Journal of Medicinal Chemistry

Article

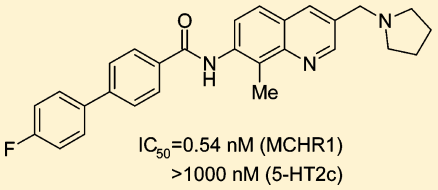
pubs.acs.org/jmc

Melanin-Concentrating Hormone Receptor 1 Antagonists. Synthesis and Structure−Activity Relationships of Novel 3-(Aminomethyl)quinolines

Makoto Kamata,* Toshiro Yamashita, Toshihiro Imaeda, Toshio Tanaka, Shinichi Masada, Masahiro Kamaura, Shizuo Kasai, Ryoma Hara, Shigekazu Sasaki, Shiro Takekawa, Asano Asami, Tomoko Kaisho, Nobuhiro Suzuki, Shuntaro Ashina, Hitomi Ogino, Yoshihide Nakano, Yasutaka Nagisa, Koki Kato, Kaneyoshi Kato, and Yuji Ishihara

Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, 26-1 Muraokahigashi, 2-Chome, Fujisawa, Kanagawa 251-8555, Japan

ABSTRACT: It was found that 3-(aminomethyl)quinoline derivatives showed high binding affinities for melanin-concentrating hormone receptor 1 (MCHR1) with reduced affinity for serotonin receptor 2c (5-HT2c) when the dihydronaphthalene nucleus of compound **1** (human MCHR1, IC_{50} = 1.9 nM; human 5-HT2c receptor, IC_{50} = 0.53 nM) was replaced by other bicyclic core scaffolds. Among the synthesized compounds, 8-methylquinoline derivative **5v** especially showed high binding affinity (IC_{50} = 0.54 nM), potent in vitro antagonistic activity (IC_{50} = 2.8 nM) for MCHR1, and negligible affinity for 5-HT2c receptor (IC_{50} > 1000 nM). Oral administration of **5v** significantly and dose-dependently suppressed nocturnal food intake in diet-induced obese rats and did not affect food intake in MCHR1-deficient mice. These results and rat pharmacokinetic study findings suggested that compound **5v** is a highly potent, orally bioavailable, and centrally acting nonpeptide MCHR1 antagonist.



INTRODUCTION

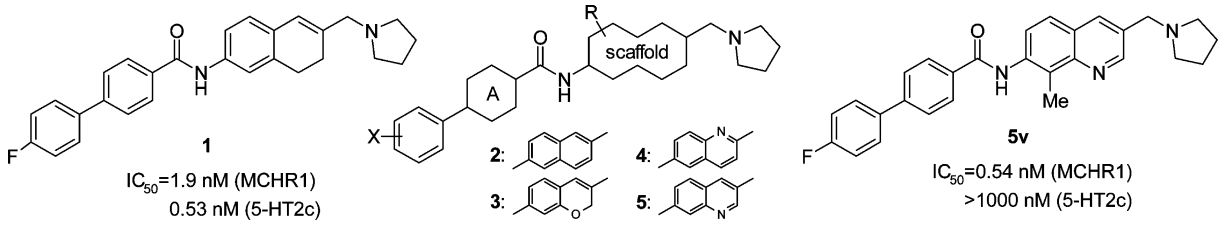
Melanin-concentrating hormone receptor 1 (MCHR1) antagonism has been recognized as a promising target in obesity treatment. Tetrahydronaphthalene derivative T-226296[1] has been reported to be an MCHR1 antagonist, and exhibits a potent in vitro binding affinity and in vivo anorectic effect. In our previous paper,[2] we reported that dihydronaphthalene derivative **1** also exhibited potent binding affinity for MCHR1 and significantly reduced the nocturnal food intake of KKA^y mice and Sprague−Dawley rats after oral administration. However, further investigation revealed that compound **1** showed poor receptor selectivity, especially antagonist activity for 5-HT2c receptor. While 5-HT2c receptor agonists are known as antiobesity drugs as they suppressed the appetite in clinical trials,[3−6] the relationship between 5-HT2c receptor antagonists and food intake still remains obscure. It has been suggested that the 5-HT2c receptor plays a role in central nervous system (CNS) disorders, for example, anxiety, depression, and drug dependence.[7−9] To clarify the anorectic effect on the basis of MCHR1 antagonism, we replaced the dihydronaphthalene nucleus and the biaryl moiety of **1** with other bicyclic scaffolds and equivalent groups that may exhibit less affinity for the 5-HT2c receptor. In this paper, we report the structure−activity relationship (SAR) study that led us to identify 8-methylquinoline derivative **5v** as a potent MCHR1 antagonist that is highly selective (>1800-fold) over the 5-HT2c receptor.

CHEMISTRY

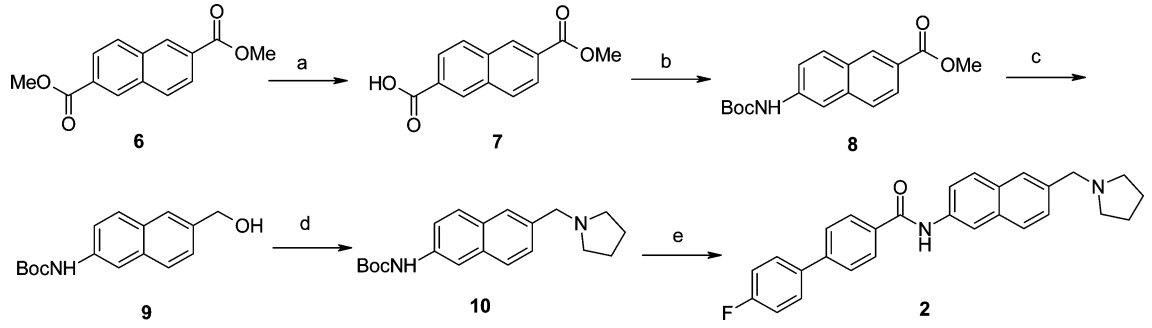
Naphthalene derivative **2** was synthesized as shown in Scheme 1. Partial hydrolysis of commercially available diester **6** with 1 M NaOH gave carboxylic acid **7** in 60% yield. Curtius rearrangement of the acid **7** with diphenylphosphoryl azide in *t*-BuOH gave methyl ester **8**, which was converted to alcohol **9** by reduction with lithium aluminum hydride. Compound **10** was obtained by mesylation of alcohol **9** and subsequent amine substitution of the resulting mesylate in the presence of pyrrolidine. The Boc group in **10** was deprotected, and the generated amine was condensed with 4′-fluorobiphenylcarboxylic acid using the peptide coupling method to provide naphthalene derivative **2**.

The synthetic route of chromene derivative **3** is shown in Scheme 2. Michael addition of 3-(acetylamino)phenol (**11**) to ethyl acrylate in the presence of Triton B and subsequent acid hydrolysis of the resulting phenoxy ester **12** with HCl gave 3-phenoxypropionic acid **13** in 40% yield. Friedel−Crafts cyclization of the 3-phenoxypropionyl chloride, which was obtained by treatment of **13** with thionyl chloride, regioselectively gave ketone **14** in 70% yield. Condensation of **14** with dimethylformamide dimethyl acetal gave enaminone **15**. Replacement of the dimethylamino group in **15** with pyrrolidine and subsequent reduction with $NaBH_4$ under acidic conditions followed by dehydration and deprotection with HCl afforded chromen-7-ylamine derivative **16** in 54% yield. Amine

Received: November 25, 2011
Published: February 6, 2012

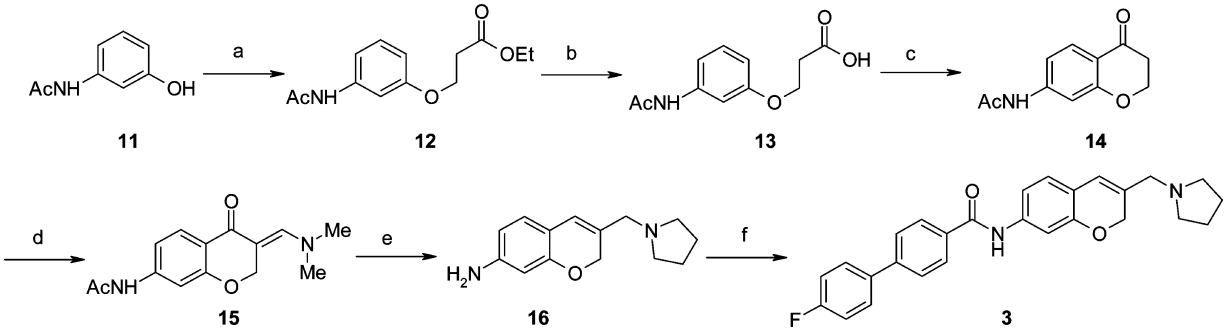


Scheme 1[a]



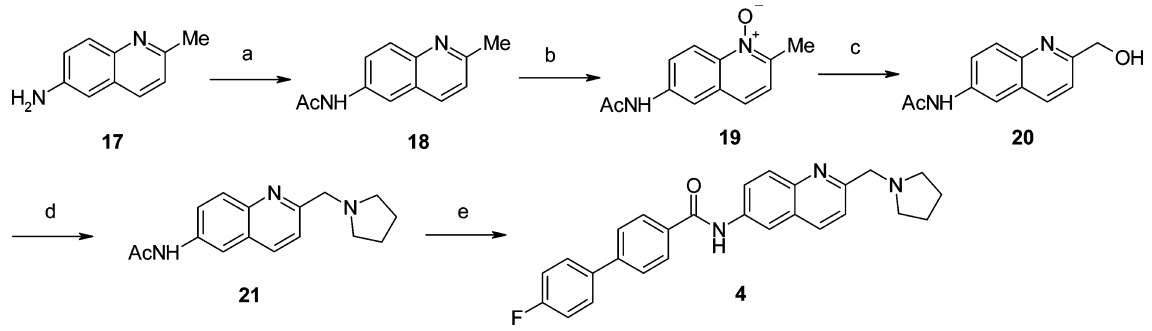
[a]Reagents and conditions: (a) 1 M NaOH, DMF; (b) DPPA, TEA, *t*-BuOH; (c) $LiAlH_4$, THF; (d) (i) MsCl, TEA, THF; (ii) pyrrolidine, K_2CO_3, DMF; (e) (i) TFA; (ii) 4′-fluorobiphenylcarboxylic acid, EDC·HCl, DMAP, DMF.

Scheme 2[a]



[a]Reagents and conditions: (a) ethyl acrylate, Triton B; (b) 5 M HCl, AcOH; (c) $SOCl_2$, $EtNO_2$, then $AlCl_3$; (d) dimethylformamide dimethyl acetal; (e) (i) pyrrolidine; (ii) $NaBH_4$, AcOH, 2-PrOH; (iii) 6 M HCl; (f) 4′-fluorobiphenylcarboxylic acid, EDC·HCl, HOBt, DMAP, DMF.

Scheme 3[a]



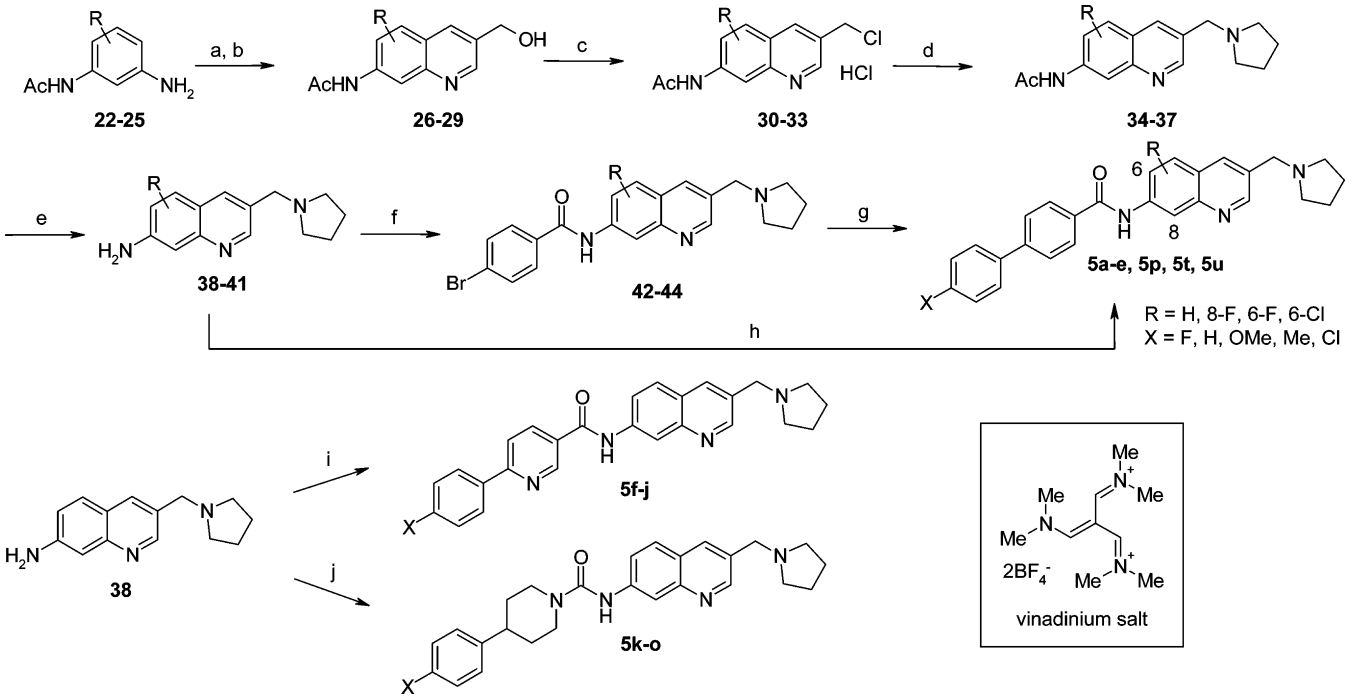
[a]Reagents and conditions: (a) Ac_2O, pyridine; (b) *m*CPBA, $CHCl_3$; (c) (i) Ac_2O; (ii) 1 M NaOH, MeOH; (d) (i) MsCl, TEA, DMF; (ii) pyrrolidine, K_2CO_3; (e) (i) concentrated HCl; (ii) 4′-fluorobiphenylcarboxylic acid, EDC·HCl, DMAP, DMF.

16 was condensed with 4′-fluorobiphenyl carboxylic acid to provide chromene derivative **3**.

Quinoline derivative **4** was synthesized as shown in Scheme 3. (Acetylamino)quinoline derivative **18**, which was obtained by acetylation of commercially available quinoline **17**, was oxidized with *m*-chloroperbenzoic acid (*m*CPBA) to give quinoline *N*-oxide **19** in 82% yield. Rearrangement of *N*-oxide **19** with acetic anhydride and subsequent hydrolysis of the resulting acetate with NaOH afforded the key intermediate **20** in 57% yield. Mesylation of alcohol **20** and subsequent amine substitution of the resulting mesylate gave **21** in moderate yields. After deprotection of the acetyl group in **21** by HCl, the generated amine was condensed with 4′-fluorobiphenylcarboxylic acid to provide quinoline derivative **4**.

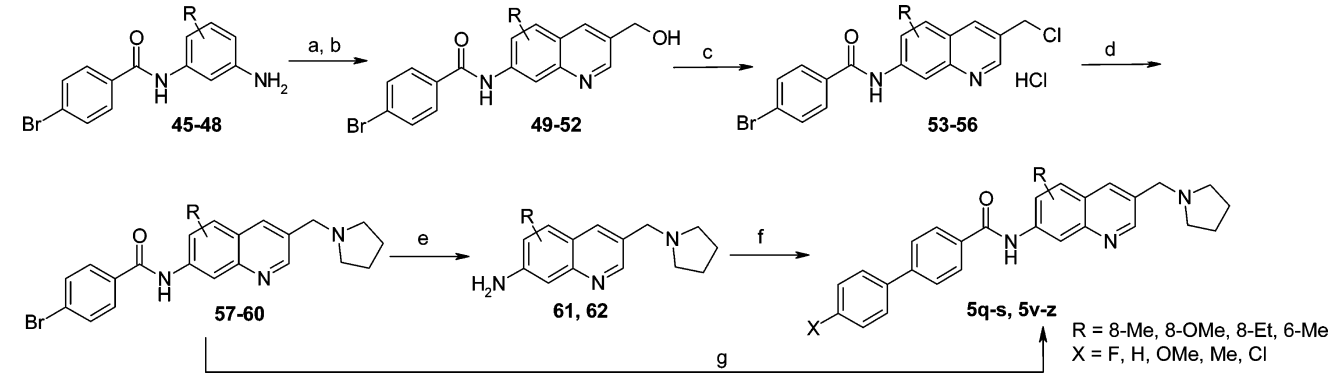
dx.doi.org/10.1021/jm201596h | *J. Med. Chem.* 2012, 55, 2353−2366

Scheme 4[a]



[a]Reagents and conditions: (a) vinadinium salt, BuOH; (b) $NaBH_4$, EtOH, THF; (c) $SOCl_2$; (d) pyrrolidine, K_2CO_3, DMF; (e) concentrated HCl; (f) 4-bromobenzoyl chloride, TEA, THF; (g) substituted phenylboronic acids, $Pd(PPh_3)_4$, 2 M Na_2CO_3, THF; (h) substituted biphenylcarboxylic acids, EDC·HCl, DMAP, DMF or substituted benzoyl chlorides, TEA, THF; (i) substituted nicotinic acids, EDC·HCl, DMAP, DMF; (j) substituted phenylpiperidines, CDI, DMA.

Scheme 5[a]



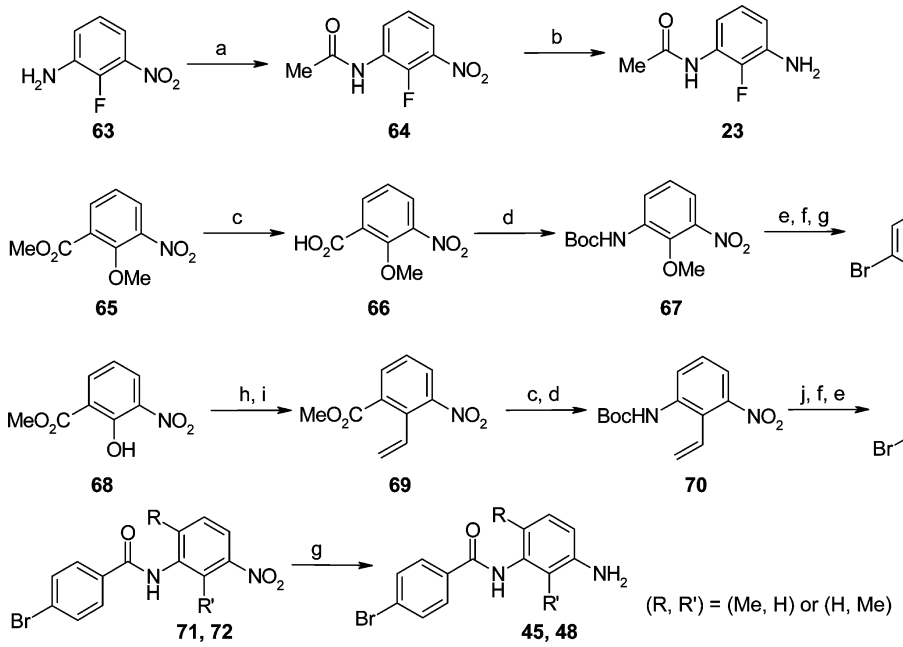
[a]Reagents and conditions: (a) vinadinium salt, BuOH; (b) $NaBH_4$, EtOH, THF; (c) $SOCl_2$; (d) pyrrolidine, K_2CO_3, DMF; (e) concentrated HCl; (f) substituted biphenylcarboxylic acids, EDC·HCl, DMAP, DMF; (g) substituted phenylboronic acids, $Pd(PPh_3)_4$, 2 M Na_2CO_3, THF.

Quinoline derivatives **5a−p**, **5t**, and **5u** were synthesized by the general procedure shown in Scheme 4. Reaction of *N*-(3-aminophenyl)acetamide derivatives **22−25** with a vinadinium salt gave 3-formylquinoline derivatives in one step,[10] which were converted to alcohols **26−29** by reduction with sodium borohydride. Chlorination of **26−29** with thionyl chloride, followed by introduction of the pyrrolidinyl group into **30−33** and subsequent deacylation of **34−37** under acidic conditions, afforded intermediary 7-aminoquinolines **38−41**. Compound **38** was acylated with the appropriate carboxylic acids to produce biphenylcarboxamides **5a−e**. Alternatively, acylation of **39−41** with 4-bromobenzoyl chloride, followed by the Suzuki coupling reaction with **42−44** and 4-fluorophenylboronic acid, afforded biphenylcarboxamides **5p**, **5t**, and **5u**. Phenylnicotinamides **5f−j** were also obtained by acylation of compound **38** with appropriate nicotinic acids. In addition, reaction of **38** and phenylpiperidine derivatives afforded urea analogues **5k−o** using 1,1′-carbonyldiimidazole (CDI).

An alternative route (Scheme 5) was developed in the quinoline series containing an electron-donating group such as methyl, ethyl, and methoxy. The requisite 7-[(4-bromobenzoyl)amino]quinolines **57−60** were prepared from corresponding anilines **45−48** in a manner similar to that described in Scheme 4, i.e., cyclization with a vinadinium salt, reduction, chlorination, and amination. Finally, compounds **57−60** were converted to the desired biphenylcarboxamides **5q−s** and **5v−z** by the Suzuki coupling reaction with various phenylboronic acids or by the peptide coupling reaction using amines **61** and **62**.

dx.doi.org/10.1021/jm201596h | *J. Med. Chem.* 2012, 55, 2353−2366

Scheme 6[a]



[a]Reagents and conditions: (a) Ac_2O, pyridine; (b) 10% Pd/C, cyclohexene, EtOH; (c) 1 M NaOH, MeOH; (d) DPPA, TEA, *t*-BuOH; (e) 4 M HCl–EtOAc; (f) 4-bromobenzoyl chloride, TEA, THF; (g) Fe, $CaCl_2$, aq EtOH; (h) $PhN(SO_2Me)SO_2CF_3$, DIEA, THF; (i) $CH_2{=}CHSn(n\text{-}Bu)_3$, $Pd(PPh_3)_4$, DMF; (j) H_2, 10% Pd/C, EtOH.

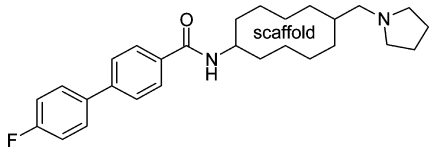
The synthetic route used in preparation of starting materials **23** and **45**–**48** is outlined in Scheme 6. Acetylation of 2-fluoro-3-nitroaniline (**63**), followed by reduction of the nitro group, provided compound **23**. Hydrolysis of methyl 3-nitrobenzoate **65** gave carboxylic acid **66**, which was converted to protected aniline **67** by the Curtius rearrangement. Deprotection of **67**, followed by acylation and successive reduction of the nitro group, afforded compound **46**. The Stille coupling reaction of the triflate prepared from phenol derivative **68** with tributylvinyltin proceeded smoothly to give vinylbenzene derivative **69**. Hydrolysis of ester **69**, followed by the Curtius rearrangement reaction, afforded Boc-protected aniline **70**. Reduction of the double bond and nitro group of **70** was followed by acylation and then deprotection of the furnished compound **47**. Compounds **45** and **48** were prepared by reduction of the corresponding nitrobenzenes **71** and **72** by using iron powder, respectively.

RESULTS AND DISCUSSION

In Vitro Studies. Compounds prepared in this study were evaluated for their binding affinities to hMCHR1 and rMCHR1 and human 5-HT2c receptor by using a stably transfected Chinese hamster ovary (CHO) cell line. Binding assays of the test compounds were performed in the presence of [^{125}I]MCH-(4–19) for MCHR1 or [^{3}H]mesulergine for 5-HT2c. Secondary functional cell-based assays for the inhibition of MCH-stimulated arachidonic acid release from CHO cells were also performed, and the test compounds were found to be antagonists.

Binding affinities for MCHR1 and 5-HT2c receptor of naphthalene, 2,6- and 3,7-substituted quinoline, chromene derivatives, and corresponding dihydronaphthalene derivative **1** are shown in Table 1. Compounds **4** and **5a** exhibited equipotent affinity, and compounds **2** and **3** showed slightly more potent activities for MCHR1 in comparison with **1**. In contrast, compounds **2** and **5a** exhibited less potency for 5-HT2c receptor with submicromolar IC_{50} values. Although the 3,7-substituted quinoline derivative **5a** showed less potent affinity for MCHR1 than **2**, the quinoline scaffold was selected for further optimization in the view of potential increased absorption in the intestine by good solubility in aqueous solution (JP2 solution).

Table 1. In Vitro Binding Affinity and Antagonist Activity[a] and Approximate Solubility of Various Fused Ring Systems



Compd.	scaffold	hMCHR1 Binding IC_{50} (nM)	hMCHR1 AA IC_{50} (nM)[c]	5-HT2c Binding IC_{50} (nM)	Solubility[b] μg/mL
1		1.9	17	0.53	<0.03
2		0.76	9.0	120	0.11
3		0.91	10	3.1	0.17
4		2.7	40	36	-
5a		2.8	9.2	160	1.5

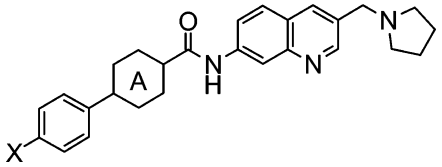
[a]IC_{50} values are calculated with one experiment performed in duplicate, with a standard deviation of 3-fold. [b]The solubility was determined by the addition of 10 mM DMSO solution of the test compound to JP2 until opalescence. [c]Inhibitory activity of MCH-stimulated arachidonic acid (AA) release.

The previous study revealed that small lipophilic groups (X) at the 4′-position of the terminal phenyl ring were important for potential activity.[2] The 4′-substituent (X) selected from hydrogen, methoxy, fluoro, methyl, and chloro groups on the

dx.doi.org/10.1021/jm201596h | J. Med. Chem. 2012, 55, 2353–2366

terminal phenyl ring was investigated for 3,7-substituted quinoline derivatives **5** to evaluate the affinity of MCHR1 as well as 5-HT2c receptor. In addition, the replacement of the A-ring of the biphenyl moiety with a more hydrophilic ring such as pyridine or piperidine was also examined with the goal of achieving high solubility while retaining potency against MCHR1 and selectivity against 5-HT2c. The results of in vitro activities are summarized in Table 2. Incorporation of a

Table 2. In Vitro Binding Affinity and Antagonist Activity of Quinoline Derivatives 5b−o[a]



Compd.	A	X	hMCHR1 Binding IC_{50} (nM)	hMCHR1 AA IC_{50} (nM)[b]	5-HT2c Binding IC_{50} (nM)
5b		H	13	-	310
5c		OMe	3.7	-	>1000
5d		Me	2.2	-	660
5e		Cl	0.74	8.5	630
5f		F	25	-	830
5g		H	73	-	-
5h		OMe	26	-	-
5i		Me	18	-	570
5j		Cl	4.1	14	930
5k		F	35	-	-
5l		H	100	-	-
5m		OMe	48	-	-
5n		Me	23	-	-
5o		Cl	6.6	-	55

[a] IC_{50} values are calculated with one experiment performed in duplicate, with a standard deviation of 3-fold. [b] Inhibitory activity of MCH-stimulated arachidonic acid (AA) release.

chlorine atom into the terminal phenyl group tended to enhance the activity for MCHR1 as previously reported (cf. **5e** vs **5b**, **5j** vs **5g**, and **5o** vs **5l**). Interestingly, the rank order of binding affinity for MCHR1 is the same in three series (Cl > Me > F > OMe > H). Next the A-ring was converted to a hydrophilic moiety with the aim of lowering the molecular lipophilicity and enhancing aqueous solubility. However, contrary to expectation, biphenyl (A = benzene) was more favorable than phenylpyridine (A = pyridine) and phenylpiperidine (A = piperidine) in binding affinities for MCHR1 (e.g., **5e** vs **5j**, **5o**). This result suggested that the lipophilicity of the A-ring should be important for the interaction with hydrophobic amino acid side chains of the receptor. Among these compounds, 4′-chlorobiphenylcarboxamide **5e** exhibited the most potent affinity (IC_{50} = 0.74 nM) and effective antagonistic activity (IC_{50} = 8.5 nM). Moreover, the biphenylcarboxamides **5a−e** showed moderate submicromolar affinities for the 5-HT2c receptor, indicating good receptor selectivity compared to that of **1** (IC_{50} = 0.53 nM). On the basis of these results, the biphenylcarboxamide moiety was selected as the 7-substituent on the quinoline ring.

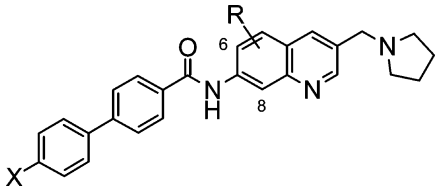
Next we examined the effects of a 6- or an 8-substituent (R) on the quinoline ring (Table 3). Incorporation of a substituent into the 6- or 8-position should effectively stabilize the molecular conformation by steric hindrance or hydrogen bonding with the amide moiety and lead to variation in activity of the MCHR1 and 5-HT2c receptor. Introduction of a methyl, fluoro, or chloro moiety into the 6- or 8-position surprisingly increased the affinities for MCHR1 in spite of their possible conformational change, whereas the incorporation of a methoxy (**5q**) or ethyl (**5r**) group into the 8-position decreased the affinities compared to that of the nonsubstituted analogue. In addition, compounds possessing nano- or subnanomolar MCHR1 affinities exhibited potent functional antagonism with an IC_{50} value of 2.3−12 nM. These results suggest that it is important to have a small lipophilic group such as methyl, fluoro, or chloro at the 6- or 8-position for both high binding affinity and antagonistic activity. As two different active conformations, A (8-F, 8-Me) and B (6-F, 6-Me),[12] could be preferable as illustrated in Figure 1, the existence of a wide space in MCHR1 corresponding to a methylquinolinyl moiety was implicated. Concerning the binding affinity for the 5-HT2c receptor, a detailed SAR study of the 5-HT2c receptor binding by incorporation of a substituent at the 6- or 8-position unfortunately gave obscure results. However, we found that 8-methylquinolines **5v−z** were less potent than the other compounds and, intriguingly, 6-methylquinoline **5s** was more potent than the other 6-substituted compounds (e.g., **5t** and **5u**). In view of their potent affinity for MCHR1 (IC_{50} < 1 nM) and excellent 5-HT2c receptor selectivity (IC_{50} > 1000 nM), the 8-methyl-substituted compounds **5v**, **5x**, and **5z** were selected for further pharmacokinetic evaluation. Among them, compound **5v** had favorable pharmacokinetic profiles in Fischer 344 (F344) rats as shown in Table 4.

In Vivo Studies. Compound **5v**, which exhibited potent binding affinity (IC_{50} = 1.7 nM) for rMCHR1, was assessed for an anorectic effect in the DIO rat model. The results indicated that **5v** induced dose-dependent inhibition of food intake 17 h after administration that reached significance at 1 mg/kg (Figure 2). Moreover, the anorectic effect of **5v** at 3 mg/kg was equipotent to the effect of the centrally acting antiobesity agent sibutramine [1 mg/kg, po (per os, orally)]. The pharmacokinetic study in F344 rats confirmed that **5v** is orally bioavailable and can penetrate the brain [1 mg/kg, po; C_{max} = 610 ng/g, T_{max} = 8 h, AUC = 9343 ng h/g (brain)]. To clarify the selectivity of the anorectic property to MCHR1 antagonism, the effect of **5v** on food intake in MCHR1-deficient mice and wild-type mice was examined. Compound **5v** showed no effect on food intake of MCHR-deficient mice, while it significantly reduced food intake in wild-type mice in a dose-dependent manner (Figure 3). In addition, **5v** showed negligible activity for other receptors, transporters, and enzymes (data not shown). These results indicate that **5v** is orally bioavailable and can penetrate the brain and that its anorectic effect results from its antagonistic activity for MCHR1. Although compound **5v** appeared a favorable candidate for future studies, **5v** was identified as a potent hERG K^+ channel blocker.

CONCLUSION

We replaced the dihydronaphthalene nucleus of **1** with other cores to find a novel MCHR1 antagonist with improved receptor selectivity, especially for the 5-HT2c receptor. The SAR investigation revealed that the 3,7-substituted 8-methylquinoline core was an excellent scaffold compared with

Table 3. In Vitro Binding Affinity and Antagonist Activity of Quinoline Derivatives 5p−z[a]



			hMCHR1		5-HT2c
compd	R	X	binding IC_{50} (nM)	AA IC_{50}[b] (nM)	binding IC_{50} (nM)
5p	8-F	F	0.92	2.3	78
5q	8-OMe	F	110		
5r	8-Et	F	100		>1000
5s	6-Me	F	1.3	10	7.4
5t	6-F	F	1.4	8.4	280
5u	6-Cl	F	1.4	12	240
5v	8-Me	F	0.54	2.8	>1000
5w	8-Me	H	1.8	7.0	760
5x	8-Me	OMe	0.53	4.3	>1000
5y	8-Me	Me	1.0	11	540
5z	8-Me	Cl	0.36	7.6	>1000

[a]IC_{50} values are calculated with one experiment performed in duplicate, with a standard deviation of 3-fold. [b]Inhibitory activity of MCH-stimulated arachidonic acid (AA) release.

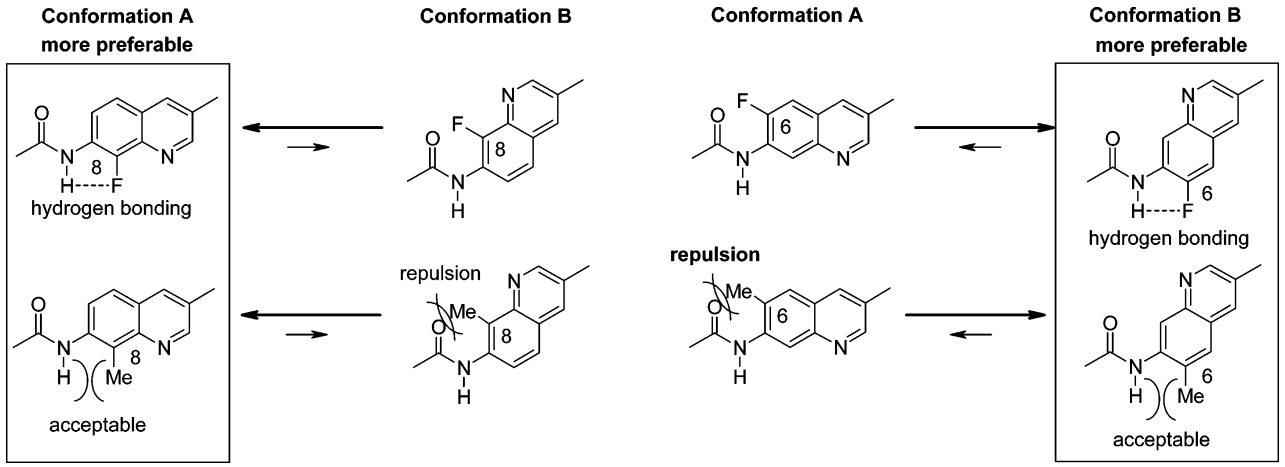


Figure 1. Possible conformational change by introduction of a Me or F group at the 6- or 8-position in the quinoline scaffold.

Table 4. In Vivo Pharmacokinetic Profile of 5v[a]

		iv (0.3 mg/kg)			po (1 mg/kg)		
compd	F^b (%)	$CL_{total}{}^c$ (L/h/kg)	$V_{ss}{}^d$ (L/kg)	$T_{1/2}{}^e$ (h)	$C_{max}{}^f$ (ng/mL)	$T_{max}{}^g$ (h)	AUC^h (ng h/mL)
5v	39	2.4	20	7.7	9.0	4.0	160

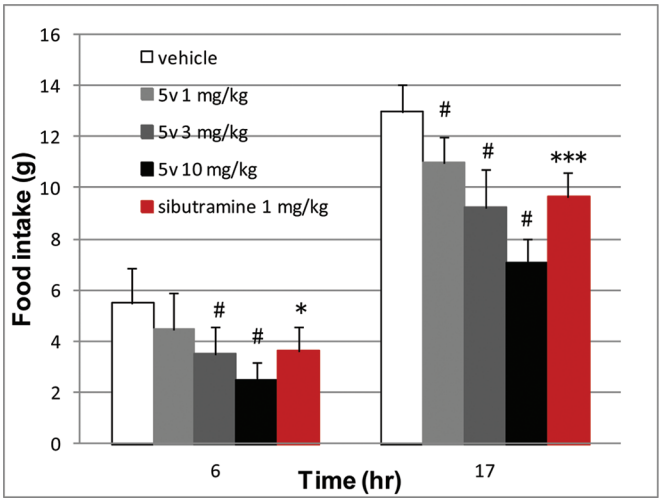
[a]n = 3; F344 rats (male, 16 W). [b]Rat bioavailability. [c]Total clearance. [d]Volume of distribution at the steady state. [e]Half-life. [f]Maximal plasma concentration. [g]Time of maximal concentration. [h]Area under the blood concentration time curve.

dihydronaphthalene in terms of the MCHR1 binding affinity, antagonistic activity, and receptor selectivity. We identified **5v** as the potent nonpeptide MCHR1 antagonist. This compound exhibited subnanomolar binding affinity (IC_{50} = 0.54 nM) and potent antagonistic activity (IC_{50} = 2.8 nM) for MCHR1, while showing significantly reduced affinity for the 5-HT2c receptor (IC_{50} = 1000 nM). Oral administration of **5v** significantly suppressed food intake in DIO rats and did not affect food intake in MCHR1-deficient mice. A pharmacokinetic study confirmed that **5v** was orally bioavailable and could penetrate the brain. These results showed that **5v** is a highly potent, orally active nonpeptide MCHR1 antagonist. Our medicinal chemistry efforts to identify potent MCHR1 antagonists without hERG-associated liabilities will be reported in due course.

EXPERIMENTAL SECTION

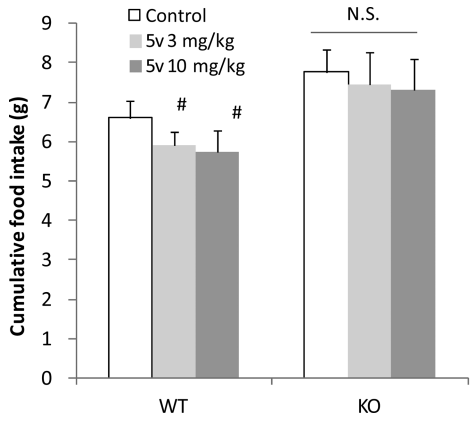
Melting points (mp's) were determined on a Yanagimoto micro melting point apparatus or Buchi melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian Gemini-200 (200 MHz) and JEOL JNM-LA300 (300 MHz) NMR spectrometers. Chemical shifts are reported in δ value (ppm) with tetramethylsilane as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; dd, double doublet; br s, broad singlet; m, multiplet. Coupling constants (J) are reported in hertz. Elemental analyses (C, H, N) were carried out by Takeda Analytical Research Laboratories, Ltd., and the results were within 0.4% of theoretical values. Thin-layer chromatography (TLC) analyses were performed with silica gel 60 F_{254} plate (Merck, article no. 5715), alumina 60 F_{254} plates (type E) and NH

dx.doi.org/10.1021/jm201596h | J. Med. Chem. 2012, 55, 2353−2366



	Inhibition%	
	6h	17h
vehicle	-	-
5v, 1 mg/kg	18.8%	15.5%$^{\#}$
5v, 3 mg/kg	36.7%$^{\#}$	28.9%$^{\#}$
5v, 10 mg/kg	55.7%$^{\#}$	45.8%$^{\#}$
Sibutramine, 1 mg/kg	34.6%*	25.8%***

Figure 2. Effects of **5v** (1, 3, 10 mg/kg, po) and sibutramine (3 mg/kg, po) on food intake in DIO-F344 rats. Cumulative food intake for 6 and 17 h was measured. Each value represents the mean ± SD (n = 6) Key: #, P < 0.025 in the Williams test; *, P < 0.05 in the t test; ***, P < 0.001 in the t test.



		inhibition%
WT	vehicle	-
	5v 3 mg/kg	10.2%$^{\#}$
	5v 10 mg/kg	13.2%$^{\#}$
KO	vehicle	-
	5v 3 mg/kg	4.1%
	5v 10 mg/kg	5.7%

Figure 3. Effects of **5v** on food intake in MCHR1-deficient mice and wild-type mice. The mice were given a high-fat diet. The cumulative food intake was measured for 2 days. Each value represents the mean ± SD (n = 6). Key: #, P < 0.025 in the Williams test.

TLC plates (Fuji Silysia Chemical Ltd.). Chromatographic separations were performed with Merck aluminum oxide 90 (basic, activity III) and NH silica gel (Fuji Silysia Chemical Ltd.). Yields are unoptimized. The purities of all compounds tested in biological systems were assessed as being >95% using elemental analysis.

6-(Methoxycarbonyl)naphthalene-2-carboxylic acid (7). To a solution of 2,6-naphthalenedicarboxylic acid dimethyl ester (**6**) (26.0 g, 0.106 mol) in *N*,*N*-dimethylformamide (DMF) (500 mL) was added 1 M NaOH solution (106 mL, 0.106 mol) portionwise over 30 min at 100 °C. The reaction mixture was stirred at 100 °C for 3 h and concentrated in vacuo. Water was added to the residue, and insoluble solids were filtered off. To the filtrate was added concentrated HCl (8 mL), and the precipitates were filtered. The precipitates were washed with water and recrystallized from MeOH to give the title compound **7** (14.6 g, 60%) as a white powder. ^{1}H NMR (DMSO-d_6): δ 3.94 (3H, s), 8.06 (2H, m), 8.24 (2H, m), 8.69 (2H, s).

***tert*-Butyl 6-(Hydroxymethyl)-2-naphthylcarbamate (9).** To a mixture of **7** (5.00 g, 21.7 mmol), triethylamine (3.93 mL, 28.2 mmol), and *t*-BuOH (65 mL) was added diphenylphosphoryl azide (5.62 mL, 26.1 mmol), and the mixture was stirred at room temperature for 30 min and then at 100 °C for 6 h. Sodium bicarbonate solution was added to the reaction mixture, and extraction with EtOAc was performed. The extract was washed with 10% citric acid solution and brine, dried over Na_2SO_4, and concentrated in vacuo to give crude *tert*-butyl 6-(methoxycarbonyl)-2-naphthylcarbamate (**8**) (3.20 g, 49%).

To an ice-cooled solution of crude **8** (2.89 g, 9.59 mmol) in THF (50 mL) was added lithium aluminum hydride (728 mg, 19.2 mmol), and the mixture was stirred at room temperature for 3 h. To the reaction mixture was slowly added 10% citric acid solution, and extraction with EtOAc was performed. The extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (toluene−EtOAc, 10:1) and crystallized from diisopropyl ether and hexane to give **9** (2.26 g, 78%) as a white powder. ^{1}H NMR (DMSO-d_6): δ 1.51 (9H, s), 4.61 (2H, d, J = 5.7 Hz), 5.24 (1H, t, J = 5.7 Hz), 7.40 (1H, d, J = 8.4 Hz), 7.49 (1H, m), 7.70−7.78 (3H, m), 8.07 (1H, s), 9.52 (1H, s).

***tert*-Butyl 6-(Pyrrolidinylmethyl)-2-naphthylcarbamate (10).** To an ice-cooled mixture of **9** (500 mg, 1.83 mmol), triethylamine (0.254 mL, 1.83 mmol), and THF (9 mL) was added methanesulfonyl chloride (0.142 mL, 1.83 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was filtered, and the filtrate was dried over Na_2SO_4 and concentrated in vacuo to give a colorless oil. To a mixture of the crude mesylate, K_2CO_3 (758 mg, 5.49 mmol), and CH_3CN (9 mL) was added pyrrolidine (0.153 mL, 1.83 mmol), and the mixture was stirred at 60 °C for 3 h. Water was added to the reaction mixture, and extraction with EtOAc was performed. The extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (EtOAc) to give **10** (388 mg, 65%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.55 (9H, s), 1.80 (4H, m), 2.55 (4H, m), 3.74 (2H, s), 6.62 (1H, s), 7.30 (1H, m), 7.45 (1H, m), 7.69 (3H, m), 7.96 (1H, s).

4′-Fluoro-*N*-[6-(1-pyrrolidinylmethyl)-2-naphthyl][1,1′-biphenyl]-4-carboxamide (2). A mixture of **10** (387 mg, 1.19 mmol) and trifluoroacetic acid (TFA) (6 mL) was stirred at room

dx.doi.org/10.1021/jm201596h | J. Med. Chem. 2012, 55, 2353−2366

temperature for 1 h and concentrated in vacuo. Aqueous K_2CO_3 solution was added to the residue, and extraction with EtOAc was performed. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was solidified with hexane to afford 6-(pyrrolidin-1-ylmethyl)naphthalen-2-ylamine (242 mg, 90%). To an ice-cooled mixture of the obtained amine (100 mg, 0.442 mmol), 4′-fluorobiphenylcarboxylic acid (95.5 mg, 0.442 mmol), and 4-(dimethylamino)pyridine (54.0 mg, 0.442 mmol) in DMF (2 mL) was added EDC·HCl (84.7 mg, 0.442 mmol), and the mixture was stirred at room temperature for 16 h. Aqueous K_2CO_3 solution was added to the reaction mixture, and extraction with EtOAc was performed. The extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on alumina with EtOAc and crystallized from EtOAc−diisopropyl ether to give title compound **2** (121 mg, 64%) as a white powder. Mp: 218−220 °C. ^{1}H NMR (DMSO-d_6): δ 1.71 (4H, m), 2.47 (4H, m), 3.72 (2H, s), 7.35 (2H, m), 7.46 (1H, m), 7.75−7.90 (8H, m), 8.11 (2H, d, J = 8.4 Hz), 8.45 (1H, s), 10.47 (1H, s). Anal. Calcd for $C_{28}H_{25}FN_2O$: C, 79.22; H, 5.94; N, 6.60. Found: C, 79.02; H, 6.08; N, 6.63.

Ethyl 3-[3-(Acetylamino)phenoxy]propionate (12). To a mixture of 3-hydroxyacetoanilide (**11**) (25.0 g, 0.165 mol) and ethyl acrylate (50 mL) was added Triton B (40% methanol solution, 3.46 mL, 8.37 mmol), and the reaction mixture was heated at reflux for 2 days. The reaction mixture was concentrated in vacuo. The residue was chromatographed on alumina (EtOAc−hexane, 1:1) and solidified with EtOAc and hexane to give **12** (17.6 g, 43%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 1.27 (3H, t, J = 7.0 Hz), 2.16 (3H, s), 2.77 (2H, t, J = 6.4 Hz), 4.15−4.26 (4H, m), 6.65 (1H, d, J = 7.8 Hz), 6.97 (1H, d, J = 7.8 Hz), 7.16−7.22 (1H, m), 7.26 (1H, s), 7.31 (1H, br s).

3-[3-(Acetylamino)phenoxy]propionic Acid (13). A mixture of **12** (3.82 g, 15.1 mmol), 5 M HCl (15 mL), and AcOH (15 mL) was stirred at 60 °C for 4 h and concentrated in vacuo. Water was added to the residue, and extraction with EtOAc was performed. The extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was solidified from EtOAc and hexane to give **13** (3.10 g, 92%) as a white powder. ^{1}H NMR (DMSO-d_6): δ 2.01 (3H, s), 2.65−2.68 (2H, m), 4.07−4.11 (2H, m), 6.58 (1H, d, J = 7.2 Hz), 7.07−7.18 (3H, m), 7.29 (1H, s), 9.96 (1H, s).

***N*-(4-Oxo-3,4-dihydro-2*H*-chromen-7-yl)acetamide (14).** To a solution of **13** (1.28 g, 5.73 mmol) in nitroethane (15 mL) was added thionyl chloride (0.82 g, 6.88 mmol) in one portion, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was cooled to 5 °C with an ice bath, then anhydrous aluminum chloride (2.29 g, 17.2 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for 30 min. Water was added to the reaction mixture, and extraction with EtOAc was performed. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on alumina, eluting with EtOAc, and solidified from EtOAc and hexane to give **14** (820 mg, 70%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 2.21 (3H, s), 2.78 (2H, t, J = 6.4 Hz), 4.52 (2H, t, J = 6.4 Hz), 6.95 (1H, dd, J = 2.0, 8.4 Hz), 7.45 (1H, s), 7.53 (1H, br s), 7.84 (1H, d, J = 8.4 Hz).

***N*-[3-[(Dimethylamino)methylidene]-4-oxo-3,4-dihydro-2*H*-chromen-7-yl]acetamide (15).** A mixture of **14** (810 mg, 3.95 mmol) and dimethylformamide dimethyl acetal (20 mL) was stirred at 130 °C for 4 h and concentrated in vacuo. A solution of EtOAc and hexane (1:1) was added to the residue, and the precipitates were collected and washed with diisopropyl ether to give **15** (850 mg, 83%) as a yellow powder. ^{1}H NMR ($CDCl_3$): δ 3.04 (3H, s), 3.10 (6H, s), 5.52 (2H, s), 6.44 (1H, d, J = 2.4 Hz), 6.62 (1H, dd, J = 2.4, 8.4 Hz), 7.51 (1H, s), 7.58(1H, s), 7.86 (1H, d, J = 8.4 Hz).

3-(Pyrrolidin-1-ylmethyl)-2*H*-chromen-7-ylamine (16). A solution of **15** (2.00 g, 7.68 mmol) in pyrrolidine (20 mL) was heated at 100 °C for 6 h. The reaction mixture was concentrated in vacuo, and the residue was solidified with water. The resulting solid was collected and dried. The crude solid was suspended with EtOAc, collected, and washed with the same solvent. To an ice-cooled mixture of the obtained solid, AcOH (3.5 mL), and 2-PrOH (7.1 mL) was slowly added $NaBH_4$ (809 mg, 21.4 mmol), and the mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with 1 M HCl (24.9 mL) below 10 °C and then neutralized with 4 M NaOH. The aqueous solution was subjected to extraction with EtOAc, and the extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give *N*-[4-hydroxy-3-(pyrrolidin-1-ylmethyl)-3,4-dihydro-2*H*-chromen-7-yl]acetamide as an oil. A mixture of the obtained oil and 6 N HCl (20 mL) was stirred at 100 °C for 3 h. After cooling, the reaction mixture was neutralized with 4 M NaOH, and the solution was subjected to extraction with EtOAc. The extract was concentrated in vacuo, and the residue was chromatographed on NH-silica gel (EtOAc−hexane, 1:1) to give **16** (449 mg, 54%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.73−1.78 (4H, m), 2.46−2.49 (4H, m), 3.11 (3H, s), 3.65 (2H, br s), 4.74 (2H, s), 6.15−6.22 (3H, m), 6.75 (1H, d, J = 7.8 Hz).

4′-Fluoro-*N*-[3-(1-pyrrolidinylmethyl)-2*H*-chromen-7-yl]-biphenyl-4-carboxamide (3). To a mixture of **16** (70.0 mg, 0.304 mmol), 4′-fluorobiphenylcarboxylic acid (65.7 mg, 0.304 mmol), 4-(dimethylamino)pyridine (37.1 mg, 0.304 mmol), and 1-hydroxybenzotriazole (46.5 mg, 0.304 mmol) in DMF (1.4 mL) was added EDC·HCl (58.3 mg, 0.304 mmol), and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc, washed with K_2CO_3 solution and brine, and concentrated in vacuo. The residue was chromatographed on NH-silica gel, eluting with EtOAc. The resulting solid was triturated with diisopropyl ether to give **3** (82.3 mg, 63%) as a yellow powder. Mp: 186−187 °C. ^{1}H NMR ($CDCl_3$): δ 1.57−1.59 (4H, m), 1.748−1.80 (4H, m), 3.15 (2H, s), 4.81 (2H, s), 6.30 (1H, s), 6.95 (1H, d, J = 8.1 Hz), 7.12−7.21 (4H, m), 7.57−7.60 (2H, m), 7.65(2H, d, J = 8.1 Hz), 7.74 (1H, s), 7.92 (2H, d, J = 8.3 Hz). Anal. Calcd for $C_{27}H_{25}FN_2O_2$: C, 75.68; H, 5.88; N, 6.54; F, 4.43. Found: C, 75.05; H, 5.84; N, 6.48.

***N*-(2-Methyl-6-quinolinyl)acetamide (18).** To a solution of 6-methyl-2-aminoquinoline (**17**) (1.02 g, 6.45 mmol) in pyridine (30 mL) was added acetic anhydride (0.913 mL, 9.67 mmol) in one portion. The reaction mixture was stirred at room temperature for 3 h and concentrated in vacuo. Diisopropyl ether was added to the residue, and the precipitates were filtered and washed with the same solvent to give **18** (1.20 g, 93%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 2.22 (3H, s), 2.71 (3H, s), 7.25 (1H, m), 7.52 (1H, m), 7.95 (2H, m), 8.10 (1H, s), 8.30 (1H, s).

***N*-(2-Methyl-1-oxide-6-quinolinyl)acetamide (19).** To a solution of **18** (1.20 g, 5.99 mmol) in $CHCl_3$ (30 mL) was added *m*-chloroperbenzoic acid (2.48 g, 7.19 mmol) in one portion. The reaction mixture was stirred at room temperature for 3 h and concentrated in vacuo. EtOAc was added to the residue, and the precipitates were collected and washed with the same solvent to give **19** (1.06 g, 82%) as a white powder. ^{1}H NMR (DMSO-d_6): δ 2.12 (3H, s), 2.53 (3H, s), 7.51 (1H, d, J = 8.4 Hz), 7.76 (2H, m), 8.40 (1H, s), 8.48 (1H, d, J = 9.3 Hz), 10.36 (1H, s).

***N*-[2-(Hydroxymethyl)-6-quinolinyl]acetamide (20).** A mixture of **19** (4.64 g, 21.5 mmol) and acetic anhydride (110 mL) was stirred at 80 °C for 4 h and concentrated in vacuo. The residue was chromatographed on alumina, eluting with EtOAc, to give a colorless oil. To an ice-cooled solution of the acetate in MeOH (110 mL) was added 1 M NaOH solution (21.5 mL, 21.5 mmol), and the mixture was stirred at room temperature for 1 h and concentrated in vacuo. The residue was diluted with EtOAc, and the solution was washed with brine and dried over Na_2SO_4. The residue was chromatographed on alumina (EtOAc−MeOH, 5:1) and solidified with EtOAc−diisopropyl ether to give **20** (2.65 g, 57%) as a white powder. ^{1}H NMR (CD_3OD): δ 2.23 (3H, s), 4.89 (2H, s), 7.68 (1H, d, J = 8.7 Hz), 7.78 (1H, d, J = 8.7 Hz), 7.95 (1H, d, J = 8.7 Hz), 8.27 (1H, d, J = 8.7 Hz), 8.33 (1H, s).

***N*-[2-(1-Pyrrolidinylmethyl)-6-quinolinyl]acetamide (21).** To an ice-cooled mixture of **20** (1.00 g, 4.62 mmol) and triethylamine (0.708 mL, 5.09 mmol) in DMF (23 mL) was added methanesulfonyl chloride (0.394 mL, 5.09 mmol), and the mixture was stirred for 30 min. Pyrrolidine (0.772 mL, 9.25 mmol) and K_2CO_3 (1.92 g, 13.9 mmol) were added to the reaction mixture, and the mixture was stirred for 60 °C for 16 h. Aqueous K_2CO_3 solution was added to the reaction mixture, and extraction with EtOAc was performed. The extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The

residue was chromatographed on silica gel, eluting with EtOAc, and solidified with diisopropyl ether and hexane to give **21** (558 mg, 45%). ^{1}H NMR ($CDCl_3$): δ 1.85 (4H, m), 2.24 (3H, s), 2.70 (4H, m), 3.99 (2H, s), 7.58 (2H, m), 7.80 (1H, s), 7.98 (1H, d, J = 9.0 Hz), 8.07 (1H, d, J = 8.4 Hz), 8.29 (1H, s).

4′-Fluoro-*N*-[2- (1-pyrrolidinylmethyl)-6-quinolinyl][1,1′-biphenyl]-4-carboxamide (4). A mixture of **21** (530 mg, 1.97 mmol) and concentrated HCl (10 mL) was stirred at 110 °C for 2 h and concentrated in vacuo. Aqueous K_2CO_3 solution was added to the reaction mixture, and extraction with EtOAc was performed. The extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give crude 2-[(dimethylamino)methyl]quinolin-6-ylamine as a colorless oil (447 mg, quantitative). To an ice-cooled mixture of the oil (334 mg, 1.47 mmol), 4′-fluorobiphenylcarboxylic acid (349 mg, 1.62 mmol), and 4-(dimethylamino)pyridine (180 mg, 1.47 mmol) in DMF (7 mL) was added EDC·HCl (310 mg, 1.62 mmol), and the mixture was stirred at room temperature for 16 h. Aqueous K_2CO_3 solution was added to the reaction mixture, and extraction with EtOAc was performed. The extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on alumina (EtOAc) and crystallized from EtOAc and diisopropyl ether to give **4** (424 mg, 68%) as white crystals. Mp: 190–193 °C. ^{1}H NMR (DMSO-d_6): δ 1.76 (4H, m), 2.61 (4H, m), 3.94 (2H, s), 7.36 (2H, m), 7.59 (1H, d, J = 8.4 Hz), 7.87 (4H, m), 7.99–8.14 (4H, m), 8.30 (1H, d, J = 8.4 Hz), 8.54 (1H, d, J = 2.0 Hz), 10.61 (1H, s). Anal. Calcd for $C_{27}H_{24}FN_3O\cdot0.3H_2O$: C, 75.26; H, 5.75; N, 9.79. Found: C, 75.22; H, 5.72; N, 9.83.

***N*-[3-(Hydroxymethyl)-7-quinolinyl]acetamide (26).** A solution of *N*-(3-aminophenyl)acetamide (**22**) (5.34 g, 35.6 mmol) and vinamidinium bis(tetrafluoroborate) (38.1 g, 107 mmol) in ethanol (370 mL) was heated at reflux for 1 day. After the solution was cooled to room temperature, the solvent was removed by rotary evaporation. Tetrahydrofuran (185 mL) and 1 M HCl (185 mL) were added to the residue, and the mixture was stirred at room temperature for 4 h. The reaction mixture was neutralized with aqueous K_2CO_3 solution, and extraction with EtOAc was performed. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on alumina, eluting with EtOAc, to give 5.68 g of *N*-(3-formylquinolin-7-yl)acetamide as a powder. To an ice-cooled solution of the above product (5.68 g, 26.5 mmol) in ethanol (60 mL) was slowly added sodium borohydride (2.01 g, 53.0 mmol), and the reaction mixture was stirred at room temperature for 3 h. Water was added to the mixture, and the solution was subjected to extraction with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was solidified with EtOAc to give **26** (4.47 g, 78%) as a white powder. ^{1}H NMR (DMSO-d_6): δ 2.12 (3H, s), 4.67 (2H, d, J = 5.4 Hz), 5.40 (1H, t, J = 5.4 Hz), 7.67 (1H, dd, J = 1.8, 9.0 Hz), 7.88 (1H, d, J = 9.0 Hz), 8.12 (1H, s), 8.39 (1H, s), 8.78 (1H, d, J = 1.8 Hz), 10.27 (1H, s).

***N*-[8-Fluoro-3-(hydroxymethyl)-7-quinolinyl]acetamide (27).** Compound **27** was prepared in the same manner as described for **26**. Yield: 77%. ^{1}H NMR (DMSO-d_6): δ 2.16 (3H, s), 4.72 (2H, s), 5.52 (1H, s), 7.76 (1H, d, J = 9.1 Hz), 8.08 (1H, m), 8.25 (1H, s), 8.87 (1H, s), 10.11 (1H, s).

***N*-[6-Fluoro-3-(hydroxymethyl)-7-quinolinyl]acetamide (28).** Compound **28** was prepared in the same manner as described for **26**. Yield: 15%. ^{1}H NMR (DMSO-d_6): δ 2.18 (3H, s), 4.69 (2H, d, J = 5.6 Hz), 5.44 (1H, t, J = 5.6 Hz), 7.83 (1H, d, J = 11.8 Hz), 8.15 (1H, s), 8.67 (1H, d, J = 7.6 Hz), 8.78 (1H, s), 9.98 (1H, s).

***N*-[6-Chloro-3-(hydroxymethyl)-7-quinolinyl]acetamide (29).** Compound **29** was prepared in the same manner as described for **26**. Yield: 69%. ^{1}H NMR (DMSO-d_6): δ 2.12 (3H, s), 7.42 (1H, d, J = 8.8 Hz), 4.66 (2H, s), 7.56 (1H, d, J = 8.8 Hz), 7.94 (1H, s), 9.48 (1H, s), 9.63 (1H, s), 9.81 (1H, s).

***N*-[3-(Chloromethyl)-7-quinolinyl]acetamide Hydrochloride (30).** A mixture of **26** (4.47 g, 20.7 mmol) in thionyl chloride (60 mL) was stirred at room temperature for 2 h and concentrated in vacuo. The resulting precipitates were collected and washed with diisopropyl ether to give **30** (5.55 g, 99%) as a powder. ^{1}H NMR (CD_3OD): δ 2.27 (3H, s), 5.02 (2H, s), 7.82 (1H, dd, J = 1.8, 9.0 Hz), 8.27 (1H, d, J = 9.0 Hz), 9.03 (1H, d, J = 1.8 Hz), 9.14 (1H, s), 9.20 (1H, d, J = 1.8 Hz).

***N*-[3-(Chloromethyl)-8-fluoro-7-quinolinyl]acetamide Hydrochloride (31).** Compound **31** was prepared in the same manner as described for **30**. Yield: quantitative. ^{1}H NMR ($CDCl_3$): δ 2.25 (3H, s), 4.90 (2H, s), 7.74 (1H, d, J = 9.0 Hz), 8.26 (1H, m), 8.40 (1H, s), 8.91 (1H, s).

***N*-[3-(Chloromethyl)-6-fluoro-7-quinolinyl]acetamide Hydrochloride (32).** Compound **32** was prepared in the same manner as described for **30**. Yield: 88%. ^{1}H NMR (CD_3OD): δ 2.33 (3H, s), 5.02 (2H, s), 8.13 (1H, d, J = 11.0 Hz), 9.11 (1H, s), 9.22 (1H, d, J = 2.0 Hz), 9.35 (1H, d, J = 6.8 Hz).

***N*-[6-Chloro-3-(chloromethyl)-7-quinolinyl]acetamide Hydrochloride (33).** Compound **33** was prepared in the same manner as described for **30**. Yield: quantitative. ^{1}H NMR (DMSO-d_6): δ 2.22 (3H, s), 5.02 (2H, s), 8.32 (1H, s), 8.50 (1H, s), 8.61 (1H, s), 9.02 (1H, s), 9.78 (1H, s).

***N*-[3-(Pyrrolidinylmethyl)-7-quinolinyl]acetamide (34).** A mixture of **30** (4.00 g, 14.8 mmol), pyrrolidine (6.16 mL, 73.8 mmol), and K_2CO_3 (6.12 g, 44.3 mmol) in DMF (40 mL) was heated at 80 °C for 2 h. Water was added to the reaction mixture, and extraction with EtOAc was performed. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give **34** (3.97 g, quantitative) as an oil. ^{1}H NMR ($CDCl_3$): δ 1.81 (4H, m), 2.24 (3H, s), 2.56 (4H, m), 3.78 (2H, s), 7.74 (1H, d, J = 8.9 Hz), 7.85 (1H, s), 7.93 (1H, d, J = 8.9 Hz), 7.99–8.09 (2H, m), 8.85 (1H, d, J = 1.9 Hz).

***N*-[8-Fluoro-3-(1-pyrrolidinylmethyl)-7-quinolinyl]-acetamide (35).** Compound **35** was prepared in the same manner as described for **34**. Yield: quantitative. ^{1}H NMR ($CDCl_3$): δ 1.82 (4H, m), 2.31 (3H, s), 2.56 (4H, m), 3.80 (2H, s), 7.58 (1H, dd, J = 1.5, 9.0 Hz), 8.07 (1H, s), 8.57 (1H, m), 8.90 (1H, d, J = 2.1 Hz).

***N*-[6-Fluoro-3-(1-pyrrolidinylmethyl)-7-quinolinyl]-acetamide (36).** Compound **36** was prepared in the same manner as described for **34**. Yield: quantitative. ^{1}H NMR ($CDCl_3$): δ 1.85 (4H, m), 2.30(3H, s), 2.67 (4H, m), 3.87 (2H, s), 7.31 (1H, m), 7.43 (1H, d, J = 11.4 Hz), 7.84 (1H, br s), 8.04 (1H, s), 8.83 (1H, s).

***N*-[6-Chloro-3-(1-pyrrolidinylmethyl)-7-quinolinyl]-acetamide (37).** Compound **37** was prepared in the same manner as described for **34**. Yield: 28%. ^{1}H NMR ($CDCl_3$): δ 1.81 (4H, m), 2.30 (3H, s), 2.55 (4H, m), 3.77 (2H, s), 7.08 (1H, d, J = 8.5 Hz), 7.80 (1H, br s), 7.82 (1H, s), 7.93 (1H, d, J = 1.2 Hz), 8.86 (1H, d, J = 2.2 Hz).

3-(1-Pyrrolidinylmethyl)-7-quinolinylamine Hydrochloride (38). A solution of **34** (3.97 g, 14.8 mmol) in concentrated HCl (40 mL) was heated at 100 °C for 1 h, and the mixture was cooled to room temperature. The solution was poured into aqueous K_2CO_3 solution, and the resulting solution was subjected to extraction with EtOAc. The extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was chromatographed on alumina, eluting with EtOAc. The oil was converted to monohydrochloride salt using 4 M HCl–EtOAc to give **38** (3.70 g, 95%) as a powder. ^{1}H NMR (CD_3OD): δ 2.11 (4H, m), 3.40 (4H, m), 4.54 (2H, m), 7.02 (1H, d, J = 2.4 Hz), 7.19 (1H, dd, J = 9.0, 2.1 Hz), 7.78 (1H, d, J = 9.0 Hz), 8.46 (1H, d, J = 2.4 Hz), 8.74 (1H, d, J = 2.1 Hz).

8-Fluoro-3-(1-pyrrolidinylmethyl)-7-quinolinylamine (39). Compound **39** was prepared in the same manner as described for **38**. Yield: 36%. ^{1}H NMR ($CDCl_3$): δ 1.80 (4H, m), 2.55 (4H, m), 3.75 (2H, s), 4.11 (2H, br s), 7.06 (1H, m), 7.40 (1H, d, J = 8.7 Hz), 7.96 (1H, m), 8.80 (1H, d, J = 2.1 Hz).

6-Fluoro-3-(1-pyrrolidinylmethyl)-7-quinolinylamine (40). Compound **40** was prepared in the same manner as described for **38**. Yield: 82%. ^{1}H NMR ($CDCl_3$): δ 1.80 (4H, m), 2.52 (4H, m), 3.73 (2H, s), 4.24 (2H, br s), 7.32 (2H, m), 7.89 (1H, s), 8.69 (1H, d, J = 1.5 Hz).

6-Chloro-3-(1-pyrrolidinylmethyl)-7-quinolinylamine (41). Compound **41** was prepared in the same manner as described for **38**. Yield: 46%. ^{1}H NMR ($CDCl_3$): δ 1.80 (4H, m), 2.54 (4H, m), 3.72 (2H, s), 4.42 (2H, br s), 7.32 (1H, s), 7.74 (1H, s), 7.85 (1H, m), 8.72 (1H, d, J = 2.2 Hz).

dx.doi.org/10.1021/jm201596h | *J. Med. Chem.* 2012, 55, 2353–2366

4-Bromo-*N*-[8-fluoro-3-(1-pyrrolidinylmethyl)-7-quinolinyl]-benzamide (42). To a solution of **39** (1.31 g, 5.30 mmol) in DMA (26.6 mL) was added 4-bromobenzoyl chloride (1.29 g, 5.90 mmol), and the reaction mixture was stirred for 5 h. The solution was poured into aqueous K_2CO_3 solution, and the resulting solution was subjected to extraction with EtOAc The extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was chromatographed on NH-silica gel, eluting with EtOAc, to give **42** (1.82 g, 80.0%) as a powder. ^{1}H NMR (DMSO-d_6): δ 1.73 (4H, m), 2.51 (4H, m), 3.81 (2H, s), 7.75−7.83 (4H, m), 7.98 (2H, d, J = 8.4 Hz), 8.30 (1H, s), 8.90 (1H, d, J = 2.1 Hz), 10.54 (1H, s).

4-Bromo-*N*-[6-fluoro-3-(1-pyrrolidinylmethyl)-7-quinolinyl]-benzamide (43). Compound **43** was prepared in the same manner as described for **42**. Yield: 38%. ^{1}H NMR (DMSO-d_6): δ 1.73 (4H, m), 2.50 (4H, m), 3.78 (2H, s), 7.78 (2H, d, J = 8.4 Hz), 7.89 (1H, d, J = 11.1 Hz), 7.95 (2H, d, J = 8.4 Hz), 8.22 (1H, s), 8.33 (1H, d, J = 7.5 Hz), 8.82 (1H, d, J = 1.8 Hz), 10.47 (1H, s).

4-Bromo-*N*-[6-chloro-3-(1-pyrrolidinylmethyl)-7-quinolinyl]-benzamide (44). Compound **44** was prepared in the same manner as described for **42**. Yield: 64%. ^{1}H NMR (DMSO-d_6): δ 1.73 (4H, m), 2.50 (4H, m), 3.80 (2H, s), 1.98 (2H, s), 7.46 (2H, d, J = 8.1 Hz), 7.63 (2H, d, J = 8.3 Hz), 8.26 (3H, m), 8.88 (1H, d, J = 1.5 Hz), 10.37 (1H, s).

***N*-[3-(1-Pyrrolidinylmethyl)-7-quinolinyl][1,1′-biphenyl]-4-carboxamide (5b).** To a solution of **38** (150 mg, 0.569 mmol), [1,1′-biphenyl]-4-carboxylic acid (124 mg, 0.626 mmol), 4-(dimethylamino)pyridine (70 mg, 0.569 mmol), and triethylamine (79.1 mL, 0.569 mmol) in DMF (3 mL) was added EDC·HCl (120 mg, 0.626 mmol) with ice-bath cooling, and the mixture was stirred at room temperature for 16 h. The suspension was diluted with EtOAc, and the solution was washed with aqueous K_2CO_3 and brine and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was chromatographed on alumina, eluting with EtOAc, and crystallized from EtOAc and diisopropyl ether to give **5b** (61.5 mg, 26.5%) as a powder. Mp: 192−194 °C. ^{1}H NMR (DMSO-d_6): δ 1.73 (4H, m), 2.50 (4H, m), 3.77 (2H, s), 7.44 (1H, m), 7.53 (2H, m), 7.78 (2H, d, J = 6.9 Hz), 7.88 (2H, d, J = 8.7 Hz), 7.96 (2H, m), 8.14 (3H, m), 8.59 (1H, s), 8.81 (1H, d, J = 2.1 Hz), 10.61 (1H, s). Anal. Calcd for $C_{27}H_{25}N_3O\cdot0.9H_2O$: C, 77.86; H, 6.29; N, 10.09. Found: C, 77.96; H, 6.30; N, 10.21.

4′-Fluoro-*N*-[3-(1-pyrrolidinylmethyl)-7-quinolinyl][1,1′-biphenyl]-4-carboxamide (5a). Compound **5a** was prepared in the same manner as described for **5b**. Yield: 42%. Mp: 210−212 °C. ^{1}H NMR (DMSO-d_6): δ 1.72 (4H, m), 2.50 (4H, m), 3.77 (2H, s), 7.35 (2H, m), 7.85 (4H, m), 7.97 (2H, m), 8.14 (3H, m), 8.59 (1H, d, J = 1.8 Hz), 8.81 (1H, d, J = 2.1 Hz), 10.61 (1H, s). Anal. Calcd for $C_{27}H_{24}FN_3O$: C, 76.21; H, 5.69; N, 9.88. Found: C, 75.99; H, 5.78; N, 9.93.

4′-Methoxy-*N*-[3-(1-pyrrolidinylmethyl)-7-quinolinyl][1,1′-biphenyl]-4-carboxamide (5c). Compound **5c** was prepared in the same manner as described for **5b**. Yield: 49%. Mp: 202−204 °C. ^{1}H NMR (DMSO-d_6): δ 1.72 (4H, m), 2.50 (4H, m), 3.76 (2H, s), 3.82 (3H, s), 7.08 (2H, d, J = 8.7 Hz), 7.74 (2H, d, J = 8.7 Hz), 7.83 (2H, d, J = 8.4 Hz), 7.97 (2H, m), 8.10 (2H, d, J = 8.7 Hz), 8.15 (1H, d, J = 1.2 Hz), 8.59 (1H, d, J = 1.8 Hz), 8.81 (1H, d, J = 2.1 Hz), 10.57 (1H, s). Anal. Calcd for $C_{28}H_{27}N_3O_2\cdot0.3H_2O$: C, 75.93; H, 6.28; N, 9.49. Found: C, 75.99; H, 6.23; N, 9.63.

4′-Methyl-*N*-[3-(1-pyrrolidinylmethyl)-7-quinolinyl][1,1′-biphenyl]-4-carboxamide (5d). Compound **5d** was prepared in the same manner as described for **5b**. Yield: 30%. Mp: 206−208 °C. ^{1}H NMR (DMSO-d_6): δ 1.72 (4H, m), 2.37 (3H, s), 2.50 (4H, m), 3.77 (2H, s), 7.33 (2H, d, J = 7.8 Hz), 7.68 (2H, d, J = 8.4 Hz), 7.85 (2H, d, J = 8.4 Hz), 7.97 (2H, m), 8.11 (2H, d, J = 8.7 Hz), 8.16 (1H, d, J = 1.5 Hz), 8.59 (1H, d, J = 1.8 Hz), 8.81 (1H, d, J = 2.1 Hz), 10.59 (1H, s). Anal. Calcd for $C_{28}H_{27}N_3O\cdot0.3H_2O$: C, 78.77; H, 6.52; N, 9.84. Found: C, 78.77; H, 6.35; N, 9.63.

4′-Chloro-*N*-[3-(1-pyrrolidinylmethyl)-7-quinolinyl][1,1′-biphenyl]-4-carboxamide (5e). Compound **5e** was prepared in the same manner as described for **5b**. Yield: 50%. Mp: 217−220 °C. ^{1}H NMR (DMSO-d_6): δ 1.72 (4H, m), 2.50 (4H, m), 3.77 (2H, s), 7.58 (2H, d, J = 8.7 Hz), 7.82 (2H, d, J = 8.4 Hz), 7.88 (2H, d, J = 8.4 Hz), 7.97 (2H, m), 8.13 (2H, d, J = 8.7 Hz), 8.16 (1H, d, J = 1.2 Hz), 8.59 (1H, s), 8.81 (1H, d, J = 2.1 Hz), 10.62 (1H, s). Anal. Calcd for $C_{27}H_{24}ClN_3O$: C, 73.38; H, 5.47; N, 9.51. Found: C, 73.35; H, 5.45; N, 9.53.

6-(4-Fluorophenyl)-*N*-[3-(1-pyrrolidinylmethyl)-7-quinolinyl]nicotinamide (5f). Compound **5f** was prepared in the same manner as described for **5b**. Yield: 64%. Mp: 218−220 °C. ^{1}H NMR (DMSO-d_6): δ 1.72 (4H, m), 2.50 (4H, m), 3.76 (2H, s), 7.38 (2H, m), 7.96 (2H, m), 8.18 (2H, m), 8.28 (2H, m), 8.45 (1H, dd, J = 8.4, 2.4 Hz), 8.59 (1H, s), 8.82 (1H, d, J = 2.1 Hz), 9.25 (1H, d, J = 1.5 Hz), 10.76 (1H, s). Anal. Calcd for $C_{26}H_{23}FN_4O\cdot0.5H_2O$: C, 71.71; H, 5.55; N, 12.87. Found: C, 71.55; H, 5.59; N, 12.84.

6-Phenyl-*N*-[3-(1-pyrrolidinylmethyl)-7-quinolinyl]-nicotinamide (5g). Compound **5g** was prepared in the same manner as described for **5b**. Yield: 32%. Mp: 208−210 °C. ^{1}H NMR (DMSO-d_6): δ 1.72 (4H, m), 2.50 (4H, m), 3.76 (2H, s), 7.55 (3H, m), 7.96 (2H, m), 8.20 (4H, m), 8.45 (1H, dd, J = 8.4, 2.4 Hz), 8.59 (1H, s), 8.82 (1H, d, J = 2.1 Hz), 9.26 (1H, d, J = 1.8 Hz), 10.76 (1H, s). Anal. Calcd for $C_{26}H_{24}N_4O\cdot0.5H_2O$: C, 74.80; H, 6.04; N, 13.42. Found: C, 74.95; H, 5.98; N, 13.35.

6-(4-Methoxyphenyl)-*N*-[3-(1-pyrrolidinylmethyl)-7-quinolinyl]nicotinamide (5h). Compound **5h** was prepared in the same manner as described for **5b**. Yield: 32%. Mp: 246−248 °C. ^{1}H NMR (DMSO-d_6): δ 1.72 (4H, m), 2.50 (4H, m), 3.77 (2H, s), 3.85 (3H, s), 7.10 (2H, d, J = 9.3 Hz), 7.96 (2H, m), 8.11 (1H, d, J = 8.1 Hz), 8.19 (3H, m), 8.40 (1H, dd, J = 8.4, 2.1 Hz), 8.58 (1H, s), 8.82 (1H, d, J = 2.1 Hz), 9.21 (1H, d, J = 1.5 Hz), 10.72 (1H, s). Anal. Calcd for $C_{27}H_{26}N_4O_2$: C, 73.95; H, 5.98; N, 12.78. Found: C, 73.66; H, 6.04; N, 12.74.

6-(4-Methylphenyl)-*N*-[3-(1-pyrrolidinylmethyl)-7-quinolinyl]nicotinamide (5i). Compound **5i** was prepared in the same manner as described for **5b**. Yield: 64%. Mp: 226−228 °C. ^{1}H NMR (DMSO-d_6): δ 1.72 (4H, m), 2.39 (3H, s), 2.50 (4H, m), 3.77 (2H, s), 7.36 (2H, d, J = 8.1 Hz), 7.96 (2H, m), 8.11 (2H, d, J = 8.1 Hz), 8.17 (2H, m), 8.42 (1H, dd, J = 8.4, 2.4 Hz), 8.59 (1H, s), 8.82 (1H, d, J = 2.1 Hz), 9.23 (1H, m), 10.74 (1H, s). Anal. Calcd for $C_{27}H_{26}N_4O$: C, 76.75; H, 6.20; N, 13.26. Found: C, 76.47; H, 6.29; N, 13.13.

6-(4-Chlorophenyl)-*N*-[3-(1-pyrrolidinylmethyl)-7-quinolinyl]nicotinamide (5j). Compound **5j** was prepared in the same manner as described for **5b**. Yield: 54%. Mp: 223−225 °C. ^{1}H NMR (DMSO-d_6): δ 1.72 (4H, m), 2.50 (4H, m), 3.77 (2H, s), 7.62 (2H, d, J = 9.0 Hz), 7.96 (2H, m), 8.17−8.26 (4H, m), 8.47 (1H, dd, J = 8.4, 2.4 Hz), 8.59 (1H, s), 8.82 (1H, d, J = 2.1 Hz), 9.26 (1H, d, J = 1.5 Hz), 10.77 (1H, s). Anal. Calcd for $C_{26}H_{23}ClN_4O$: C, 70.50; H, 5.23; N, 12.65; Cl, 8.00. Found: C, 70.28; H, 5.20; N, 12.91.

4-Phenyl-*N*-[3-(1-pyrrolidinylmethyl)-7-quinolinyl]-1-piperidinecarboxamide (5l). To a solution of **38** (150 mg, 0.569 mmol) and triethylamine (79.1 μL, 0.569 mmol) in DMA (3 mL) was added 1,1′-carbonyldiimidazole (111 mg, 0.682 mmol) at 0 °C. After this solution was stirred for 1 h, 4-phenylpiperidine hydrochloride (124 mg, 0.626 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, and the solution was washed with aqueous K_2CO_3 and brine. The extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was chromatographed on alumina, eluting with EtOAc, and crystallized from EtOAc and diisopropyl ether to give **5l** (18.8 mg, 8%) as a powder. Mp: 222−224 °C. ^{1}H NMR (DMSO-d_6): δ 1.59−1.67 (2H, m), 1.71 (4H, m), 1.81−1.85 (2H, m), 2.50 (4H, m), 2.77 (1H, m), 2.94 (2H, m), 3.73 (2H, s), 4.32−4.36 (2H, m), 7.18−7.34 (5H, m), 7.73−7.82 (2H, m), 8.07 (1H, s), 8.16 (1H, d, J = 2.1 Hz), 8.73 (1H, d, J = 2.4 Hz), 8.87 (1H, s). Anal. Calcd for $C_{26}H_{30}N_4O$: C, 75.33; H, 7.29; N, 13.52. Found: C, 75.15; H, 7.35; N, 13.47.

4-(4-Fluorophenyl)-*N*-[3-(1-pyrrolidinylmethyl)-7-quinolinyl]-1-piperidinecarboxamide (5k). Compound **5k** was prepared in the same manner as described for **5l**. Yield: 38%. Mp: 239−241 °C. ^{1}H NMR (DMSO-d_6): δ 1.56−1.64 (2H, m), 1.71 (4H, m), 1.80−1.84 (2H, m), 2.47 (4H, m), 2.78 (1H, m), 2.92 (2H, m), 3.73 (2H, s), 4.31−4.36 (2H, m), 7.12 (2H, m), 7.32 (2H, m), 7.73−7.82 (2H, m), 8.06 (1H, d, J = 1.5 Hz), 8.16 (1H, d, J = 2.1 Hz), 8.72 (1H, d, J = 1.8

Hz), 8.87 (1H, s). Anal. Calcd for $C_{26}H_{29}FN_4O$: C, 72.20; H, 6.76; N, 12.95. Found: C, 71.94; H, 6.77; N, 12.90.

4-(4-Methoxyphenyl)-*N*-[3-(1-pyrrolidinylmethyl)-7-quinolinyl]-1-piperidinecarboxamide (5m). Compound **5m** was prepared in the same manner as described for **5l**. Yield: 29%. Mp: 241−243 °C. ^{1}H NMR (DMSO-d_6): δ 1.55−1.62 (2H, m), 1.71 (4H, m), 1.78−1.82 (2H, m), 2.49 (4H, m), 2.71 (1H, m), 2.91 (2H, m), 3.72 (5H, m), 4.31−4.35 (2H, m), 6.87 (2H, d, J = 8.7 Hz), 7.19 (2H, d, J = 8.7 Hz), 7.77 (2H, m), 8.07 (1H, s), 8.16 (1H, s), 8.72 (1H, d, J = 2.1 Hz), 8.88 (1H, s). Anal. Calcd for $C_{27}H_{32}N_4O_2$: C, 72.94; H, 7.26; N, 12.60. Found: C, 72.75; H, 7.30; N, 12.56.

4-(4-Methylphenyl)-*N*-[3-(1-pyrrolidinylmethyl)-7-quinolinyl]-1-piperidinecarboxamide (5n). Compound **5n** was prepared in the same manner as described for **5l**. Yield: 34%. Mp: 244−246 °C. ^{1}H NMR (DMSO-d_6): δ 1.55−1.65 (2H, m), 1.71 (4H, m), 1.78−1.82 (2H, m), 2.26 (3H, s), 2.47 (4H, m), 2.72 (1H, m), 2.92 (2H, m), 3.72 (2H, s), 4.31−4.35 (2H, m), 7.09−7.17 (4H, m), 7.73−7.82 (2H, m), 8.07 (1H, s), 8.15 (1H, d, J = 1.8 Hz), 8.72 (1H, d, J = 1.8 Hz), 8.88 (1H, s). Anal. Calcd for $C_{27}H_{32}N_4O$: C, 75.67; H, 7.53; N, 13.07. Found: C, 75.45; H, 7.56; N, 13.03.

4-(4-Chlorophenyl)-*N*-[3-(1-pyrrolidinylmethyl)-7-quinolinyl]-1-piperidinecarboxamide (5o). Compound **5o** was prepared in the same manner as described for **5l**. Yield: 37%. Mp: 249−251 °C. ^{1}H NMR (DMSO-d_6): δ 1.56−1.64 (2H, m), 1.71 (4H, m), 1.80−1.84 (2H, m), 2.47 (4H, m), 2.79 (1H, m), 2.92 (2H, m), 3.72 (2H, s), 4.31−4.36 (2H, m), 7.30−7.38 (4H, m), 7.72−7.82 (2H, m), 8.06 (1H, s), 8.16 (1H, s), 8.72 (1H, d, J = 1.8 Hz), 8.87 (1H, s). Anal. Calcd for $C_{26}H_{29}ClN_4O{\cdot}0.3H_2O$: C, 68.73; H, 6.57; N, 12.33. Found: C, 68.67; H, 6.52; N, 12.33.

4′-Fluoro-*N*-[8-fluoro-3-(1-pyrrolidinylmethyl)-7-quinolinyl]-[1,1′-biphenyl]-4-carboxamide (5p). To a solution of **42** (200 mg, 0.467 mmol), 4-fluorophenyboronic acid (98.0 mg, 0.700 mmol), and 2 M Na_2CO_3 (0.70 mL, 1.40 mmol) in 1, 2-dimethoxyethane (4.67 mL) was added tetrakis(triphenylphosphine)palladium (27.0 mg, 0.0234 mmol), and the reaction mixture was heated to 85 °C for 5 h under nitrogen. The reaction mixture was poured into 1 M NaOH, and the solution was subjected to extraction with THF. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on NH-silica gel, eluting with EtOAc, to give white solids. Recrystallization from EtOAc and diisopropyl ether gave **5p** (72.3 mg, 35%) as crystals. Mp: 190−192 °C. ^{1}H NMR (DMSO-d_6): δ 1.74 (4H, m), 2.51 (4H, m), 3.83 (2H, s), 7.35 (2H, m), 7.80−7.90 (6H, m), 8.14 (2H, d, J = 8.4 Hz), 8.31 (1H, s), 8.90 (1H, d, J = 1.8 Hz), 10.49 (1H, s). Anal. Calcd for $C_{27}H_{23}F_2N_3O.0.3H_2O$: C, 72.24; H, 5.30; N, 9.36. Found: C, 72.04; H, 5.13; N, 9.17.

4′-Fluoro-*N*-[6-fluoro-3-(1-pyrrolidinylmethyl)-7-quinolinyl]-[1,1′-biphenyl]-4-carboxamide (5t). Compound **5t** was prepared in the same manner as described for **5p**. Yield: 53%. Mp: 198−200 °C. ^{1}H NMR (DMSO-d_6): δ 1.73 (4H, m), 2.50 (4H, m), 3.80 (2H, s), 7.36 (2H, m), 7.82−7.93 (5H, m), 8.12 (2H, d, J = 8.4 Hz), 8.23 (1H, s), 8.37 (1H, d, J = 8.1 Hz), 8.83 (1H, s), 10.45 (1H, s). Anal. Calcd for $C_{27}H_{23}F_2N_3O$: C, 73.12; H, 5.23; N, 9.47. Found: C, 72.92; H, 5.18; N, 9.36.

4′-Fluoro-*N*-[6-chloro-3-(1-pyrrolidinylmethyl)-7-quinolinyl]-[1,1′-biphenyl]-4-carboxamide (5u). Compound **5u** was prepared in the same manner as described for **5p**. Yield: 53%. Mp: 188 °C. ^{1}H NMR (DMSO-d_6): δ 1.73 (4H, m), 2.50 (4H, m), 3.80 (2H, s), 7.36 (2H, m), 7.82 (2H, m), 7.87 (2H, m), 8.14 (2H, d, J = 7.8 Hz), 8.26 (1H, s), 8.29 (2H, d, J = 6.8 Hz), 8.89 (1H, s), 10.32 (1H, s). Anal. Calcd for $C_{27}H_{23}ClFN_3O$: C, 70.51; H, 5.04; N, 9.14; Cl, 7.71; F, 4.13. Found: C, 70.37; H, 5.01; N, 8.73.

4-Bromo-*N*-[3-(hydroxymethyl)-8-methyl-7-quinolinyl]-benzamide (49). Compound **49** was prepared in the same manner as described for **26**. Yield: 80%. ^{1}H NMR (DMSO-d_6): δ 2.65 (3H, s), 4.74 (2H, d, J = 5.4 Hz), 5.48 (1H, t, J = 5.4 Hz), 7.60 (1H, d, J = 8.7 Hz), 7.78 (2H, d, J = 8.1 Hz), 7.82 (1H, d, J = 8.7 Hz), 7.99 (2H, d, J = 8.1 Hz), 8.22 (1H, d, J = 1.5 Hz), 8.89 (1H, d, J = 1.5 Hz), 10.31 (1H, s).

4-Bromo-*N*-[3-(hydroxymethyl)-8-methoxy-7-quinolinyl]-benzamide (50). Compound **50** was prepared in the same manner as described for **26**. Yield: 55%. ^{1}H NMR (DMSO-d_6): δ 4.11 (3H, s), 4.73 (2H, d, J = 5.7 Hz), 5.48 (1H, t, J = 5.4 Hz), 7.71−7.78 (3H, m), 7.96−8.03 (3H, m), 8.22 (1H, s), 8.87 (1H, d, J = 1.8 Hz), 10.02 (1H, s).

4-Bromo-*N*-[8-ethyl-3-(hydroxymethyl)-7-quinolinyl]-benzamide (51). Compound **51** was prepared in the same manner as described for **26**. Yield: 28%. ^{1}H NMR (DMSO-d_3): δ 1.15(3H, t, J = 7.4 Hz), 3.28 (2H, q, J = 7.0 Hz), 4.74 (2H, s), 5.46 (1H, t, J = 3.6 Hz), 7.54 (2H, d, J = 8.8 Hz), 7.72−7.80 (3H, m), 7.84−8.00 (2H, m), 8.22 (1H, s), 8.89 (1H, d, J = 1.8 Hz), 10.25 (1H, s).

4-Bromo-*N*-[3-(hydroxymethyl)-6-methyl-7-quinolinyl]-benzamide (52). Compound **52** was prepared in the same manner as described for **26**. Yield: 85%. ^{1}H NMR (DMSO-d_6): δ 2.44 (3H, s), 4.71 (2H, d, J = 4.8 Hz), 5.46 (1H, m), 7.78 (2H, d, J = 8.4 Hz), 7.84 (1H, s), 7.98 (2H, d, J = 8.4 Hz), 8.07 (1H, s), 8.15 (1H, m), 8.80 (1H, m), 10.18 (1H, s).

4-Bromo-*N*-[3-(chloromethyl)-8-methyl-7-quinolinyl]-benzamide hHydrochloride (53). Compound **53** was prepared in the same manner as described for **30**. Yield: 67%. ^{1}H NMR (CD_3OD): δ 2.74 (3H, s), 5.09 (2H, s), 7.76 (2H, d, J = 6.6 Hz), 7.97 (2H, d, J = 6.6 Hz), 8.09 (1H, d, J = 9.0 Hz), 8.24 (1H, d, J = 9.0 Hz), 9.25 (1H, d, J = 2.1 Hz), 9.26 (1H, d, J = 2.1 Hz).

4-Bromo-*N*-[3-(chloromethyl)-8-methoxy-7-quinolinyl]-benzamide Hydrichloride (54). Compound **54** was prepared in the same manner as described for **30**. Yield: quantitative. ^{1}H NMR (CD_3OD): δ 4.09 (3H, s), 5.07 (2H, s), 7.76 (2H, d, J = 8.4 Hz), 7.96 (2H, d, J = 8.8 Hz), 8.11 (1H, d, J = 9.2 Hz), 8.52 (1H, d, J = 9.0 Hz), 9.24 (2H, s).

4-Bromo-*N*-[3-(chloromethyl)-8-ethyl-7-quinolinyl]-benzamide Hydrochloride (55). Compound **55** was prepared in the same manner as described for **30**. Yield: 78%. ^{1}H NMR (CD_3OD): δ 1.30 (3H, t, J = 7.6 Hz), 3.33 (2H, q, J = 7.4 Hz), 5.10 (2H, s), 7.75 (2H, d, J = 8.8 Hz), 7.96 (2H, d, J = 8.8 Hz), 8.14 (1H, d, J = 8.8 Hz), 8.26 (1H, d, J = 8.8 Hz), 9.28−9.30 (2H, m).

4-Bromo-*N*-[3-(chloromethyl)-6-methyl-7-quinolinyl]-benzamide Hydrochloride (56). Compound **56** was prepared in the same manner as described for **30**. Yield: quantitative. ^{1}H NMR (DMSO-d_6): δ 2.55 (3H, s), 5.08 (2H, s), 7.79 (2H, d, J = 8.4 Hz), 8.00 (2H, d, J = 8.4 Hz), 8.10 (1H, s), 8.50 (1H, s), 8.80 (1H, s), 9.16 (1H, s), 10.34 (1H, s).

4-Bromo-*N*-[8-methyl-3-(1-pyrrolidinylmethyl)-7-quinolinyl]benzamide (57). Compound **57** was prepared in the same manner as described for **34**. Yield: 72%. ^{1}H NMR (DMSO-d_6): δ 1.72 (4H, m), 2.50 (4H, m), 2.64 (3H, s), 3.80 (2H, s), 7.59 (1H, d, J = 8.7 Hz), 7.78 (2H, d, J = 9.0 Hz), 7.82 (1H, d, J = 8.7 Hz), 7.98 (2H, d, J = 9.0 Hz), 8.22 (1H, d, J = 2.1 Hz), 8.88 (1H, d, J = 2.1 Hz), 10.32 (1H, s).

4-Bromo-*N*-[8-methoxy-3-(1-pyrrolidinylmethyl)-7-quinolinyl]benzamide (58). Compound **58** was prepared in the same manner as described for **34**. Yield: 88%. ^{1}H NMR (DMSO-d_6): δ 1.72 (4H, m), 2.50−2.54 (4H, m), 3.78 (2H, s), 4.11 (3H, s), 7.69−7.79 (3H, m), 7.96−8.00 (3H, m), 8.21 (1H, d, J = 1.8 Hz), 8.85 (1H, d, J = 1.8 Hz), 10.03 (1H, s).

4-Bromo-*N*-[8-ethyl-3-(1-pyrrolidinylmethyl)-7-quinolinyl]-benzamide (59). Compound **59** was prepared in the same manner as described for **34**. Yield: 91%. ^{1}H NMR (DMSO-d_6): δ 1.15 (3H, t, J = 7.2 Hz), 1.73−1.79 (4H, m), 2.50−2.51 (4H, m), 3.27 (2H, q, J = 7.4 Hz), 3.80 (2H, s), 7.54 (1H, d, J = 8.8 Hz), 7.76−7.85 (3H, m), 7.99 (2H, d, J = 8.4 Hz), 8.22 (1H, d, J = 2.2 Hz), 8.88 (1H, d, J = 2.2 Hz), 10.28 (1H, s).

4-Bromo-*N*-[6-methyl-3-(1-pyrrolidinylmethyl)-7-quinolinyl]benzamide (60). Compound **60** was prepared in the same manner as described for **34**. Yield: 56%. ^{1}H NMR (DMSO-d_6): δ 1.71 (4H, m), 2.44 (3H, s), 2.48 (4H, m), 3.76 (2H, s), 7.77 (2H, d, J = 8.8 Hz), 7.83 (1H, s), 7.97 (2H, d, J = 8.8 Hz), 8.06 (1H, s), 8.12 (1H, m), 8.78 (1H, d, J = 2.2 Hz), 10.16 (1H, s).

8-Methyl-3-(1-pyrrolidinylmethyl)-7-quinolinamine (61). Compound **61** was prepared in the same manner as described for **38**. Yield: quantitative. ^{1}H NMR ($CDCl_3$): δ 1.79 (4H, m), 2.54 (4H, m), 2.59 (3H, s), 3.74 (2H, s), 3.98 (2H, s), 6.98 (1H, d, J = 8.7 Hz),

dx.doi.org/10.1021/jm201596h | J. Med. Chem. 2012, 55, 2353−2366

7.47 (1H, d, J = 8.7 Hz), 7.91 (1H, d, J = 2.2 Hz), 8.76 (1H, d, J = 2.2 Hz).

6-Methyl-3-(1-pyrrolidinylmethyl)-7-quinolinamine Hydrochloride (62). Compound **62** was prepared in the same manner as described for **38**. Yield: 94%. ^{1}H NMR (CD_3OD): δ 2.05−2.22 (4H, m), 3.34−3.52 (4H, m), 4.57 (2H, s), 7.13 (1H, s), 7.75 (1H, s), 8.48 (1H, s), 8.73 (1H, m).

4′-Fluoro-*N*-[8-methyl-3-(1-pyrrolidinylmethyl)-7-quinolinyl][1,1′-biphenyl]-4-carboxamide (5v). Compound **5v** was prepared in the same manner as described for **5a**. Yield: 37%. Mp: 220−222 °C. ^{1}H NMR (DMSO-d_6): δ 1.73 (4H, m), 2.50 (4H, m), 2.67 (3H, s), 3.80 (2H, s), 7.35 (2H, m), 7.62 (1H, d, J = 8.7 Hz), 7.81−7.87 (5H, m), 8.14 (2H, d, J = 8.1 Hz), 8.22 (1H, d, J = 1.8 Hz), 8.88 (1H, d, J = 1.8 Hz), 10.28 (1H, s). Anal. Calcd for $C_{28}H_{26}FN_3O$: C, 76.51; H, 5.96; N, 9.56. Found: C, 76.24; H, 6.04; N, 9.57.

4′-Methoxy-*N*-[8-methyl-3-(1-pyrrolidinylmethyl)-7-quinolinyl][1,1′-biphenyl]-4-carboxamide (5x). Compound **5x** was prepared in the same manner as described for **5a**. Yield: 44%. Mp: 210−213 °C. ^{1}H NMR (DMSO-d_6): δ 1.73 (4H, m), 2.50 (4H, m), 2.67 (3H, s), 3.80 (2H, s), 3.82 (3H, s), 7.08 (2H, d, J = 8.7 Hz), 7.62 (1H, d, J = 8.7 Hz), 7.74 (2H, d, J = 8.7 Hz), 7.83 (3H, m), 8.12 (2H, d, J = 8.4 Hz), 8.21 (1H, d, J = 2.1 Hz), 8.88 (1H, d, J = 1.8 Hz), 10.23 (1H, s). Anal. Calcd for $C_{29}H_{29}N_3O_2\cdot 0.7H_2O$: C, 75.04; H, 6.60; N, 9.05. Found: C, 74.86; H, 6.40; N, 8.73.

4′-Chloro-*N*-[8-methyl-3-(1-pyrrolidinylmethyl)-7-quinolinyl][1,1′-biphenyl]-4-carboxamide (5z). Compound **5z** was prepared in the same manner as described for **5a**. Yield: 18%. Mp: 227−279 °C. ^{1}H NMR (DMSO-d_6): δ 1.73 (4H, m), 2.50 (4H, m), 2.67 (3H, s), 3.81 (2H, s), 7.57 (2H, d, J = 8.7 Hz), 7.62 (1H, d, J = 9.0 Hz), 7.81−7.89 (5H, m), 8.15 (2H, d, J = 8.1 Hz), 8.23 (1H, s), 8.88 (1H, d, J = 2.1 Hz), 10.29 (1H, s). Anal. Calcd for $C_{28}H_{26}ClN_3O\cdot 0.3H_2O$: C, 72.89; H, 5.81; N, 9.11. Found: C, 72.95; H, 5.78; N, 9.17.

***N*-[8-Methyl-3-(1-pyrrolidinylmethyl)-7-quinolinyl][1,1′-biphenyl]-4-carboxamide (5w).** Compound **5w** was prepared in the same manner as described for **5l**. Yield: 69%. Mp: 184−186 °C. ^{1}H NMR (DMSO-d_6): δ 1.73 (4H, m), 2.50 (4H, m), 2.67 (3H, s), 3.81 (2H, s), 7.46 (1H, m), 7.53 (2H, m), 7.63 (1H, d, J = 9.0 Hz), 7.77−7.88 (5H, m), 8.15 (2H, d, J = 8.7 Hz), 8.22 (1H, d, J = 1.8 Hz), 8.88 (1H, d, J = 2.1 Hz), 10.28 (1H, s). Anal. Calcd for $C_{28}H_{27}N_3O\cdot 0.3H_2O$: C, 78.77; H, 6.52; N, 9.84. Found: C, 78.67; H, 6.33; N, 9.57.

4′-Methyl-*N*-[8-methyl-3-(1-pyrrolidinylmethyl)-7-quinolinyl][1,1′-biphenyl]-4-carboxamide (5y). Compound **5y** was prepared in the same manner as described for **5l**. Yield: 68%. Mp: 177−179 °C. ^{1}H NMR (DMSO-d_6): δ 1.72 (4H, m), 2.37 (3H, s), 2.50 (4H, m), 2.67 (3H, s), 3.80 (2H, s), 7.34 (2H, m), 7.61−7.72 (3H, m), 7.81−7.85 (2H, m), 7.93 (1H, d, J = 8.1 Hz), 8.13 (2H, d, J = 8.1 Hz), 8.20 (1H, m), 8.88 (1H, d, J = 1.8 Hz), 10.27 (1H, s). Anal. Calcd for $C_{29}H_{29}N_3O\cdot 0.6H_2O$: C, 78.03; H, 6.82; N, 9.41. Found: C, 77.97; H, 6.53; N, 9.26.

4′-Fluoro-*N*-[8-methoxy-3-(1-pyrrolidinylmethyl)-7-quinolinyl][1,1′-biphenyl]-4-carboxamide (5q). Compound **5q** was prepared in the same manner as described for **5p**. Yield: 70%. Mp: 142−144 °C. ^{1}H NMR (DMSO-d_6): δ 1.74 (4H, m), 2.48−2.54 (4H, m), 3.81 (2H, s), 4.13 (3H, s), 7.30−7.39 (2H, m), 7.73 (1H, d, J = 8.6 Hz), 7.79−7.87 (4H, m), 8.04−8.15 (3H, m), 8.23 (1H, d, J = 2.2 Hz), 8.86 (1H, d, J = 2.2 Hz), 9.97 (1H, s). Anal. Calcd for $C_{28}H_{26}FN_3O_2\cdot 0.25H_2O$: C, 73.10; H, 5.81; N, 9.13. Found: C, 73.32; H, 5.67; N, 9.34.

***N*-[8-Ethyl-3-(1-pyrrolidinylmethyl)-7-quinolinyl]-4′-fluoro-[1,1′-biphenyl]-4-carboxamide (5r).** Compound **5r** was prepared in the same manner as described for **5p**. Yield: 70%. Mp: 266−267 °C. ^{1}H NMR (DMSO-d_6): δ 1.17 (3H, t, J = 7.2 Hz), 1.73 (4H, m), 2.50 (4H, m), 2.91−3.35 (2H, m), 3.80 (2H, s), 7.31−7.40 (2H, m), 7.57 (1H, d, J = 8.4 Hz), 7.80−7.88 (5H, m), 8.14 (2H, d, J = 8.4 Hz), 8.22 (1H, d, J = 1.8 Hz), 8.90 (1H, d, J = 1.8 Hz), 10.25 (1H, s). Anal. Calcd for $C_{29}H_{28}FN_3O\cdot 0.3H_2O$: C, 75.89; H, 6.28; N, 9.16. Found: C, 75.86; H, 6.14; N, 9.05.

4′-Fluoro-*N*-[6-methyl-3-(1-pyrrolidinylmethyl)-7-quinolinyl][1,1′-biphenyl]-4-carboxamide (5u). The title compound was prepared according to the same procedure described for **5a** as a powder. Yield: 35%. Mp: 182−187 °C. ^{1}H NMR ($CDCl_3$): δ 1.82 (4H, m), 2.53 (3H, s), 2.56 (4H, m), 3.78 (2H, s), 7.12−7.22 (2H, m), 7.54−7.72 (5H, m), 7.94−8.04 (4H, m), 8.75 (1H, s), 8.83 (1H, d, J = 1.6 Hz). Anal. Calcd for $C_{28}H_{26}FN_3O\cdot 0.5H_2O$: C, 74.98; H, 6.07; N, 9.37. Found: C, 74.80; H, 5.93; N, 9.29.

***N*-(2-Fluoro-3-nitrophenyl)acetamide (64).** To a solution of 2-fluoro-3-nitroaniline (**63**) (18.2 g, 116 mmol) in pyridine (233 mL) was added acetic anhydride (27.4 mL, 291 mmol), and the reaction mixture was stirred for 16 h at room temperature. The solvent was evaporated in vacuo, and the residue was solidified with diisopropyl ether to give **64** (19.2 g, 83%) as a powder. ^{1}H NMR ($CDCl_3$): δ 2.30 (3H, s), 7.24−7.34 (1H, m), 7.56−7.70 (1H, m), 7.72−7.81 (1H, m), 8.64−8.72 (1H, m).

***N*-(3-Amino-2-fluorophenyl)acetamide (23).** A mixture of **64** (18.2 g, 91.7 mmol), 10% Pd/C (1.82 g), and cyclohexene (27.9 mL, 275 mmol) in ethanol (183 mL) was heated at 60 °C for 21 h under N_2 and cooled to room temperature. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was solidified with diisopropyl ether to give **23** (14.2 g, 92%) as a powder. ^{1}H NMR ($CDCl_3$): δ 2.20 (3H, s), 3.62−3.82 (2H, br s), 6.48−6.58 (1H, m), 6.85−6.94 (1H, m), 7.28−7.46 (1H, br s), 7.56−7.76 (1H, m).

2-Methoxy-3-nitrobenzoic Acid (66). A mixture of methyl 2-methoxy-3-nitrobenzoate (**65**) (4.96 g, 23.5 mmol) and 1 M NaOH (50 mL, 50 mmol) in methanol (50 mL) was stirred for 2 h at 50 °C. The reaction mixture was concentrated in vacuo and poured into 1 M HCl, and extraction with EtOAc was performed. The extract was dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was solidified with hexane and EtOAc to give **66** (4.37 g, 94%) as a light yellow powder. ^{1}H NMR ($CDCl_3$): δ 4.02 (3H, s), 7.25−7.34 (1H, m), 7.91 (1H, dd, J = 1.8, 8.0 Hz), 8.10 (1H, dd, J = 1.8, 8.4 Hz).

4-Bromo-*N*-(2-methoxy-3-nitrophenyl)benzamide (67). To a solution of **66** (9.25 g, 46.9 mmol) in *t*-BuOH (350 mL) were added triethylamine (9.9 mL, 70.4 mmol) and diphenylphosphoryl azide (11.2 mL, 51.6 mmol), and the reaction mixture was heated at reflux for 5 h. After removal of the solvent in vacuo, the residue was chromatographed on silica gel (hexane−EtOAc, 5:1) to give a Boc-protected aniline derivative. To this compound in EtOAc (50 mL) was added 4 M HCl−EtOAc (100 mL), the mixture was heated at 50 °C for 2 h, and the solvent was removed in vacuo. The residue was collected and washed with diisopropyl ether. To a suspension of aniline derivative in tetrahydrofuran (150 mL) were added 4-bromobenzoyl chloride (10.0 g, 45.8 mmol) and triethylamine (17.5 mL, 125 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was poured into 1 M NaOH, and extraction with EtOAc was performed. The extract was washed with brine and dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was solidified with EtOAc and hexane to give **67** (14.2 g, 86%) as a yellow powder. ^{1}H NMR ($CDCl_3$): δ 3.99 (3H, s), 7.24−7.33 (1H, m), 7.64−7.79 (5H, m), 8.53 (1H, br s) 8.78 (1H, dd, J = 1.8, 8.4 Hz).

***N*-(3-Amino-2-methoxyphenyl)-4-bromobenzamide (46).** A mixture of **67** (14.2 g, 40.5 mmol), reduced iron (11.3 g, 20.3 mmol), and $CaCl_2$ (2.25 g, 20.3 mmol) in 90% aqueous ethanol (440 mL) was heated at reflux for 4 h. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was dissolved with EtOAc, and the solution was washed with brine. The extract was dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was solidified with hexane and EtOAc to give **46** (11.2 g, 86%) as a colorless powder. ^{1}H NMR ($CDCl_3$): δ 3.76−3.82 (5H, m), 6.54 (1H, dd, J = 1.2, 7.8 Hz), 6.94−6.99 (1H, m), 7.62−7.65 (2H, m), 7.73−7.77 (2H, m), 7.82 (1H, dd, J = 1.5, 8.4 Hz), 8.37 (1H, br s).

Methyl 3-Nitro-2-vinylbenzoate (69). To a mixture of methyl 2-hydroxy-3-nitrobenzoate (**68**) (10.0 g, 50.9 mmol) in tetrahydrofuran (200 mL) were added *N*,*N*-diisopropylethylamine (13.3 mL, 76.4 mmol) and *N*-(methylsulfonyl)-*N*-phenylmethanesulfonamide (21.8 g, 61.0 mmol) at 0 °C. After being stirred at room temperature for 2 days, the mixture was concentrated in vacuo. The residue was dissolved with EtOAc, and the solution was washed with aqueous

$NaHCO_3$, 1 M HCl, and brine. The extract was dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was chromatographed on silica gel (hexane−EtOAc, 1:2) to give methyl 3-nitro-2-{[(trifluoromethyl)sulfonyl]oxy}benzoate (16.7 g, 99.4%) as a light yellow oil. ^{1}H NMR ($CDCl_3$): δ 4.00 (3H, s), 7.60−7.68 (1H, m), 8.19−8.33 (2H, m).

To a solution of the obtained oil (10.0 g, 30.4 mmol) in DMF (150 mL) were added tributylvinyltin (10.7 mL, 36.5 mmol) and tetrakis(triphenylphosphine)palladium (1.76 g, 1.52 mmol), and the reaction mixture was heated at 80 °C for 1 day under N_2. The mixture was diluted with EtOAc, and the solution was washed with aqueous $NaHCO_3$ and brine. The extract was dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was chromatographed on silica gel (hexane−EtOAc, 2:1) to give **69** (4.91 g, 78%) as a light yellow powder. ^{1}H NMR ($CDCl_3$): δ 3.89 (3H, s), 5.24 (1H, dd, J = 1.0, 17.6 Hz), 5.42 (1H, dd, J = 1.2, 11.8 Hz), 7.17 (1H, dd, J = 11.4, 17.6 Hz), 7.44−7.52 (1H, m), 7.89 (1H, dd, J = 1.4, 8.4 Hz), 7.98 (1H, dd, J = 1.6, 7.8 Hz).

3-Nitro-2-vinylbenzoic Acid. The title compound was prepared according to the same procedure described for **13** (4.23 g, 92%) as a light yellow powder. ^{1}H NMR ($CDCl_3$): δ 5.26 (1H, d, J = 18.0 Hz), 5.40 (1H, dd, J = 0.6, 13.2 Hz), 7.21 (1H, dd, J = 11.4, 17.6 Hz), 7.42−7.49 (1H, m), 7.83 (1H, dd, J = 1.2, 8.2 Hz), 8.05 (1H, dd, J = 1.2, 7.8 Hz), 10−12 (1H, br s).

***tert*-Butyl 3-Nitro-2-vinylphenylcarbamate (70).** To a solution of 3-nitro-2-vinylbenzoic acid (7.86 g, 40.7 mmol) in *t*-BuOH (400 mL) were added triethylamine (8.6 mL, 61.1 mmol) and diphenylphosphoryl azide (9.65 mL, 44.8 mmol), and the reaction mixture was heated at reflux for 1 day. After removal of the solvent in vacuo, the residue was chromatographed on silica gel (hexane−EtOAc, 3:1) to give **70** (9.99 g, 93%) as a light yellow powder. ^{1}H NMR ($CDCl_3$): δ 1.52 (9H, s), 5.43 (1H, dd, J = 1.0, 18.0 Hz), 5.72−5.78 (1H, m), 6.82 (1H, dd, J = 11.4, 18.4 Hz), 7.02 (1H, br s), 7.33−7.38 (1H, m), 7.42−7.59 (1H, m), 8.42 (1H, d, J = 8.4 Hz).

***N*-(3-Amino-2-methylphenyl)-4-bromobenzamide (47).** A mixture of **70** (5.0 g, 18.9 mmol) and 5% Pd/C (1.0 g) in ethanol (100 mL) was stirred for 5 h under H_2. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (hexane−EtOAc, 3:1) to give *tert*-butyl 3-amino-2-ethylphenylcarbamate (3.88 g, 87%) as a light yellow powder. ^{1}H NMR ($CDCl_3$): δ 1.15 (3H, t, J = 7.8 Hz), 1.51 (9H, s), 2.52 (2H, q, J = 7.5 Hz), 3.62 (2H, br s), 6.21 (1H, br s), 6.48 (1H, dd, J = 1.2, 8.1 Hz), 6.96−7.02 (1H, m), 7.16 (1H, d, J = 8.4 Hz).

To a suspension of the obtained aniline derivative (3.78 g, 16.0 mmol) in tetrahydrofuran (50 mL) were added 4-bromobenzoyl chloride (3.87 g, 17.6 mmol) and triethylamine (6.70 mL, 48.0 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1 M NaOH, and extraction with EtOAc was performed. The extract was washed with brine and dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was crystallized from EtOAc and hexane to give *tert*-butyl 3-[(4-bromobenzoyl)amino]-2-methylphenylcarbamate (6.58 g, 98%) as a yellow powder. ^{1}H NMR ($CDCl_3$): δ 1.17 (3H, t, J = 7.6 Hz), 1.52 (9H, s), 2.62 (2H, q, J = 6.6 Hz), 6.27 (1H, s), 7.19−7.27 (1H, m), 7.48 (1H, d, J = 7.8 Hz), 7.59−7.68 (6H, m).

To a mixture of the obtained 4-bromobenzoyl derivative (6.48 g, 15.5 mmol) in EtOAc (50 mL) and tetrahydrofuran (30 mL) was added 4 M HCl−EtOAc (60 mL), and the mixture was heated at 60 °C for 3 h. The solution was washed with aqueous K_2CO_3 and brine. The solvent was removed in vacuo to afford **47** (4.53 g, 92%) as a colorless powder. ^{1}H NMR ($CDCl_3$): δ 1.20 (3H, d, J = 7.6 Hz), 2.57 (2H, q, J = 7.6 Hz), 3.70 (2H, br s), 6.61 (1H, dd, J = 1.2, 7.8 Hz), 7.02−7.09 (1H, m), 7.16−7.20 (1H, br s), 7.60−7.64 (3H, m), 7.73 (2H, d, J = 8.4 Hz).

***N*-(3-Amino-2-methylphenyl)-4-bromobenzamide (45).** Compound **45** was prepared in the same manner as described for **46**. Yield: quantitative. ^{1}H NMR (DMSO-d_6): δ 1.90 (3H, s), 4.91 (2H, s), 6.48 (1H, d, J = 7.6 Hz), 6.55 (1H, d, J = 8.0 Hz), 6.88 (1H, m), 7.72 (2H, d, J = 8.6 Hz), 7.90 (2H, d, J = 8.6 Hz), 9.81 (1H, s).

***N*-(5-Amino-2-methylphenyl)-4-bromobenzamide (48).** Compound **48** was prepared in the same manner as described for **46**. Yield: 92%. ^{1}H NMR ($CDCl_3$): δ 2.22 (3H, s), 3.66 (2H, br s), 6.42−6.52 (1H, m), 6.99 (1H, d, J = 8.0 Hz), 7.44−7.50 (1H, m), 7.54−7.68 (3H, m), 7.73 (2H, d, J = 8.4 Hz).

Measurement of Binding Affinities. The membrane fractions from CHO cells stably expressing human MCHR1, rat MCHR1,[1,11] or human 5-HT2c were incubated at room temperature for 1 h with the radiolabeled ligand ([^{125}I]MCH-(4−19) for MCHR1 binding assays and [^{3}H]mesulergine for 5-HT2c binding assay) in the presence of the compound at various concentrations. Binding reaction was terminated by rapid filtration through a GF/C glass filter, and the radioactivity retained in the filters was measured with a scintillation counter. The evaluation method for binding affinities to 5-HT2c receptor has been described in other reports.

Measurement of Arachidonic Acid Release. CHO cells expressing the human MCHR1 were plated in 24-well plates at a density of 50 000 cells/well and cultured for 1 day. The cells were incubated with [^{3}H]arachidonic acid (0.2 μCi/well) for 16 h and washed twice with 500 μL of Dulbecco's modified Eagle's medium (DMEM) supplemented with 20 mM *N*-(2-hydroxyethyl)piperazine-*N*′-ethanesulfonic acid (HEPES) (pH 7.4) and 0.2% bovine serum albumin. The cells were then preincubated with compounds at various concentrations at 37 °C for 30 min, and the reaction was started by addition of MCH. After incubation for 45 min, the radioactivity in the medium was measured with a liquid scintillation counter.

Animal Experiments. All animal experiments were performed in compliance with the Guidelines for the Care and Use of Laboratory Animals of Takeda Pharmaceutical Co.

Food Intake Inhibition in DIO Rats. Male 52 week old F344/Jcl rats loaded with a high-fat diet (Research Diets, D12451) from 5 weeks of age were used (DIO-F344 rats). Before the start of the experiment, the rats were independently raised, a powder high-fat diet (D12451M, Research Diets) was given, and tap water (0.5 mL) was administered for acclimation. The body weight and food intake from evening to morning of the next day were measured. The rats were grouped on the basis of the food intake and the body weight as indices. At 15:00, 0.5% methylcellulose solution was administered orally to the control group, and a 0.5% methylcellulose suspension of compound **5v** (1, 3, and 10 mg/kg) and sibutramine (1 mg/kg) were administered orally to the compound administration groups at 2 mL/kg (six rats per group). Food intake was measured 6 and 17 h after administration. The food intake inhibition rate of each compound administration group to the control group was calculated. Each datum represents the mean ± SD.

In Vivo Selectivity of Anorectic Action by Using MCHR1-Deficient Mice. Male MCHR1-deficient mice and wild-type litter mate mice (34 weeks old) loaded with a high-fat diet (Research Diets, D12451) from 5 weeks of age were used. Before the start of the experiment, the mice were independently raised, a high-fat diet (D12451) was given, and tap water (0.5 mL) was administered for acclimation. The mice were grouped on the basis of food intake from day −5 to day −1 and body weight of day −1 as indices. On day 0 and day 1 at 16:00, 0.5% methylcellulose solution was administered orally to the control group, and a 0.5% methylcellulose suspension of the compound (3 and 10 mg/kg) was administered orally to the compound **5v** administration groups at 10 mL/kg (six mice per group). Food intake for 2 days was measured. Each datum represents the mean ± SD.

AUTHOR INFORMATION

Corresponding Author

*Phone: +81-466-32-1130. Fax: +81-466-29-4451. E-mail: Kamata_Makoto@takeda.co.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Mr. K. Ohnishi and Mr. M. Yamaguchi for the pharmacokinetic study. We express our sincere gratitude to Dr. M. Fujino, Dr. O. Nishimura, Dr. A. Miyake, and Dr. H. Onda for their encouragement and helpful discussion for this work.

■ ABBREVIATIONS USED

MCH, melanin-concentrating hormone; 5-HT2c, serotonin receptor 2c; GPCR, G protein-coupled receptor; SAR, structure−activity relationship; hMCHR1, human MCH receptor 1; rMCHR1, rat MCH receptor 1; CHO, Chinese hamster ovary; DIO, diet-induced obesity; EDC, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide

■ REFERENCES

(1) Takekawa, S.; Asami, A.; Ishihara, Y.; Terauchi, J.; Kato, K.; Shimomura, Y.; Mori, M.; Murakoshi, H.; Kato, K.; Suzuki, N.; Nishimura, O.; Fujino, M. T-226296: A Novel, Orally Active and Selective Melanin-Concentrating Hormone Receptor Antagonist. *Eur. J. Pharmacol.* **2002**, *438*, 129−135.

(2) Kamata, M.; Yamashita, T.; Imaeda, T.; Tanaka, T.; Terauchi, J.; Miyamoto, M.; Ora, T.; Tawada, M.; Endo, S.; Takekawa, S.; Asami, A.; Suzuki, N.; Nagisa, Y.; Nakano, Y.; Watanabe, K.; Ogino, H.; Kato, K.; Kato, K.; Ishihara, Y. Discovery, Synthesis, and Structure-Activity Relationship of 6-Aminomethyl-7,8-dihydronaphthalenes as Human Melanin-Concentrating Hormone Receptor 1 Antagonists. *Bioorg. Med. Chem.* **2011**, *19*, 5539−5552.

(3) Sargent, P. A.; Sharpley, A. L.; Williams, C.; Goodall, E. M.; Cowen, P. J. 5-HT2c Receptor Activation Decreases Appetite and Body Weight in Obese Subjects. *Psychopharmacology (Berlin)* **1997**, *133*, 309−312.

(4) Halford, J. C.; Harrold, J. A.; Lawton, C. L.; Blundell, J. E. Serotonin (5-HT) Drugs: Effects on Appetite Expression and Use for the Treatment of Obesity. *Curr. Drug Targets* **2005**, *6*, 201−213.

(5) Smith, S. R.; Prosser, W. A.; Donahue, D. J.; Morgan, M. E.; Anderson, C. M.; Shanahan, W. R. APD356-004 Study Group. Lorcaserin (APD356), a Selective 5-HT2c Agonist, Reduces Body Weight in Obese Men and Women. *Obesity (Silver Spring)* **2009**, *17*, 494−503.

(6) Thomsen, W. J.; Grottick, A. J.; Menzaghi, F.; Reyes-Saldana, H.; Espitia, S.; Yuskin, D.; Whelan, K.; Martin, M.; Morgan, M.; Chen, W.; Al-Shamma, H.; Smith, B.; Chalmers, D.; Behan, D. Lorcaserin, a Novel Selective Human 5-Hydroxytryptamine2c Agonist: In Vitro and in Vivo Pharmacological Characterization. *J. Pharmacol. Exp. Ther.* **2008**, *325*, 577−587.

(7) Lee, J.; Jung, M. E.; Lee, J. 5-HT2c Receptor Modulators: A Patent Survey. *Expert Opin. Ther. Pat.* **2010**, *20*, 1429−1455.

(8) Carney, R. M.; Shelton, R. C. Agomelatine for the Treatment of Major Depressive Disorder. *Expert Opin. Pharmacother.* **2011**, *12*, 2411−2419.

(9) Kennett, G. A.; Wood, M. D.; Bright, F.; Trail, B.; Riley, G.; Holland, V.; Avenell, K. Y.; Stean, T.; Upton, N.; Bromidge, S.; Forbes, I. T.; Brown, A. M.; Middlemiss, D. N.; Blackburn, T. P. SB 242084, a Selective and Brain Penetrant 5-HT2c Receptor Antagonist. *Neuropharmacology* **1997**, *36*, 609−620.

(10) Tom, N. J.; Ruel, E. M. An Efficient Synthesis of Substituted Quinolines. *Synthesis* **2001**, *2001*, 1351−1355.

(11) Shimomura, Y.; Mori, M.; Sugo, T.; Ishibashi, Y.; Abe, M.; Kurokawa, T.; Onda, H.; Nishimura, O.; Sumino, Y.; Fujino, M. Isolation and Identification of Melanin-Concentrating Hormone as the Endogenous Ligand of the SLC-1 Receptor. *Biochem. Biophys. Res. Commun.* **1999**, *261*, 622−626.

(12) Marsham, P. R.; Jackman, A. L.; Barker, A. J.; Boyle, F. T.; Pegg, S. J.; Wardleworth, J. M.; Kimbell, R.; O'Connor, B. M.; Calvert, A. H.; Hughes, L. R. Quinazoline Antifolate Thymidylate Synthase Inhibitors: Replacement of Glutamic Acid in the C2-Methyl Series. *J. Med. Chem.* **1995**, *38*, 994−1004.