-induced hyperactivity in the absence and presence of fluoxetine, a selective serotonin reuptake inhibitor. The experimental details of this model have been published elsewhere.[52] Details for the procedures used in this manuscript are available in the Supporting Information.

Fluoxetine-Induced Sexual Dysfunction. The experimental details for performing this model have been published elsewhere.[46] Data and an experimental description can be found in the Supporting Information.

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Supporting Information Available: Detailed experimental protocols for the pharmacology assays and a graph depicting the effect of compound **10b** on fluoxetine-induced sexual dysfunction. This material is available free of charge via the Internet at http://pubs.acs.org.

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