Synthesis, Structure−Activity Relationships, and Biological Profiles of a Quinazolinone Class of Histamine H_3 Receptor Inverse Agonists

Tsuyoshi Nagase, Takashi Mizutani, Shiho Ishikawa, Etsuko Sekino, Takahide Sasaki, Takashi Fujimura, Sayaka Ito, Yuko Mitobe, Yasuhisa Miyamoto, Ryo Yoshimoto, Takeshi Tanaka, Akane Ishihara, Norihiro Takenaga, Shigeru Tokita, Takehiro Fukami, and Nagaaki Sato*

Tsukuba Research Institute, Merck Research Laboratories, Banyu Pharmaceutical Co., Ltd, Okubo 3, Tsukuba, Ibaraki 300-2611, Japan

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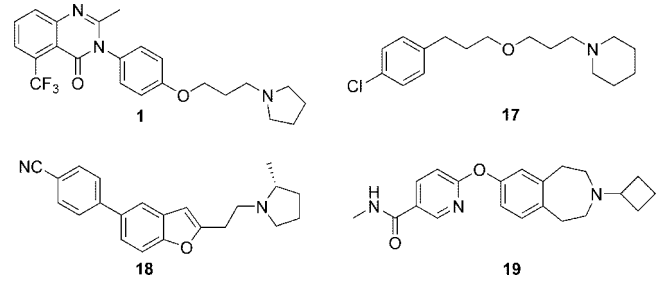
A new series of quinazolinone derivatives was synthesized and evaluated as nonimidazole H_3 receptor inverse agonists. 2-Methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-5-(trifluoromethyl)-4(3*H*)-quinazolinone (**1**) was identified as a promising derivative for further evaluation following optimization of key parameters. Compound **1** has potent H_3 inverse agonist activity and excellent selectivity over other histamine receptor subtypes and a panel of 115 unrelated diverse binding sites. Compound **1** also shows satisfactory pharmacokinetic profiles and brain penetrability in laboratory animals. Two hours after oral administration of 30 mg/kg of **1** to SD rats, significant elevation of brain histamine levels was observed where the brain H_3 receptor was highly occupied (>90%). On the basis of species differences in P-glycoprotein (P-gp) susceptibility of **1** between human and rodent P-gps, the observed rodent brain permeability of **1** is significantly limited by P-gp mediated efflux in rodents, whereas the extent of P-gp mediated efflux in humans should be very small or negligible. The potential of **1** to be an efficacious drug was demonstrated by its excellent brain penetrability and receptor occupancy in P-gp-deficient CF-1 mice.

Introduction

Histamine plays a variety of physiological roles in the CNS[a] and peripheral tissues. In the CNS, histaminergic neurons are exclusively localized in the tuberomammillary nucleus of the hypothalamus, but project widely throughout the CNS.[1] There are four known G protein-coupled receptors for histamine: H_1, H_2, H_3, and H_4.[2] The histamine receptors have unique signal transduction pathways and distributions, leading to the exhibition of a variety of physiological roles for histamine. Of these receptors, H_3 is predominantly expressed in the CNS while H_1 and H_2 are expressed in both central and peripheral tissues.[3,4] The H_4 receptor is predominantly expressed in inflammatory cells, suggesting its critical role in the regulation of inflammatory and immune responses.[5]

The H_3 receptor was pharmacologically discovered in 1983[6] and genetically identified in 1999.[3] The genetic identification of the H_3 receptor gained much attention and redirected both the detailed pharmacological characterization of the receptor and efforts to find drugs that bind specifically to H_3 from academia to the pharmaceutical industry.[7] Signaling through the H_3 receptor activates G proteins that inhibit adenylate cyclase activity and reduce intracellular cAMP levels.[3,8] In the CNS, the H_3 receptor is localized on the presynaptic membrane as an autoreceptor and negatively regulates the release and synthesis of histamine.[6] In addition, the H_3 receptor is known to modulate the release of other neurotransmitters such as norepinephrine, dopamine, acetylcholine, serotonin, and GABA.[9] The H_3 receptor signals constitutively, which serves to tonically suppress target neuronal activities such as histamine release to baseline levels.[10] Agonist-induced signaling that occurs in the presence of elevated histamine levels further suppresses histamine release.

Chart 1. Structures of Nonimidazole H_3 Receptor Antagonists and Inverse Agonists



While classical antagonists would interfere with histamine-mediated negative feedback, H_3 receptor inverse agonists have been demonstrated to decrease constitutive H_3 signaling, thus blocking tonic inhibition of histamine release and further potentiating histaminergic effects. Because of the effects of H_3 signaling on multiple neuronal transmitters, it has been suggested that H_3 antagonists/inverse agonists could be effective therapeutics for several CNS-related disorders.[11] In animal models, H_3 receptor antagonists/inverse agonists have been shown to enhance wakefulness and attentive and cognitive behavior while reducing feeding and body weight.[12,13] Moreover, very recently, it has been reported that **17** (BF2.649) (Chart 1), a potent and selective H_3 receptor inverse agonist, suppressed the excessive daytime sleep of narcoleptic patients.[14]

First-generation imidazole-based H_3 antagonists have inhibitory actions on cytochrome P_{450} activity, which results in drug−drug interactions against coadministered drugs by inhibiting hepatic clearance.[15] Because of these liabilities, current efforts have focused on nonimidazole classes of H_3 receptor antagonists/inverse agonists. Since the identification of the H_3 receptor genes, various classes of nonimidazole H_3 receptor antagonists have been developed to target the CNS H_3 receptors.[7,12,16] Among them, **17**,[14,17] **18** (ABT-239),[18] and **19** (GSK189254)[19] (Chart 1) have entered clinical trials and target

* To whom correspondence should be addressed. Phone: 81-29-877-2004. Fax: 81-29-877-2029. E-mail: nagaaki_sato@merck.com.

[a] Abbreviations: P-gp, P-glycoprotein; SD rat, Sprague−Dawley rat; SAR, structure−activity relationship; hERG, human ether-a-go-go-related gene; CHO, Chinese hamster ovary; HEK, human embryonic kidney; CNS, central nervous system; Ts, 4-toluenesulfonyl.

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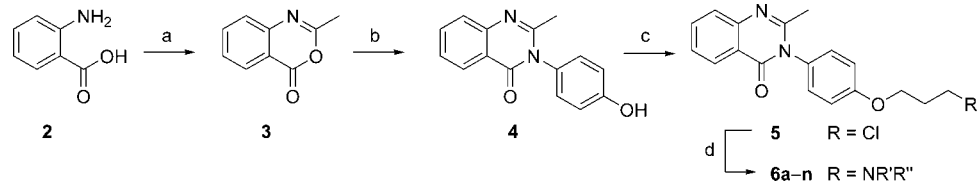
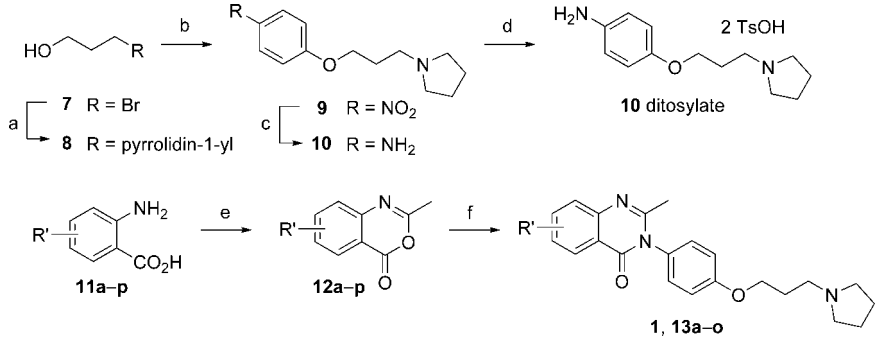
Scheme 1[a]



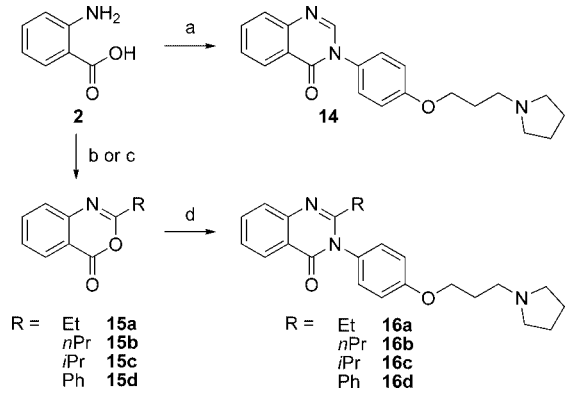
[a] Reagents and conditions: (a) Ac_2O, 130 °C; (b) 4-aminophenol, DMF, 120 °C; (c) 1-bromo-3-chloropropane, K_2CO_3, DMF, 80 °C; (d) HNR′R″, KI, K_2CO_3, DMF, 80 °C.

Scheme 2[a]



[a] Reagents and conditions: (a) pyrrolidine, K_2CO_3, THF, reflux; (b) 4-fluoronitrobenzene, NaH, DMF, 0 °C to rt; (c) H_2, Pd/C (10%), MeOH; (d) TsOH·H_2O; (e) Ac_2O, 130 °C; (f) **10**, AcOH, 130 °C or **10** ditosylate, NaOAc, AcOH, THF, rt.

Scheme 3[a]



[a] Reagents and conditions: (a) **10** ditosylate, $Yb(OTf)_3$, $HC(OEt)_3$, THF, 60 °C; (b) $(RCO)_2O$, 100 °C; (c) benzoyl chloride, pyridine, 50 °C then $(COCl)_2$, cat. DMF, CH_2Cl_2, 0 °C to rt; (d) **10**, AcOH, 130 °C or **10** ditosylate, NaOAc, AcOH, THF, rt.

CNS disorders such as excessive daytime sleepiness, schizophrenia, and cognitive dysfunctions.

Our corporate chemical collection was screened against human H_3 receptor, resulting in the identification of the quinazolinone **6a**. The right-hand amine part and substituents on the quinazolinone ring were optimized for H_3 affinity and hERG inhibitory activity. Advanced derivatives were further evaluated for their metabolic stability and P-gp susceptibility. Compound **1** showed excellent in vitro profiles and therefore progressed to in vivo studies (Chart 1). In this report, the detailed SAR for the quinazolinone class of H_3 inverse agonists, and the in vitro and in vivo characterization of **1**, are described.

Chemistry

The synthesis of quinazolinone H_3 receptor inverse agonists reported herein is outlined in Schemes 1–3. The anthranilic acids employed in the present study were commercially available. For the SAR studies of the amine portion, the target compounds were prepared according to Scheme 1. Anthranilic acid (**2**) was treated with acetic anhydride to provide the benzoxazinone **3**.[20] Treatment of **3** with 4-aminophenol in DMF gave the phenol **4**,[21] which was alkylated with 1-bromo-3-chloropropane to afford **5**. The resultant chloride **5** was reacted with the desired amines to furnish **6a**−**n**. Derivatives that have substituents at the 5- to 8-positions of the quinazolinone ring were prepared according to Scheme 2. The key intermediate, 4-(3-pyrrolidin-1-yl-propoxy)aniline (**10**), was prepared from 3-bromopropanol in three steps. Alkylation of pyrrolidine with 3-bromopropanol provided **8**, which was coupled with 4-fluoronitrobenzene in the presence of sodium hydride to afford **9**. The resulting nitro compound **9** was hydrogenated over Pd/C to furnish the key aniline intermediate **10**. Coupling of **10** with substituted benzoxazinones **12a**−**p**,[22] which were derived from the various anthranilic acids **11a**−**p**, furnished **1** and **13a**−**o** in moderate to good yield.[23] Because the aniline **10** was sensitive to air, a ditosylate salt of **10** was prepared as a stable crystal. Although this ditosylate salt participates in the quinazolinone ring formation reaction, the yield from the reaction was significantly lower than that with the corresponding free base. It was subsequently found that addition of 2 equiv of sodium acetate to the ditosylate salt of **10** improved the yield dramatically. Derivatives varying in the 2-substituent were prepared according to Scheme 3. Compound **14** was prepared by the reaction of anthranilic acid, **10** ditosylate, and triethyl orthoformate in the presence of a catalytic amount of $Yb(OTf)_3$.[24] Anthranilic acid was reacted with the desired anhydride or acid chloride to give the benzoxazinones **15a**−**d**,[22] which were coupled with **10** to furnish **16a**−**d**.

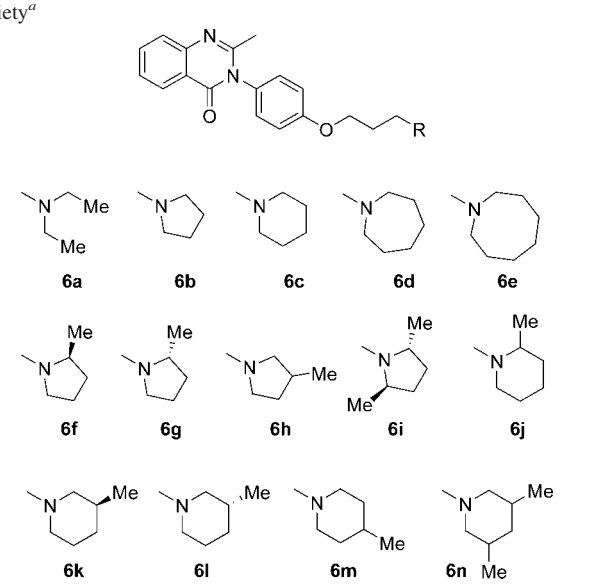
Results and Discussion

Structure−Activity Relationships. The compounds were tested using the [^{35}S]GTPγS binding assay in membranes isolated from cells transfected with cloned human H_3 receptors. All the quinazolinone derivatives reported herein reduced basal GTPγS binding, indicating that they are inverse agonists. Selected compounds were evaluated for hERG K^+ channel

inhibitory activity using the [^{35}S]*N*-[(4*R*)-1′-[(2*R*)-6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl]-3,4-dihydro-4-hydroxyspiro-[2*H*-1-benzopyran-2,4′-piperidin]-6-yl]methanesulfonamide binding assay to assess QTc prolongation liability.[25] High-throughput screening of Merck sample collections against human H_3 receptor led to the identification of **6a**, which has an IC_{50} value of 33 nM. Replacement of the diethylamino fragment of **6a** with a piperidine, common to many nonimidazole H_3 antagonists, resulted in **6c**, which exhibited a 10-fold increase in potency compared to **6a**. We focused our modification efforts on **6c** in order to investigate (i) the SAR of the quinazolinone class of H_3 inverse agonists in terms of functional activity toward the human H_3 receptor and (ii) the selectivity of these compounds against the hERG channel. The SAR for the amine moiety was investigated first by altering the ring size of the cyclic amine moiety. The pyrrolidine derivative **6b** was equipotent to the piperidine derivative **6c**, and the azacycloheptane derivative **6d** was 2-fold more potent, whereas the azacyclooctane derivative **6e** exhibited a 3-fold decrease in potency relative to the piperidine **6c**. Subsequently, the effects of substituents on the pyrrolidine and piperidine rings were examined. The 2-(*S*)-methylpyrrolidine derivative **6f** was the most potent derivative (IC_{50} = 2.2 nM) among the substituted pyrrolidine derivatives **6f**−**i**. As for the substituted piperidine derivatives **6j**−**n**, the 3-(*S*)-methylpiperidine derivative **6k** was 4-fold more potent (IC_{50} = 0.72 nM) than the parent **6c**, whereas its corresponding enantiomer **6l** displayed a significant decrease in potency (IC_{50} = 41 nM). The hERG inhibitory activities of the potent derivatives were subsequently assessed. As shown in Table 1, the pyrrolidine and 2-(*R*)-methylpyrrolidine derivatives (**6b** and **6g**) had the lowest hERG channel inhibition risk. We herein focus on pyrrolidine derivative **6b** and describe further SAR studies for substituent effects on the quinazolinone ring.

The effects of substitutions on the quinazolinone ring of **6b** are summarized in Table 2. At the 2-position, removal of the 2-methyl group, as in **14**, resulted in a significant increase in hERG inhibitory activity (IC_{50} = 0.71 μM) while retaining H_3 activity. Substitution with sterically more demanding substituents such as phenyl, *i*-propyl, *n*-propyl, and ethyl groups, as in **16a**−**d**, led to a 2−5 fold increase in potency; however, the increased hERG inhibitory activities of **16a**−**d** (IC_{50} = 1.1−5.0 μM) are evident. The methyl group emerged as the most suitable substituent for the 2-position. Next, we investigated the effect of substitution on the 5- to 8-positions of the quinazolinone ring. Introduction of small substituents such as Cl, Me, MeO, F, and CF_3 groups at the 5- to 8-positions resulted in the identification of a number of potent derivatives (IC_{50} < 2 nM). Among them, **1**, **13e**, **13f**, and **13l** displayed negligible hERG inhibitory activities (IC_{50} > 10 μM). These compounds were further evaluated for rat hepatic clearance and P-gp susceptibility using in vitro studies. Rat hepatic clearance was assessed by the in vitro serum incubation method previously reported by our laboratory.[26] All four compounds showed very good hepatic clearance values (CL_h ≤ 11 mL/min/kg) (Table 3). P-gp susceptibility was evaluated by transcellular transport ratios obtained from human *MDR1*- and mouse *mdr1a*-transfected porcine renal epithelial (LLC-PK1) cell monolayers.[27] P-gp is expressed in the blood−brain barrier and excludes its substrates from the brain. The transcellular transport ratios of the tested compounds (B-to-A/A-to-B ratio) are summarized in Table 3. In this P-gp transport assay, a compound with its B-to-A/A-to-B ratio above 3 is considered to be a P-gp substrate. All four compounds were mouse P-gp substrates (B-to-A/A-to-B ratio = 5.1−13), and **13e** and **13l** were additionally substrates for human P-gp. Compounds **1** and **13f** were considered not to be human P-gp substrates (2.4 and 3.0, respectively). Compound **1** was selected for further evaluation to minimize the risk of diminished brain penetrability in humans. Note that **1** is also a substrate for rat P-gp (transcellular transport ratio (B-to-A/A-to-B) obtained from rat *mdr1a* = 7.3).

Table 1. SAR of Quinazolinone Derivatives; Variation of the Amine Moiety[a]

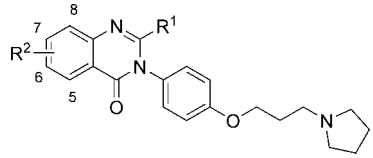


compd	human H_3[b] (IC_{50}, nM)	hERG[c] (IC_{50}, μM)
6a	33 ± 7	*d*
6b	3.5 ± 0.7	>10
6c	3.1 ± 0.6	8.6 ± 0.8
6d	1.6 ± 0.03	6.6 ± 0.7
6e	10 ± 2	*d*
6f	2.2 ± 0.8	6.0 ± 0.5
6g	4.3 ± 1.1	>10
6h	5.8 ± 0.6	6.4 ± 0.6
6i	20 ± 3	*d*
6j	11 ± 2	*d*
6k	0.72 ± 0.05	5.3 ± 0.4
6l	41 ± 11	*d*
6m	23 ± 11	*d*
6n	28 ± 6	*d*

[a] The values represent the mean ± SE for $n \geq 3$. [b] Inhibition of *R*-α-methylhistamine-induced binding of [^{35}S]GTPγS at human H_3 receptor. [c] Inhibition of [^{35}S]*N*-[(4*R*)-1′-[(2*R*)-6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl]-3,4-dihydro-4-hydroxyspiro[2*H*-1-benzopyran-2,4′-piperidin]-6-yl-]methanesulfonamide binding to hERG in HEK293 cells. [d] Not determined.

In Vitro and in Vivo Profiles of Compound 1. In vitro characterization of **1** was carried out by: (i) radioligand binding assays with [^{3}H]*R*-α-methylhistamine using human, rat, and rhesus monkey histamine H_3 receptors expressed in CHO or HEK293 cell membranes and (ii) functional [^{35}S]GTPγS binding assays to human H_3 receptors expressed in CHO membranes. In the radioligand binding assay, **1** displayed potent binding affinity to human, rat, and rhesus H_3 receptors with K_i values of 6.8 ± 1.3 nM, 33 ± 3 nM, and 4.3 ± 1.2 nM, respectively (n = 3). In the functional [^{35}S]GTPγS binding assay, **1** reduced basal GTPγS binding (EC_{50} value of 0.77 ± 0.12 nM (n = 3)), indicating that **1** is an inverse agonist. Compound **1** potently antagonized *R*-α-methylhistamine, a selective H_3 receptor agonist, in GTPγS binding with an IC_{50} value of 1.7 nM. The competitive antagonistic activity of compound **1** was measured by determining the dose response curve of *R*-α-methylhistamine in the presence of various concentrations of **1**. Compound **1** shifted the agonist dose response curve to the right, and the pA_2 value determined from Schild's plot was 9.2 ± 0.0 (slope

Table 2. SAR of Quinazolinone Derivatives; Substitution of the Quinazolinone Ring[a]



compd	R^1	R^2	human H_3[b] (IC_{50}, nM)	hERG[c] (IC_{50}, μM)
14	H	H	3.5 ± 0.1	0.71 ± 0.22
6b	Me	H	3.5 ± 0.7	>10
16a	Et	H	1.6 ± 0.4	5.0 ± 0.5
16b	*n*-Pr	H	0.69 ± 0.07	2.8 ± 0.5
16c	*i*-Pr	H	0.81 ± 0.18	3.9 ± 0.6
16d	Ph	H	0.66 ± 0.23	1.1 ± 0.4
13a	Me	5-Me	0.98 ± 0.11	6.6 ± 0.3
13b	Me	6-Me	3.9 ± 2.1	>10
13c	Me	7-Me	1.2 ± 0.2	6.7 ± 0.6
13d	Me	8-Me	1.7 ± 0.2	1.6 ± 0.2
13e	Me	5-MeO	1.3 ± 0.2	>10
13f	Me	6-MeO	1.1 ± 0.2	>10
13g	Me	7-MeO	2.3 ± 0.4	>10
13h	Me	8-MeO	3.7 ± 0.8	>10
13i	Me	5-F	2.2 ± 0.3	>10
13j	Me	6-F	1.6 ± 0.2	2.5 ± 0.1
13k	Me	7-F	1.8 ± 0.2	6.0 ± 1.3
13l	Me	8-F	1.5 ± 0.2	>10
13m	Me	5-Cl	1.3 ± 0.2	8.1 ± 0.4
1	Me	5-CF_3	1.7 ± 0.3	>10
13n	Me	7-CF_3	0.96 ± 0.07	2.6 ± 0.5
13o	Me	8-CF_3	2.2 ± 0.2	0.35 ± 0.04

[a] The values represent the mean ± SE for $n \geq 3$. [b] Inhibition of *R*-α-methylhistamine-induced binding of [^{35}S]GTPγS at human H_3 receptor. [c] Inhibition of [^{35}S]*N*-[(4*R*)-1′-[(2*R*)-6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl]-3,4-dihydro-4-hydroxyspiro[2*H*-1-benzopyran-2,4′-piperidin]-6-yl-]methanesulfonamide binding to hERG in HEK293 cells.

Table 3. Predicted Hepatic Clearance and P-gp Susceptibility of **1**, **13e**, **13f**, and **13l**

			predicted rat hepatic clearance[a]	P-gp susceptibility[b] transcellular transport ratio (B-to-A)/(A-to-B)	
compd	R^1	R^2	CL_h (mL/min/kg)	human *MDR1*	mouse *mdr1a*
1	Me	5-CF_3	7	2.4	13
13e	Me	5-MeO	9	11.4	7.9
13f	Me	6-MeO	<1	3.0	5.1
13l	Me	8-F	11	3.9	10

[a] Predicted rat hepatic clearance (CL_h) was determined by the serum incubation method. [b] Transcellular transport ratios ((B-to-A)/(A-to-B)) were obtained from human *MDR1*- and mouse *mdr1a*-transfected LLC-PK1 cell monolayers. The values represent the mean for $n \geq 3$.

factor = 0.93 ± 0.03) (n = 3), indicating the high intrinsic activity of **1**. Compound **1** is selective against other histamine receptor subtypes (hH_1, hH_2, hH_4; IC_{50} > 10 μM) and a panel of 115 unrelated diverse binding sites (IC_{50} > 1 μM).

The pharmacokinetic parameters of **1** were evaluated in rats, dogs, and rhesus monkeys, and the results are summarized in Table 4. **1** displayed good profiles in rats and dogs, whereas oral bioavailability and exposure are relatively low in monkeys. On the basis of the observed moderate plasma clearance (18 mL/min/kg), absorption might be an issue in the monkey pharmacokinetic profile. The brain penetrability of compound **1** was assessed in SD rats. Compound **1** showed moderate brain penetrability 2 h after 10 mg/kg oral dosing despite its P-gp susceptibility (brain = 1.67 nmol/g, plasma = 1.58 μM, brain-to-plasma ratio = 1.1). Compound **1** showed no significant competitive inhibitory activity against CYP1A2, 2A6, 2C9, 2C19, 2D6, and 3A4 (IC_{50} > 27 μM), and no time dependent inhibition of CYP3A4.

Table 4. Pharmacokinetic Parameters of **1** in Rats, Dogs, and Rhesus Monkeys[a]

	iv (1 mg/kg)			po (3 mg/kg)		
	CL_p (mL/min/kg)	V_{dss} (L/kg)	$t_{1/2}$ (h)	C_{max} (μM)	$AUC_{0-\infty}$ (μM h)	F[b] (%)
rat	12	4.4	5.5	1.01	6.35	65
dog	19	9.7	9.9	1.8	11.8	>100
monkey	18[c]	6.0[c]	5.4[c]	0.44	1.84	28

[a] The values represent the mean, n = 3 animals. [b] Based on $AUC_{0-\infty}$ values after iv and po dosings. [c] The values represent the mean, n = 2 animals.

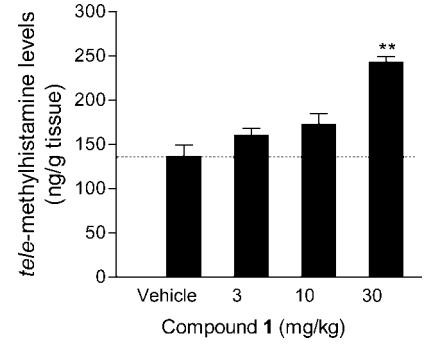


Figure 1. Brain *tele*-methylhistamine levels in SD rats after oral administration of vehicle or compound **1** (3, 10, and 30 mg/kg). Values are means ± SE, determined from five experiments. ** P < 0.01 (ANOVA Dunnett) compared with the vehicle control.

Having demonstrated the excellent potency, selectivity, and pharmacokinetic profile of **1**, this compound was tested for brain histamine release in SD rats. In our histamine release assay, the inverse agonist (po), and pargyline (ip), a monoamine oxidase inhibitor, are codosed in SD rats, and after 2 h, the whole brain is rapidly removed and the concentration of *tele*-methylhistamine, a major extracellular metabolite of histamine, is measured.[28] As shown in Figure 1, compound **1** showed a statistically significant increase in *tele*-methylhistamine levels in SD rats following 30 mg/kg oral dosing, indicating that **1** significantly elevates histamine levels in the rat brain. To investigate the correlation between efficacy in the histamine release assay and brain H_3 receptor occupancy in the rat brain, an ex vivo receptor occupancy study with **1** was performed in SD rats.[29] Two hours following oral administration of 30 mg/kg (the minimum effective dose in the histamine release assay) of **1**, ex vivo receptor occupancy in rat brain slices was determined to be greater than 90%. Although additional studies are needed, at least a certain period of high receptor occupancy seems necessary for H_3 inverse agonists to exhibit a significant increase in histamine levels in the rat brain. **1** is a significant substrate for rodent P-gp, so brain penetration by **1** in rodents is limited by P-gp mediated efflux, leading to limited receptor occupancy and therefore limited efficacy in rodents. However, **1** is a weak or negligible human P-gp substrate; therefore, we speculated that **1** may show higher brain penetrability and better receptor occupancy in humans than in rodents. To demonstrate the potential of **1**, brain and plasma exposures and receptor occupancy of **1** were studied in P-gp-deficient *mdr1a* (−/−) and wild type *mdr1a* (+/+) CF-1 mice.[30] After oral administration of 10 mg/kg of **1**, the brain-to-plasma ratio (b/p) of **1** was 14 in *mdr1a* (−/−) mice, which is remarkably higher than that in SD rats (b/p = 1.1) and *mdr1a* (+/+) mice (b/p = 0.8). Encouraged by these results, ex vivo receptor occupancy studies were conducted in *mdr1a* (−/−) and *mdr1a* (+/+) CF-1 mice to obtain plasma and brain level-receptor occupancy relationships.[29] Brain levels corresponding to 90% receptor occupancy

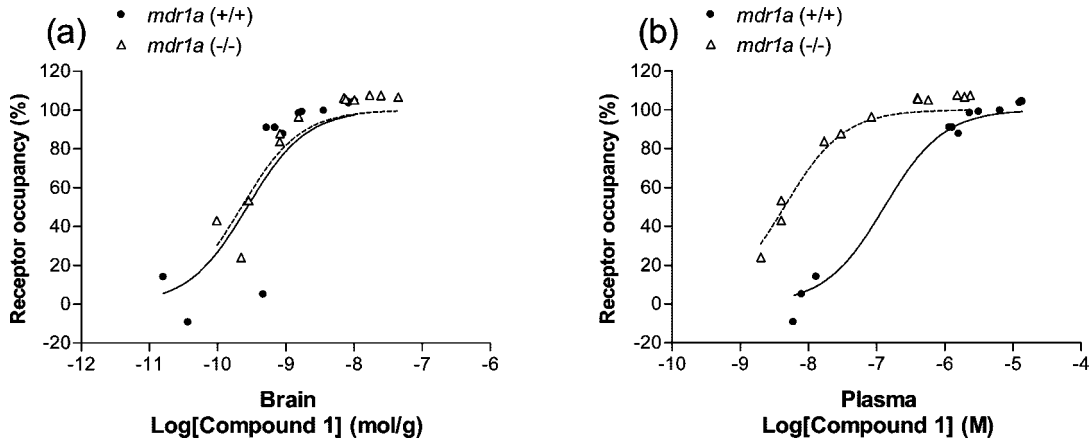


Figure 2. Relationship between (a) brain and (b) plasma concentrations of compound **1** and histamine H_3 receptor occupancy in P-gp-deficient *mdr1a* (−/−) and wild type *mdr1a* (+/+) CF-1 mice. Receptor occupancy and exposure were determined 2 or 8 h following oral administration of vehicle or compound **1** (10, 30, and 100 mg/kg). See Supporting Information for experimental details.

were 2 nmol/g in both the *mdr1a* (−/−) and *mdr1a* (+/+) CF-1 mice (Figure 2a). In contrast, a dramatic leftward shift of the titration curve for *mdr1a* (−/−) mice was observed in the plasma level−receptor occupancy relationship (Figure 2b). The plasma level required to achieve 90% receptor occupancy (Occ90) is 40 nM in *mdr1a* (−/−) mice, whereas the Occ90 value is much higher (1.17 μM) in *mdr1a* (+/+) mice. These results suggest that **1** may achieve a high degree of brain H_3 receptor occupancy at a very low plasma concentration in humans. We intend to investigate receptor occupancy in higher species in the near future by noninvasive receptor occupancy methods such as PET.

Conclusion

A new series of quinazolinone derivatives was synthesized and evaluated as H_3 inverse agonists. Compound **1** has potent H_3 inverse agonist activity and excellent selectivity over other histamine receptor subtypes and a panel of 115 unrelated binding sites. Compound **1** showed satisfactory pharmacokinetic profiles and brain penetrability in preclinical animals. Two hours following oral administration of 30 mg/kg of **1** in SD rats, brain histamine levels were significantly elevated when the brain H_3 receptor was highly occupied (>90%). Because **1** is a significant substrate for rodent P-gp, brain penetration of **1** in rodents is limited by P-gp mediated efflux. However, **1** is a weak or negligible human P-gp substrate; therefore, **1** could potentially show higher brain penetrability and receptor occupancy in humans than in rodents. To demonstrate the potential of **1**, brain and plasma exposure, and receptor occupancy of **1**, were studied in P-gp-deficient *mdr1a* (−/−) and wild type *mdr1a* (+/+) CF-1 mice. Compound **1** showed markedly higher brain penetrability and a lower plasma Occ90 value in *mdr1a* (−/−) mice than in *mdr1a* (+/+) mice. The potential cardiovascular effects of **1** were evaluated in anesthetized dogs. At 3 mg/kg iv dosing (C_{max} = 9.2 μM), no adverse treatment related cardiovascular effects were observed. Regarding gross behavior in mice, oral administration of **1** at a dose of 100 mg/kg ([plasma] = 44 μM, [brain] = 38 μM, 1 h following po dosing) caused no treatment-related changes in psychomotor activities, motor activities, muscle tone, CNS excitation, autonomic responses, and reflexes. On the basis of the profiles described in this report, compound **1** was selected as a clinical development candidate for the potential treatment of various CNS dysfunctions. Progress in this development will be reported elsewhere.

Experimental Section

Chemistry. General Procedures. Unless otherwise noted, all solvents, chemicals, and reagents were obtained commercially and used without purification. The ^{1}H NMR spectra were obtained at 400 MHz on a MERCURY-400 (Varian) or a JMN-AL400 (JEOL) spectrometer, with chemical shift (δ, ppm) reported relative to TMS as an internal standard. Mass spectra were recorded with electron-spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Waters micromass ZQ, micromass Quattro II or micromass Q-Tof-2 instrument. Flash chromatography was carried out with prepacked silica gel columns (KP-Sil silica) from Biotage. Preparative thin-layer chromatography (TLC) was performed on a TLC Silica gel 60 F (Merck KGaA). Preparative HPLC purification was carried out on a YMC-Pack *Pro* C18 (YMC, 50 mm × 30 mm id), eluting with a gradient of CH_3CN/0.1% aq CF_3CO_2H = 10/90 to 50/50 over 8 min at a flow rate of 40 mL/min. Purity of the target compounds was determined by HPLC with the two different eluting methods as follows. Analytical HPLC was performed on a SPELCO Ascentis Express (4.6 mm × 150 mm id), eluting with a gradient of (A) 0.1% H_3PO_4/CH_3CN = 95/5 to 10/90 over 7 min followed by 10/90 isocratic over 1 min and (B) 10 mM potassium phosphate buffer (pH 6.6)/CH_3CN = 95/5 to 20/80 over 7 min followed by 20/80 isocratic over 1 min (detection at 210 nm). High resolution mass spectra were recorded with electron-spray ionization on a micromass Q-Tof-2 instrument.

3-{4-[(3-Chloropropyl)oxy]phenyl}-2-methyl-4(3*H*)-quinazolinone (5). A mixture of 3-(4-hydroxyphenyl)-2-methylquinazolin-4(3*H*)-one (**4**; 2.00 g, 7.93 mmol),[21] 1-bromo-3-chloropropane (1.34 g, 7.93 mmol), and potassium carbonate (2.19 g, 15.9 mmol) in anhydrous DMF (20 mL) was stirred at 80 °C for 3 h. The mixture was concentrated, and the residue was partitioned between ethyl acetate and H_2O. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with H_2O and brine, dried over sodium sulfate, and concentrated. The residue was purified by flash chromatograpy using a gradient of hexanes/ethyl acetate (10/0, 9/1, and 7/3) to provide **5** as a pale-brown solid (2.23 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.26−2.31 (2H, m), 2.27 (3H, s), 3.78 (2H, t, J = 6.1 Hz), 4.19 (2H, t, J = 5.6 Hz), 7.06 (2H, d, J = 8.8 Hz), 7.17 (2H, d, J = 8.8 Hz), 7.47 (1H, t, J = 7.6 Hz), 7.67 (1H, d, J = 7.8 Hz), 7.77 (1H, t, J = 7.6 Hz), 8.27 (1H, d, J = 7.8 Hz). MS (ESI) m/z 329 $(M + H)^+$.

3-(4-{[3-(Diethylamino)propyl]oxy}phenyl)-2-methyl-4(3*H*)-quinazolinone (6a). A mixture of compound **5** (80 mg, 0.24 mmol), diethylamine (20 mg, 0.27 mmol), KI (61 mg, 0.36 mmol), and potassium carbonate (50 mg, 0.36 mmol) in anhydrous DMF (1 mL) was stirred at 80 °C overnight. The mixture was concentrated, and the residue was partitioned between ethyl acetate and 1N NaOH. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with H_2O and brine, dried over sodium sulfate, and concentrated. The residue was purified by preparative TLC ($CHCl_3$/MeOH = 10/1) followed by preparative HPLC to provide **6a** as a white solid (49 mg, 49%).

HPLC purity (98.8%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (6H, t, J = 7.2 Hz), 1.91−2.00 (2H, m), 2.25 (3H, s), 2.55 (4H, q, J = 6.8 Hz), 2.63 (2H, t, J = 6.8 Hz), 4.06 (2H, t, J = 6.4 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.13 (2H, d, J = 8.8 Hz), 7.44 (1H, t, J = 8.4 Hz), 7.65 (1H, d, J = 8.0 Hz), 7.74 (1H, t, J = 8.0 Hz), 8.25 (1H, d, J = 8.0 Hz). MS (ESI) m/z 366 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{22}H_{28}N_3O_2$, 366.2182; found, 366.2177.

2-Methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (6b). Compound **6b** was prepared from pyrrolidine using the procedure described for **6a** as a white solid (42% yield). HPLC purity (98.4%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78−1.82 (4H, m), 2.00−2.08 (2H, m), 2.25 (3H, s), 2.52−2.56 (4H, m), 2.64 (2H, t, J = 7.2 Hz), 4.08 (2H, t, J = 6.4 Hz), 7.03 (2H, d, J = 9.2 Hz), 7.12 (2H, d, J = 9.2 Hz), 7.44 (1H, t, J = 8.0 Hz), 7.65 (1H, d, J = 7.6 Hz), 7.74 (1H, t, J = 7.2 Hz), 8.25 (1H, d, J = 8.0 Hz). MS (ESI) m/z 364 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{22}H_{26}N_3O_2$, 364.2025; found, 364.2030.

2-Methyl-3-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (6c). Compound **6c** was prepared from piperidine using the procedure described for **6a** as a white solid (50% yield). HPLC purity (98.1%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41−1.55 (2H, m), 1.50−1.64 (4H, m), 1.97−2.04 (2H, m), 2.25 (3H, s), 2.37−2.46 (4H, br m), 2.49 (2H, t, J = 6.8 Hz), 4.06 (2H, t, J = 6.8 Hz), 7.03 (2H, d, J = 8.4 Hz), 7.12 (2H, d, J = 8.4 Hz), 7.44 (1H, t, J = 8.0 Hz), 7.65 (1H, d, J = 8.8 Hz), 7.74 (1H, t, J = 8.0 Hz), 8.25 (1H, d, J = 8.0 Hz). MS (ESI) m/z 378 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{28}N_3O_2$, 378.2182; found, 378.2190.

3-(4-{[3-(1-Azepanyl)propyl]oxy}phenyl)-2-methyl-4(3*H*)-quinazolinone (6d). Compound **6d** was prepared from azacycloheptane using the procedure described for **6a** as a white solid (58% yield). HPLC purity (99.3%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50−1.80 (8H, m), 2.01−2.06 (2H, br m), 2.25 (3H, s), 2.73 (6H, br s), 4.08 (2H, t, J = 6.2 Hz), 7.03 (2H, d, J = 8.4 Hz), 7.12 (2H, d, J = 8.4 Hz), 7.44 (1H, t, J = 8.0 Hz), 7.65 (1H, d, J = 8.8 Hz), 7.74 (1H, t, J = 8.0 Hz), 8.25 (1H, d, J = 8.0 Hz). MS (ESI) m/z 392 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{24}H_{30}N_3O_2$, 392.2338; found, 392.2336.

3-(4-{[3-(1-Azocanyl)propyl]oxy}phenyl)-2-methyl-4(3*H*)-quinazolinone (6e). Compound **6e** was prepared from azacyclooctane using the procedure described for **6a** as a white solid (55% yield). HPLC purity (98.3%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57−1.63 (10H, m), 1.92−1.99 (2H, m), 2.26 (3H, s), 2.57 (4H, br s), 2.62 (2H, t, J = 6.2 Hz), 4.08 (2H, t, J = 6.2 Hz), 7.03 (2H, d, J = 8.4 Hz), 7.12 (2H, d, J = 8.4 Hz), 7.44 (1H, t, J = 8.0 Hz), 7.65 (1H, d, J = 8.8 Hz), 7.74 (1H, t, J = 8.0 Hz), 8.25 (1H, d, J = 8.0 Hz). MS (ESI) m/z 406 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{25}H_{32}N_3O_2$, 406.2495; found, 406.2489.

2-Methyl-3-[4-({3-[(2*S*)-2-methyl-1-pyrrolidinyl]propyl}oxy)phenyl]-4(3*H*)-quinazolinone (6f). Compound **6f** was prepared from (*S*)-2-methylpyrrolidine hydrobromide[31] using the procedure described for **6a** as a pale-yellow oil (80% yield). HPLC purity (98.2%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (3H, d, J = 6.0 Hz), 1.40−1.50 (1H, m), 1.60−2.37 (11H, m), 2.97−3.03 (1H, m), 3.18−3.23 (1H, m), 4.07−4.11 (2H, m), 7.05 (2H, d, J = 9.2 Hz), 7.15 (2H, d, J = 9.2 Hz), 7.46 (1H, t, J = 7.6 Hz), 7.67 (1H, d, J = 7.6 Hz), 7.76 (1H, t, J = 7.6 Hz), 8.27 (1H, d, J = 7.6 Hz). MS (ESI) m/z 378 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{28}N_3O_2$, 378.2182; found, 378.2182.

2-Methyl-3-[4-({3-[(2*R*)-2-methyl-1-pyrrolidinyl]propyl}oxy)phenyl]-4(3*H*)-quinazolinone (6g). Compound **6g** was prepared from (*R*)-2-methylpyrrolidine benzenesulfonic acid salt[32] using the procedure described for **6a** as a pale-brown oil (63% yield). HPLC purity (98.5%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, d, J = 5.9 Hz), 1.43−1.55 (1H, m), 1.69−1.85 (2H, m), 1.93−2.54 (9H, m), 2.99−3.07 (1H, m), 3.21−3.26 (1H, m), 4.06−4.11 (2H, m), 7.05 (2H, d, J = 8.8 Hz), 7.15 (2H, d, J = 8.8 Hz), 7.46 (1H, t, J = 7.6 Hz), 7.67 (1H, d, J = 7.8 Hz), 7.78−7.74 (1H, m), 8.27 (1H, dd, J = 8.0, 1.2 Hz). MS (ESI) m/z 378 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{28}N_3O_2$, 378.2182; found, 378.2190.

2-Methyl-3-(4-{[3-(3-methyl-1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (6h). Compound **6h** was prepared from 3-methylpyrrolidine (racemate)[33] using the procedure described for **6a** as a white solid (43% yield). HPLC purity (98.7%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (3H, d, J = 6.8 Hz), 1.38−1.42 (1H, m), 2.02−2.09 (4H, m), 2.26 (3H, s), 2.28−2.30 (1H, m), 2.54−2.56 (1H, m), 2.63−2.72 (2H, m), 2.78−2.80 (1H, m), 2.92 (1H, t, J = 8.3 Hz), 4.09 (2H, t, J = 6.3 Hz), 7.04 (2H, td, J = 6.0, 3.6 Hz), 7.15 (2H, td, J = 6.0, 3.6 Hz), 7.46 (1H, t, J = 8.0 Hz), 7.67 (1H, d, J = 7.8 Hz), 7.74−7.78 (1H, m), 8.27 (1H, dd, J = 7.8, 1.5 Hz). MS (ESI) m/z 378 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{28}N_3O_2$, 378.2182; found, 378.2187.

3-[4-({3-[(2*R*,5*R*)-2,5-Dimethyl-1-pyrrolidinyl]propyl}oxy)phenyl]-4(3*H*)-quinazolinone (6i). Compound **6i** was prepared from (2*R*,5*R*)-2,5-dimethylpyrrolidine hydrochloride using the procedure described for **6a** as a colorless oil (66% yield). HPLC purity (99.1%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (6H, d, J = 4.4 Hz), 1.40−1.46 (2H, br m), 2.02−2.10 (4H, br m), 2.26 (3H, s), 2.59−2.65 (1H, br m), 2.81−2.88 (1H, br m), 3.10−3.17 (2H, br m), 4.05−4.14 (2H, m), 7.05 (2H, d, J = 8.8 Hz), 7.15 (2H, d, J = 8.8 Hz), 7.46 (1H, t, J = 7.6 Hz), 7.67 (1H, d, J = 7.8 Hz), 7.74−7.79 (1H, m), 8.27 (1H, d, J = 8.3 Hz). MS (ESI) m/z 392 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{24}H_{30}N_3O_2$, 392.2338; found, 392.2331.

2-Methyl-3-(4-{[3-(2-methyl-1-piperidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (6j). Compound **6j** was prepared from 2-methylpiperidine (racemate) using the procedure described for **6a** as a white solid (25% yield). HPLC purity (98.1%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, d, J = 5.5 Hz), 1.30−1.40(1H, br s), 1.55−1.65 (6H, br s), 2.01−2.05 (2H, m), 2.26 (3H, s), 2.42 (1H, br s), 2.59 (1H, br s), 2.92−2.96 (2H, m), 4.03−4.08 (2H, m), 7.03 (2H, d, J = 8.4 Hz), 7.12 (2H, d, J = 8.4 Hz), 7.44 (1H, t, J = 8.0 Hz), 7.65 (1H, d, J = 8.8 Hz), 7.74 (1H, t, J = 8.0 Hz), 8.25 (1H, d, J = 8.0 Hz). MS (ESI) m/z 392 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{24}H_{30}N_3O_2$, 392.2338; found, 392.2344.

2-Methyl-3-[4-({3-[(3*S*)-3-methyl-1-piperidinyl]propyl}oxy)phenyl]-4(3*H*)-quinazolinone (6k). Compound **6k** was prepared from (*S*)-3-methylpiperidine (*S*)-(+)-mandelate salt[34] using the procedure described for **6a** as a pale-pink oil (66% yield). HPLC purity (96.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87−0.89 (4H, m), 1.56−1.76 (5H, m), 1.84−1.91 (1H, m), 2.02−2.06 (2H, m), 2.26 (3H, s), 2.53 (2H, t, J = 7.2 Hz), 2.85−2.93 (2H, m), 4.07 (2H, t, J = 6.3 Hz), 7.04 (2H, d, J = 9.0 Hz), 7.15 (2H, d, J = 9.0 Hz), 7.46 (1H, t, J = 7.6 Hz), 7.67 (1H, d, J = 7.6 Hz), 7.76 (1H, t, J = 7.6 Hz), 8.27 (1H, d, J = 7.6 Hz). MS (ESI) m/z 392 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{24}H_{30}N_3O_2$, 392.2338; found, 392.2330.

2-Methyl-3-[4-({3-[(3*R*)-3-methyl-1-piperidinyl]propyl}oxy)phenyl]-4(3*H*)-quinazolinone (6l). Compound **6l** was prepared from (*R*)-3-methylpiperidine (*R*)-(−)-mandelate salt[33] using the procedure described for **6a** as a pale-pink oil (37% yield). HPLC purity (99.1%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87−0.89 (4H, m), 1.50−1.95 (6H, m), 2.00−2.05 (2H, m), 2.26 (3H, s), 2.50 (2H, t, J = 6.8 Hz), 2.89−2.97 (2H, m), 4.07 (2H, t, J = 6.4 Hz), 7.05 (2H, d, J = 8.6 Hz), 7.15 (2H, d, J = 8.6 Hz), 7.46(1H, t, J = 8.0 Hz), 7.67 (1H, d, J = 8.0 Hz), 7.76 (1H, t, J = 8.4 Hz), 8.27 (1H, d, J = 8.0 Hz). MS (ESI) m/z 392 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{24}H_{30}N_3O_2$, 392.2338; found, 392.2344.

2-Methyl-3-(4-{[3-(4-methyl-1-piperidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (6m). Compound **6m** was prepared from 4-methylpiperidine using the procedure described for **6a** as a white solid (41% yield). HPLC purity (97.7%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, d, J = 6.6 Hz), 1.22−1.26 (2H, m), 1.32−1.39 (1H, m), 1.62−1.65 (2H, m), 1.92−2.05 (4H, m), 2.25 (3H, s), 2.51 (2H, t, J = 7.6 Hz), 2.90−2.93 (2H, m), 4.06 (2H, t, J = 6.2 Hz), 7.02 (2H, d, J = 6.6 Hz), 7.12 (2H, d, J = 6.6 Hz), 7.46 (1H, t, J = 6.5 Hz), 7.65 (1H, d, J = 7.7 Hz), 7.76 (1H, t, J = 8.4 Hz), 8.26 (1H, d, J = 8.4 Hz). MS (ESI) m/z 392 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{24}H_{30}N_3O_2$, 392.2338; found, 392.2350.

3-(4-{[3-(3,5-Dimethyl-1-piperidinyl)propyl]oxy}phenyl)-2-methyl-4(3*H*)-quinazolinone (6n). Compound **6n** was prepared from 3,5-dimethylpiperidine using the procedure described for **6a** as a pale-

pink oil (22% yield). HPLC purity (98.4% as a mixture of cis and trans, cis:trans = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): for *cis*-isomer, δ 0.54 (1H, q, J = 12.8 Hz), 0.87 (6H, d, J = 6.3 Hz), 1.47 (2H, t, J = 11.0 Hz), 1.65−1.74 (1H, m), 1.87−1.92 (2H, br m), 2.00−2.07 (2H, m), 2.26 (3H, s), 2.52 (2H, t, J = 7.6 Hz), 2.91−2.86 (2H, br m), 4.07 (2H, t, J = 6.3 Hz), 7.04 (2H, d, J = 8.8 Hz), 7.15 (2H, d, J = 8.8 Hz), 7.44−7.48 (1H, m), 7.67 (1H, d, J = 7.3 Hz), 7.74−7.78 (1H, m), 8.27 (1H, dd, J = 8.0, 1.2 Hz); for *trans*-isomer, δ 0.96 (6H, d, J = 6.8 Hz), 1.25−1.31 (2H, m), 1.89−2.02 (4H, m), 2.05−2.12 (2H, br m), 2.26 (3H, s), 2.34−2.42 (3H, m), 2.46−2.53 (1H, m), 4.09 (2H, t, J = 6.6 Hz), 7.05 (2H, d, J = 9.3 Hz), 7.15 (2H, d, J = 9.3 Hz), 7.46 (1H, t, J = 7.6 Hz), 7.67 (1H, d, J = 7.3 Hz), 7.74−7.78 (1H, m), 8.27 (1H, dd, J = 7.8, 1.5 Hz). MS (ESI) m/z 406 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{25}H_{32}N_3O_2$, 406.2495; found, 406.2484.

3-(1-Pyrrolidinyl)-1-propanol (8). To a stirred solution of 3-bromopropanol (200 g, 1.27 mol) in 500 mL of THF were added potassium carbonate (260 g, 1.88 mol) and pyrrolidine (200 mL, 2.40 mol) at 0 °C, and the resulting mixture was stirred at room temperature for 15 h. The resulting mixture was diluted with ethyl acetate (500 mL) and filtered through celite pad. The filtrate was concentrated, and the residue was distilled under a reduced pressure (bp 62 °C, 1 mmHg) to give **8** as a clear oil (156 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69−1.78 (6H, m), 2.58−2.55 (4H, m), 2.73 (2H, t, J = 5.6 Hz), 3.81 (2H, t, J = 5.1 Hz). MS (ESI) m/z 130 $(M + H)^+$.

1-{3-[(4-Nitrophenyl)oxy]propyl}pyrrolidine (9). To a stirred suspension of NaH (60% oil dispersion, 1.35 g, 33.8 mmol) in 20 mL of DMF was added a solution of **8** (2.91 g, 22.5 mmol) in 100 mL of DMF dropwise at 0 °C, and the mixture was stirred at 0 °C for 10 min. To the mixture was added a solution of 4-fluoro-1-nitrobenzene (3.18 g, 22.5 mmol) in 100 mL of DMF dropwise at 0 °C. After being stirred at 0 °C for 1 h, the mixture was allowed to warm to room temperature and stirred for an additional 3 h. The resulting mixture was poured into water and extracted with ethyl acetate twice. The combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by silica gel flash column chromatography, eluting with a gradient of $CHCl_3$/MeOH (1/0, 9/1, and 6/1) to give **9** as a yellow oil (4.7 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77−1.81 (4H, m), 2.00−2.07 (2H, m), 2.50−2.54 (4H, m), 2.63 (2H, t, J = 7.2 Hz), 4.12 (2H, t, J = 6.4 Hz), 6.93 (2H, d, J = 9.6 Hz), 8.16 (2H, d, J = 9.6 Hz). MS (ESI) m/z 251 $(M + H)^+$.

1-{3-[(4-Aminophenyl)oxy]propyl}pyrrolidine (10). Compound **9** (4.7 g, 18.8 mmol) was hydrogenated over 2.0 g of 10% Pd/C in 20 mL of MeOH under an atmospheric pressure of hydrogen at room temperature for 20 h. The mixture was filtered through a pad of celite, and the filtrate was concentrated to give **10** as a brown oil (4.02 g, 97%). **10** ditosylate was prepared as follows. Compound **10** (50 mg, 0.23 mmol) and *p*-toluenesulfonic acid monohydrate (86 mg, 0.56 mmol) were dissolved in MeOH. An exccess amount of ethyl acetate was added, and the resulting precipitates were collected by filtration and dried under vacuum to provide **10** ditosylate as a pale-purple solid (120 mg, 94%). For **10**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77−1.80 (4H, m), 1.93−2.00 (2H, m), 2.49−2.54 (4H, m), 2.60 (2H, t, J = 7.6 Hz), 3.41 (2H, br s), 3.95 (2H, t, J = 6.6 Hz), 6.63 (2H, d, J = 8.8 Hz), 6.74 (2H, d, J = 9.3 Hz). MS (ESI) m/z 221 $(M + H)^+$. For **10** ditosylate, ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81−1.90 (2H, m), 1.96−2.05 (2H, m), 2.06−2.13 (2H, m), 2.29 (6H, s), 3.02−3.04 (2H, m), 3.28−3.30 (2H, m), 3.57−3.59 (2H, m), 4.05 (2H, t, J = 6.1 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.12 (4H, d, J = 7.8 Hz), 7.28 (2H, d, J = 8.8 Hz), 7.49 (4H, d, J = 7.8 Hz), 9.49 (1H, br s), 9.73 (3H, br s). MS (ESI) m/z 221 $(M + H)^+$.

2-Methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-5-(trifluoromethyl)-4(3*H*)-quinazolinone (1). A mixture of **10** ditosylate (260 mg, 0.46 mmol), **12p** (106 mg, 0.46 mmol), and sodium acetate (76 mg, 0.92 mmol) in acetic acid (1 mL) and THF (1 mL) was stirred at 40 °C for 3 days. The resulting mixture was diluted with ethyl acetate, washed with 2N NaOH and brine, dried over sodium sulfate, and concentrated. The residue was purified by preparative HPLC to give **1** as a white solid (138 mg, 70%). HPLC purity (99.9%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77−1.83 (4H, m), 2.00−2.08 (2H, m), 2.26 (3H, s), 2.51−2.57 (4H, m), 2.63 (2H, t, J = 7.2 Hz), 4.07 (2H, t, J = 6.8 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.12 (2H, d, J = 8.8 Hz), 7.79 (1H, t, J = 7.6 Hz), 7.82−7.88 (2H, m). MS (ESI) m/z 432 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{25}N_3O_2F_3$, 432.1899; found, 432.1911.

2,5-Dimethyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (13a). A mixture of **10** (126 mg, 0.528 mmol) and **12a** (100 mg, 0.528 mmol) in 1 mL of acetic acid was stirred at 130 °C for 5 h. After being cooled to room temperature, the mixture was diluted with ethyl acetate and washed with 2N NaOH and brine, dried over sodium sulfate, and concentrated. The residue was purified by preparative HPLC to give **13a** as a white solid (107 mg, 54%). HPLC purity (97.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77−1.84 (4H, m), 2.01−2.09 (2H, m), 2.22 (3H, s), 2.51−2.58 (4H, m), 2.63 (2H, t, J = 7.2 Hz), 2.81 (3H, s), 4.07 (2H, t, J = 6.4 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.12 (2H, d, J = 8.8 Hz), 7.19 (1H, d, J = 7.6 Hz), 7.48 (1H, d, J = 8.0 Hz), 7.57 (1H, t, J = 8.0 Hz). MS (ESI) m/z 378 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{28}N_3O_2$, 378.2182; found, 378.2188.

2,6-Dimethyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (13b). Compound **13b** was prepared from **12b** using the procedure described for **13a** as a white solid (56% yield). HPLC purity (99.8%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76−1.84 (4H, m), 2.00−2.09 (2H, m), 2.23 (3H, s), 2.47 (3H, s), 2.50−2.58 (4H, m), 2.64 (2H, t, J = 7.2 Hz), 4.08 (2H, t, J = 6.4 Hz), 7.02 (2H, d, J = 8.8 Hz), 7.12 (2H, d, J = 8.8 Hz), 7.55 (2H, s), 8.03 (1H, s). MS (ESI) m/z 378 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{28}N_3O_2$, 378.2182; found, 378.2181.

2,7-Dimethyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (13c). Compound **13c** was prepared from **12c** using the procedure described for **1** as a white solid (52% yield). HPLC purity (99.2%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81−1.84 (4H, m), 2.04−2.11 (2H, m), 2.24 (3H, s), 2.51 (3H, s), 2.58−2.62 (4H, br m), 2.69 (2H, t, J = 7.6 Hz), 4.09 (2H, t, J = 6.3 Hz), 7.04 (2H, d, J = 8.4 Hz), 7.14 (2H, d, J = 8.4 Hz), 7.28 (1H, dd, J = 7.8, 1.4 Hz), 7.46 (1H, s), 8.15 (1H, d, J = 7.8 Hz). MS (ESI) m/z 378 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{28}N_3O_2$, 378.2182; found, 378.2174.

2,8-Dimethyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (13d). Compound **13d** was prepared from **12d** using the procedure described for **1** as a white solid (72% yield). HPLC purity (99.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81−1.84 (4H, m), 2.03−2.10 (2H, m), 2.27 (3H, s), 2.57−2.61 (4H, br m), 2.63 (3H, s), 2.68 (2H, t, J = 7.8 Hz), 4.09 (2H, t, J = 7.2 Hz), 7.04 (2H, d, J = 8.6 Hz), 7.14 (2H, d, J = 8.8 Hz), 7.33 (1H, t, J = 7.6 Hz), 7.60 (1H, d, J = 8.0 Hz), 8.12 (1H, d, J = 8.0 Hz). MS (ESI) m/z 378 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{28}N_3O_2$, 378.2182; found, 378.2186.

5-Methoxy-2-methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (13e). Compound **13e** was prepared from **12e** using the procedure described for **13a** as a white solid (19% yield). HPLC purity (99.8%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80−1.85 (4H, m), 2.03−2.10 (2H, m), 2.21 (3H, s), 2.55−2.61 (4H, m), 2.66−2.70 (2H, m), 3.95 (3H, s), 4.08 (2H, t, J = 6.1 Hz), 6.87 (1H, d, J = 8.3 Hz), 7.01 (2H, d, J = 8.8 Hz), 7.11 (2H, d, J = 9.3 Hz), 7.23 (1H, d, J = 8.3 Hz), 7.65 (1H, t, J = 8.3 Hz). MS (ESI) m/z 394 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{28}N_3O_3$, 394.2131; found, 394.2130.

6-Methoxy-2-methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (13f). Compound **13f** was prepared from **12f** using the procedure described for **13a** as a white solid (70% yield). HPLC purity (99.8%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79−1.83 (4H, m), 2.03−2.09 (2H, m), 2.23 (3H, s), 2.52−2.58 (4H, m), 2.66 (2H, t, J = 7.2 Hz), 3.91 (3H, s), 4.10 (2H, t, J = 6.4 Hz), 7.05 (2H, d, J = 9.2 Hz), 7.14 (2H, d, J = 9.2 Hz), 7.36 (1H, dd, J = 2.8, 8.8 Hz), 7.61 (1H, d, J = 8.8 Hz), 7.63 (1H, d, J = 3.2 Hz). MS (ESI) m/z 394 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{28}N_3O_3$, 394.2131; found, 394.2146.

7-Methoxy-2-methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (13g). Compound **13g** was prepared from **12g** using the procedure described for **13a** as a pale-yellow solid (64% yield). HPLC purity (99.5%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79−1.82 (4H, m), 2.01−2.08 (2H, m), 2.24 (3H, s), 2.53−2.56 (4H, m), 2.65 (2H, t, J = 7.6 Hz), 3.93 (3H, s), 4.09 (2H, t, J = 6.3 Hz), 7.06−7.01 (4H, m), 7.14 (2H, d, J = 8.8 Hz), 8.16 (1H, d, J = 8.8 Hz). MS (ESI) m/z 394 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{28}N_3O_3$, 394.2131; found, 394.2123.

8-Methoxy-2-methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone trifluoroacetate (13h). Compound **13h** was prepared from **12h** using the procedure described for **1** as a pale-yellow solid (78% yield). HPLC purity (98.1%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20−2.09 (4H, m), 2.34−2.31 (2H, m), 2.36 (3H, s), 2.91−2.88 (2H, br m), 3.36−3.34 (2H, br m), 3.91−3.88 (2H, br m), 4.03 (3H, s), 4.12 (2H, t, J = 5.4 Hz), 7.02 (2H, d, J = 8.8 Hz), 7.17 (2H, d, J = 8.8 Hz), 7.25 (1H, d, J = 8.3 Hz), 7.43 (1H, t, J = 8.0 Hz), 7.82 (1H, dd, J = 8.3, 1.0 Hz). MS (ESI) m/z 394 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{28}N_3O_3$, 394.2131; found, 394.2135.

5-Fluoro-2-methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (13i). Compound **13i** was prepared from **12i** using the procedure described for **13a** as a pale-orange solid (32% yield). HPLC purity (99.7%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77−1.83 (4H, m), 2.00−2.08 (2H, m), 2.23 (3H, s), 2.51−2.56 (4H, m), 2.64 (2H, t, J = 7.2 Hz), 4.08 (2H, t, J = 6.4 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.02−7.11 (1H, m), 7.12 (2H, d, J = 8.8 Hz), 7.43 (1H, d, J = 8.0 Hz), 7.63−7.68 (1H, m). MS (ESI) m/z 382 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{22}H_{25}N_3O_2F$, 382.1931; found, 382.1924.

6-Fluoro-2-methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (13j). Compound **13j** was prepared from **12j** using the procedure described for **1** as a white solid (39% yield). HPLC purity (97.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82−1.85 (4H, m), 2.04−2.11 (2H, m), 2.25 (3H, s), 2.63−2.59 (4H, br m), 2.70 (2H, t, J = 7.6 Hz), 4.10 (2H, t, J = 6.3 Hz), 7.05 (2H, d, J = 8.8 Hz), 7.14 (2H, d, J = 8.8 Hz), 7.50−7.45 (1H, m), 7.68 (1H, dd, J = 9.0, 4.6 Hz), 7.89 (1H, dd, J = 8.3, 2.9 Hz). MS (ESI) m/z 382 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{22}H_{25}N_3O_2F$, 382.1931; found, 382.1920.

7-Fluoro-2-methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (13k). Compound **13k** was prepared from **12k** using the procedure described for **1** as a white solid (58% yield). HPLC purity (97.9%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81−1.85 (4H, m), 2.04−2.11 (2H, m), 2.25 (3H, s), 2.58−2.62 (4H, br m), 2.69 (2H, t, J = 7.6 Hz), 4.09 (2H, t, J = 6.3 Hz), 7.05 (2H, d, J = 8.8 Hz), 7.12−7.20 (3H, m), 7.31 (1H, dd, J = 9.8, 2.4 Hz), 8.27 (1H, dd, J = 8.8, 6.3 Hz). MS (ESI) m/z 382 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{22}H_{25}N_3O_2F$, 382.1931; found, 382.1939.

8-Fluoro-2-methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone HCl Salt (13l). Free form of compound **13l** was prepared from **12l** using the procedure described for **13a**, which was treated with 4N HCl in ethyl acetate to provide a HCl salt of **13l** as a white solid (50% yield). HPLC purity (98.7%). ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ = 10/1): δ 2.09−2.18 (2H, m), 2.21−2.29 (2H, m), 2.39−2.47 (5H, m), 2.86−2.95 (2H, m), 3.37−3.32 (2H, m), 3.83−3.89 (2H, m), 4.18 (2H, t, J = 5.4 Hz), 7.07 (2H, d, J = 8.3 Hz), 7.22 (2H, d, J = 8.8 Hz), 7.46−7.52 (1H, m), 7.57 (1H, t, J = 9.0 Hz), 8.06 (1H, d, J = 8.3 Hz). MS (ESI) m/z 382 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{22}H_{25}N_3O_2F$, 382.1931; found, 382.1925.

5-Chloro-2-methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (13m). Compound **13m** was prepared from **12m** using the procedure described for **13a** as a white solid (54% yield). HPLC purity (99.8%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77−1.84 (4H, m), 2.00−2.08 (2H, m), 2.22 (3H, s), 2.51−2.56 (4H, m), 2.64 (2H, t, J = 6.8 Hz), 4.07 (2H, t, J = 6.4 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.12 (2H, d, J = 8.8 Hz), 7.43 (1H, dd, J = 2.0, 7.6 Hz), 7.44−7.60 (2H, m). MS (ESI) m/z 398 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{22}H_{25}N_3O_2Cl$, 398.1635; found, 398.1631.

2-Methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-7-(trifluoromethyl)-4(3*H*)-quinazolinone (13n). Compound **13n** was prepared from **12n** using the procedure described for **1** as a white solid (20% yield). HPLC purity (99.8%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81−1.84 (4H, m), 2.03−2.10 (2H, m), 2.28 (3H, s), 2.61−2.57 (4H, br m), 2.69 (2H, t, J = 7.3 Hz), 4.10 (2H, t, J = 6.3 Hz), 7.06 (2H, d, J = 8.8 Hz), 7.15 (2H, d, J = 8.8 Hz), 7.65 (1H, dd, J = 8.3, 1.5 Hz), 7.96 (1H, s), 8.38 (1H, d, J = 8.3 Hz). MS (ESI) m/z 432 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{25}N_3O_2F_3$, 432.1899; found, 432.1894.

2-Methyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-8-(trifluoromethyl)-4(3*H*)-quinazolinone (13o). Compound **13o** was prepared from **12o** using the procedure described for **1** as a pale-yellow oil (40% yield). HPLC purity (99.4%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81−1.84 (4H, m), 2.03−2.10 (2H, m), 2.31 (3H, s), 2.60−2.57 (4H, br m), 2.68 (2H, t, J = 7.3 Hz), 4.10 (2H, t, J = 6.3 Hz), 7.06 (2H, d, J = 9.3 Hz), 7.14 (2H, d, J = 8.8 Hz), 7.50 (1H, t, J = 7.8 Hz), 8.07 (1H, d, J = 7.3 Hz), 8.46 (1H, d, J = 7.8 Hz). MS (ESI) m/z 432 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{25}N_3O_2F_3$, 432.1899; found, 432.1909.

3-(4-{[3-(1-Pyrrolidinyl)propyl]oxy}phenyl)- 4(3*H*)-quinazolinone (14).[23] A mixture of anthranilic acid (12.2 mg, 0.089 mmol), triethyl orthoformate (0.029 mL, 0.177 mmol), ytterbium(III) trifluoromethanesulfonate (5.49 mg, 8.85 μmol), and aniline **10** ditosylate (50 mg, 0.089 mmol) in THF (1 mL) was stirred at 60 °C overnight. After being cooled to room temperature, the mixture was diluted with ethyl acetate, washed with 2N NaOH and brine, dried over sodium sulfate, and concentrated. The residue was purified by preparative TLC ($CHCl_3$/MeOH = 10/1) to give **14** as a pale-yellow solid (10.5 mg, 34% yield). HPLC purity (96.2%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85 (4H, br s), 2.13−2.06 (2H, m), 2.65 (4H, br s), 2.73 (2H, t, J = 7.3 Hz), 4.10 (2H, t, J = 6.1 Hz), 7.04 (2H, d, J = 8.8 Hz), 7.32 (2H, d, J = 8.8 Hz), 7.55 (1H, t, J = 7.3 Hz), 7.75−7.82 (2H, m), 8.11 (1H, s), 8.37 (1H, d, J = 7.8 Hz). MS (ESI) m/z 350 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{21}H_{24}N_3O_2$, 350.1869; found, 350.1866.

2-Ethyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (16a). Compound **16a** was prepared from **15a** using the procedure described for **13a** as a pale-pink solid (50% yield). HPLC purity (99.7%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, t, J = 7.2 Hz), 1.77−1.84 (4H, m), 2.01−2.09 (2H, m), 2.46 (2H, q, J = 7.2 Hz), 2.51−2.58 (4H, m), 2.65 (2H, t, J = 6.8 Hz), 4.08 (2H, t, J = 6.4 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.12 (2H, d, J = 8.8 Hz), 7.43 (1H, t, J = 8.0 Hz), 7.67−7.76 (2H, m), 8.24 (1H, d, J = 8.4 Hz). MS (ESI) m/z 378 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{23}H_{28}N_3O_2$, 378.2182; found, 378.2180.

2-Propyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (16b). Compound **16b** was prepared from **15b** using the procedure described for **1** as a white solid (32% yield). HPLC purity (99.7%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 7.6 Hz), 1.77−1.67 (2H, m), 1.82−1.79 (4H, m), 2.09−2.02 (2H, m), 2.44−2.40 (2H, m), 2.56−2.53 (4H, m), 2.66 (2H, t, J = 7.3 Hz), 4.10 (2H, t, J = 6.6 Hz), 7.05 (2H, dd, J = 6.8, 2.4 Hz), 7.14 (2H, dd, J = 6.8, 2.4 Hz), 7.46−7.42 (1H, m), 7.77−7.68 (2H, m), 8.26 (1H, dd, J = 8.0, 1.2 Hz). MS (ESI) m/z 392 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{24}H_{30}N_3O_2$, 392.2338; found, 392.2335.

2-Isopropyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (16c). Compound **16c** was prepared from **15c** using the procedure described for **1** as a white solid (25% yield). HPLC purity (98.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (6H, d, J = 6.6 Hz), 1.83−1.80 (4H, m), 2.09−2.02 (2H, m), 2.58−2.55 (4H, m), 2.69−2.65 (2H, m), 2.79−2.72 (1H, m), 4.10 (2H, t, J = 6.3 Hz), 7.05 (2H, dd, J = 6.6, 2.2 Hz), 7.14 (2H, dd, J = 6.6, 2.2 Hz), 7.46−7.42 (1H, m), 7.77−7.69 (2H, m), 8.26 (1H, dd, J = 8.2, 1.1 Hz). MS (ESI) m/z 392 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{24}H_{30}N_3O_2$, 392.2338; found, 392.2335.

2-Phenyl-3-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-4(3*H*)-quinazolinone (16d). Compound **16d** was prepared from **15d** using the procedure described for **1** as a white solid (21% yield). HPLC purity (98.1%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82−1.78 (4H, m), 2.02−1.95 (2H, m), 2.57−2.52 (4H, m), 2.62 (2H, t, J = 7.6 Hz), 3.97 (2H, t, J = 6.3 Hz), 6.81 (2H, dd, J = 6.8, 2.4 Hz), 7.03 (2H, dd, J = 6.8, 2.0 Hz), 7.28−7.21 (3H, m), 7.35−7.33 (2H, m), 7.54−7.50 (1H, m), 7.82−7.79 (2H, m), 8.37−8.33 (1H, m). MS (ESI) m/z 426 $(M + H)^+$. HRMS $(M + H)^+$ calcd for $C_{27}H_{28}N_3O_2$, 426.2182; found, 426.2189.

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Supporting Information Available: Synthetic procedures for the preparation of compounds **3**, **4**, **12a**−**p**, and **15a**−**d**, biological methods, HPLC retention times, and purity for the target compounds, and HPLC traces for **1**, **13e**, **13f**, and **13l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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