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4-Aminoquinolines: Novel Nociceptin Antagonists with Analgesic Activity

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Small-molecule nociceptin antagonists were synthesized to examine their therapeutic potential. After a 4-aminoquinoline derivative was found to bind with the human ORL$_1$ receptor, a series of 4-aminoquinolines and related compounds were synthesized and their binding was evaluated. Elucidation of structure−activity relationships eventually led to the optimum compounds. One of these compounds, *N*-(4-amino-2-methylquinolin-6-yl)-2-(4-ethylphenoxymethyl)benzamide hydrochloride (**11**) not only antagonized nociceptin-induced allodynia in mice but also showed analgesic effect in a hot plate test using mice and in a formalin test using rats. Its analgesic effect was not antagonized by the opioid antagonist naloxone. These results indicate that this nociceptin antagonist has the potential to become a novel type of analgesic that differs from μ-opioid agonists.

Introduction

The G-protein-coupled opioid receptor-like 1 (ORL$_1$) receptor mediates the inhibition of adenylate cyclase and has a similar amino acid sequence to that of opioid receptors.[1] However, this receptor does not bind opioid peptides or ligands selective for the μ-, δ-, or κ-opioid receptors.[2] Its endogenous agonist is a heptadecapeptide known as nociceptin (also called orphanin FQ).[2] Nociceptin structurally resembles an opioid peptide, dynorphin A, but it shows little binding to μ-, δ-, or κ-opioid receptors.[3] Nociceptin has various pharmacological actions, including hyperalgesia,[2,4] allodynia,[2,4] an anti-opioid effect,[5] hypolocomotion,[6] stimulation of food intake,[7] impairment of memory,[8] attenuation of anxiety,[9] hypotension,[10] bradycardia,[10] and diuresis,[11] but its physiological role has not been defined. A selective small-molecule antagonist with good bioavailability and blood−brain barrier permeability is considered to be necessary for further pharmacological evaluation of the nociceptin−ORL$_1$ receptor system. Although small-molecule antagonists and agonists were recently synthesized, their pharmacological properties have not yet been reported.[12,13] We independently attempted to synthesize a small-molecule nociceptin antagonist in order to examine its therapeutic potential.

Here we report on the synthesis and the biological activity of 4-aminoquinoline derivatives. Structure−activity relationship (SAR) studies elucidated the structural requirements for ORL$_1$ receptor binding and eventually led to optimum compounds. The pharmacological properties of the selected compound were evaluated, and it was found to antagonize nociceptin-induced allodynia and to show an analgesic effect in vivo. This analgesic effect was not antagonized by naloxone. These studies indicated that the synthetic nociceptin antagonist, *N*-(4-amino-2-methylquinolin-6-yl)-2-(4-ethylphenoxymethyl)benzamide hydrochloride (**11**, JTC-801), has the potential to be used as a novel type of analgesic, and it is currently undergoing evaluation in clinical trials. It was recently reported that a peptide nociceptin antagonist showed a similar antinociceptive action, but this was not a small molecule.[14]

Chemistry

The method used for the synthesis of *N*-quinolinylbenzamides is shown in Scheme 1.[15] Coupling of 4-aminoacetanilide **29** with acyl acetates **30a**−**c** and subsequent cycliztion at 280 °C gave the 4-hydroxyquinolines **32a**−**c**. Methylation of **32a**−**c** with dimethyl sulfate yielded the 4-methoxyquinolines **33a**−**c**. Using **33a**−**c**, the methoxy group was converted to an amino group with ammonium acetate and the acetyl group was removed by acidic hydrolysis to give 4,6-diaminoquinolines **34a**−**c**. *N*-(Quinolin-6-yl)benzamides **35** were synthesized by the coupling of 4,6-diaminoquinolines with the corresponding benzoyl chlorides. In this reaction, benzoyl chlorides selectively reacted with the 6-amino group because the 4-amino group had a lower nucleophilicity.

Scheme 2 shows the preparation of 4,6-diaminoquinoline without an alkyl group at the 2-position.[16] The reduction of 4-nitroquinoline *N*-oxide **36** with iron gave 4-aminoquinoline **37**. Initially, the bromination of **37** was performed in order to achieve regioselective nitration of the 4-aminoquinoline ring at the 6-position. 4-Amino-3-bromoquinoline **38** was nitrated to give 6-nitroquinoline **39**, as expected. Then the 4,6-diaminoquinoline **40** was obtained by reduction of the 6-nitro group and reductive removal of the 3-bromo group of **39** using palladium carbon as the catalyst.

Preparation of the 4-(methylamino)quinoline derivative is shown in Scheme 3.[17] The 4-chloroquinoline **41** was synthesized by chlorination of **32a**. Conversion of the 4-chloro group to a methylamino group with *N*-methylformamide and subsequent removal of the acetyl group yielded 4-(methylamino)quinoline **43**. The method of synthesizing 6-(methylamino)quinoline is shown in Scheme 4.[15] *N*-Methylacetamide **44** was prepared by *N*-methylation of **33a**. Then the methoxy group of **33a** was converted to an amino group with ammonium

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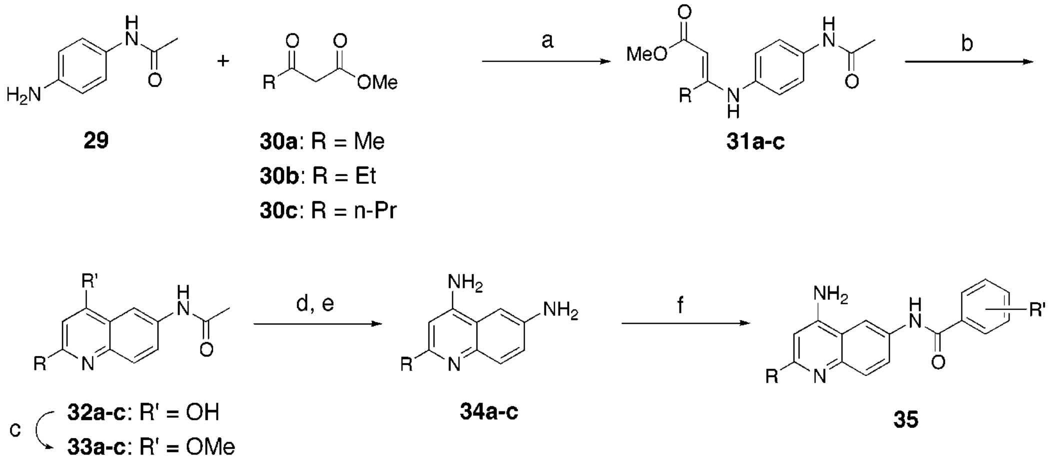
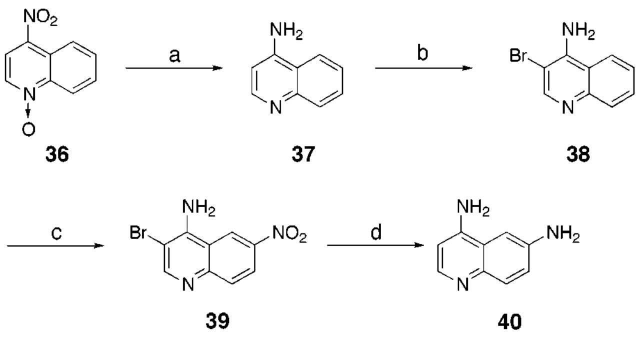
Scheme 1. Synthesis of *N*-Quinolinylbenzamide Derivatives[a]



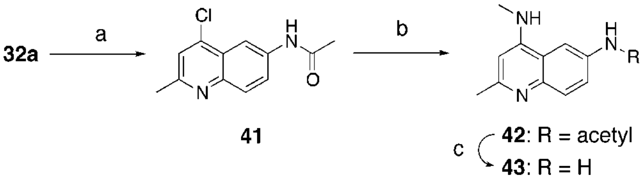
[a] Reagents: (a) methanol, reflux; (b) Dowtherm A, 280 °C; (c) Me_2SO_4, toluene, reflux; (d) $AcONH_4$, 135 °C; (e) HCl; (f) benzoyl chlorides.

Scheme 2. Preparation of 4,6-Diaminoquinoline[a]



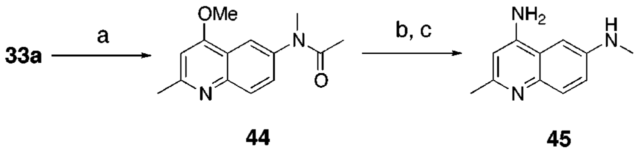
[a] Reagents: (a) Fe, AcOH; (b) Br_2, AcOH; (c) HNO_3, H_2SO_4; (d) H_2, Pd−C.

Scheme 3. Preparation of the 4-(Methylamino)-quinoline Derivative[a]



[a] Reagents: (a) $POCl_3$; (b) MeNHCHO, KOH; (c) 6 N HCl.

Scheme 4. Preparation of the 6-(Methylamino)-quinoline Derivative[a]

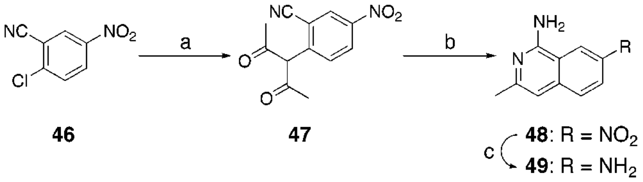


[a] Reagents: (a) NaH, MeI; (b) $AcONH_4$, 135 °C; (c) HCl.

acetate and the acetyl group was subsequently removed by acidic hydrolysis to give the 6-(methylamino)quinoline **45**.

The isoquinoline derivative was synthesized as shown in Scheme 5.[18] 2-Chloro-5-nitrobenzonitrile **46** was coupled with acetylacetone to give 2-acetylacetonyl-5-nitrobenzonitrile **47**. Deacetylation of **47** under alkaline conditions and subsequent cyclization with ammonia as the nitrogen source yielded isoquinoline **48**. The 7-nitro group of **48** was reduced with palladium carbon to give the 1,7-diaminoisoquinoline **49**.

Scheme 5. Preparation of the Isoquinoline Derivative[a]

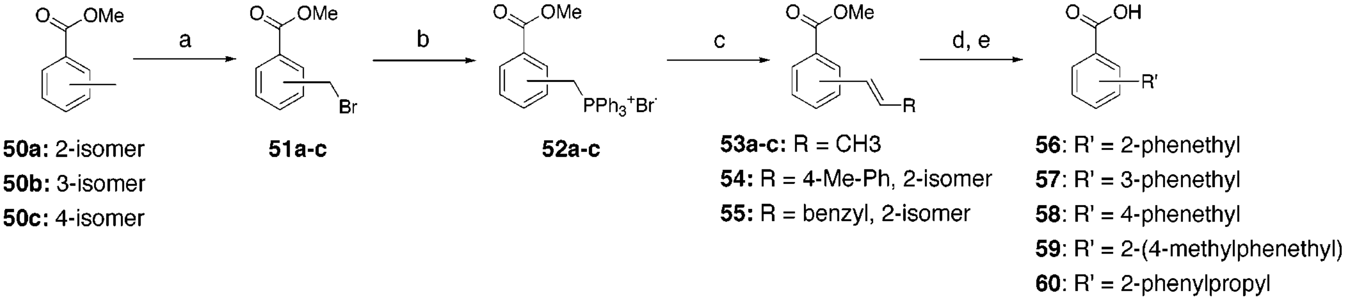


[a] Reagents: (a) acetylacetone, NaH; (b) 28% NH_3; (c) H_2, Pd−C.

The benzoic acids used as substrates for coupling with quinoline or isoquinoline derivatives were synthesized as shown in Schemes 6 and 7.[19,20] The benzylic position of methyl toluates **50a**−**c** was brominated with *N*-bromosuccinimide to give the benzyl bromides **51a**−**c**. Phosphonium salts **52a**−**c** were prepared from **51a**−**c** with triphenylphosphine. Wittig reaction of **52a**−**c** with the corresponding aldehydes gave the olefin derivatives **53a**−**c, 54,** and **55**, after which hydrogenation of **53a**−**c, 54,** and **55** with palladium carbon and subsequent hydrolysis of the methyl ester gave benzoic acid derivatives **56**−**60**. Coupling between benzyl bromide **61** and the corresponding phenols **62** with subsequent hydrolysis of the methyl ester gave 2-phenoxymethylbenzoic acids **63**−**67** and **69**−**73**. The aniline derivative **68** was synthesized by reduction of the nitro group of **67** with iron, while the methoxymethyl group of **73** was removed by acidic hydrolysis to give the phenol derivative **74**.

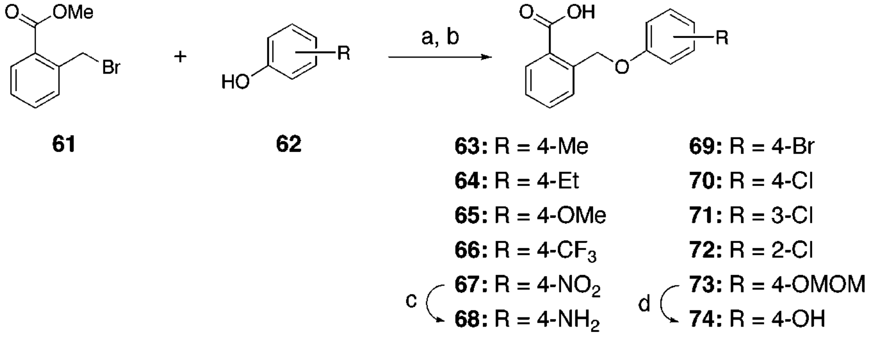
Synthesis of the reversed amide derivative **28** is shown in Scheme 8.[21] Coupling of ethyl 4-aminobenzoate **75** with ethyl acetoacetate and subsequent cyclization at 280 °C gave the quinoline derivative **77**. The Mitsunobu reaction between phenol and benzyl alcohol **78** with triphenylphosphine and diethyl azodicarboxylate yielded the phenoxymethylbenzene **79**. Then the nitro group of **79** was reduced with tin dichloride to give the 1-phenoxymethylaniline **80**, after which the amide derivative **81** was prepared by coupling **77** with **80** using 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride in the presence of 4-(dimethylamino)pyridine. Subsequently, the hydroxyl group of **81** was methylated with dimethyl sulfate and the methoxy group of **82** was converted to an amino group with ammonium acetate to give **27**.

Scheme 6. Preparation of Benzoic Acid Derivatives[a]



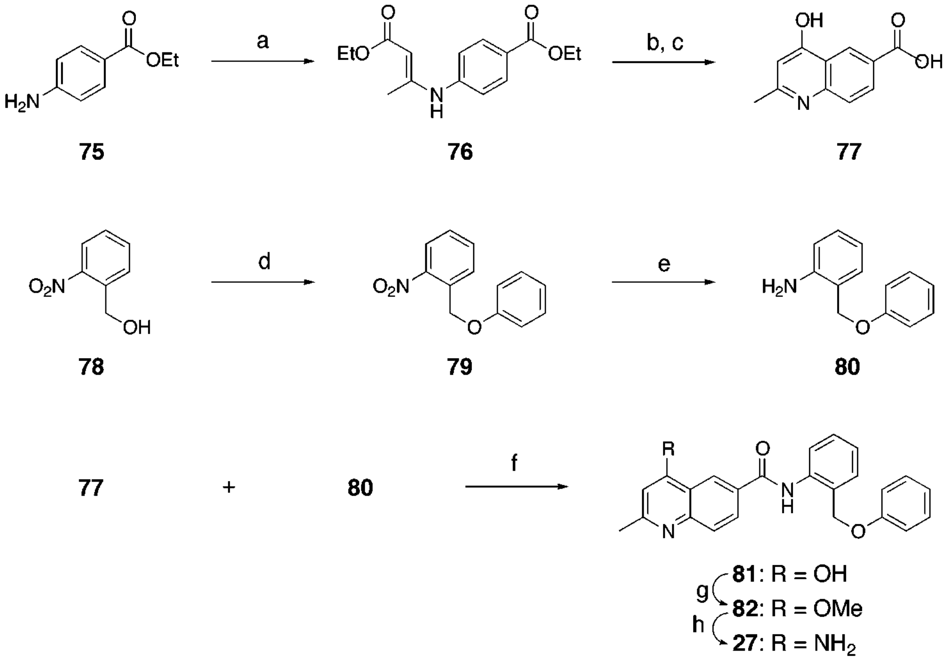
[a] Reagents: (a) NBS, Bz_2O_2; (b) Ph_3P; (c) RCHO, tBuOK; (d) H_2, Pd−C; (e) KOH.

Scheme 7. Preparation of 2-(Phenoxymethyl)benzoic Acid Derivatives[a]



[a] Reagents: (a) K_2CO_3; (b) KOH; (c) Fe; (d) 1 N HCl.

Scheme 8. Synthesis of Quinoline-6-carboxamide Derivatives[a]

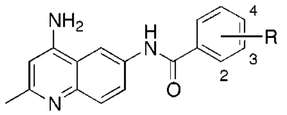


[a] Reagents: (a) ethyl acetoacetate; (b) Dowtherm A, 280 °C; (c) NaOH; (d) DEAD, PPh_3, phenol; (e) $SnCl_2$; (f) EDC, DMAP; (g) Me_2SO_4; (h) $AcONH_4$.

Results and Discussion

During random screening studies, we found that *N*-(4-amino-2-methylquinolin-6-yl)-2-phenylbenzamide (**1**) blocked 51.7% of the binding of nociceptin to the ORL_1 receptor at a concentration of 10 μM. Therefore, we performed structural modification of this compound for optimization using a receptor-binding assay with HeLa cells overexpressing the human ORL_1 receptor. We first examined the effect of changing the benzamide ring substituent in compound **1** (Table 1). Removal of the phenyl group at the *ortho* position (**2**) caused a decrease in binding. Therefore, the structure and position of the substituent on the benzamide ring were varied. Although introduction of a benzyl group at the *ortho* position (**3**) could not enhance binding, introduction of a phenethyl group (**4**), a phenoxymethyl group (**5**), or a phenylpropyl group (**6**) at the *ortho* position caused a severalfold increase in binding affinity compared with

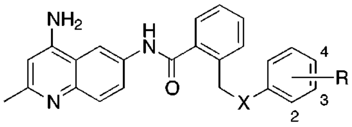
Table 1. Effect of Changing the Benzamide Ring Substituent



compd	R	K_i (nM)[a]	% inhib (10 μM)[c]
1	2-Ph	369.3 ± 132.0	51.7
2	−H	ND[b]	32.9
3	2-CH_2Ph	ND[b]	45.4
4	2-CH_2CH_2Ph	79.9 ± 10.1	90.5
5	2-CH_2OPh	50.7 ± 7.3	93.6
6	2-$CH_2CH_2CH_2$Ph	121.2 ± 17.5	98.0
7	3-CH_2CH_2Ph	ND[b]	23.0
8	4-CH_2CH_2Ph	ND[b]	48.4

[a] Displacement of [^{3}H]nociceptin (0.5 nM) binding from human ORL$_1$ receptors expressed in HeLa cells. Data are given as mean ± SE (n = 3−6). [b]ND, not determined. [c]Percent (%) inhibition of [^{3}H]nociceptin (0.5 nM) binding by test compounds at 10 μM.

Table 2. Effect of Changing the Terminal Benzene Ring Substituent



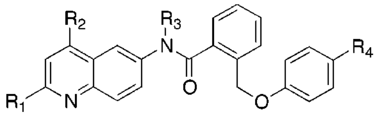
compd	R	X	K_i (nM)[a]	compd	R	X	K_i (nM)[a]
9	4-Me	CH_2	88.5 ± 9.9	**15**	4-CF_3	O	1.8 ± 0.2
10	4-Me	O	7.0 ± 1.4	**16**	4-NO_2	O	2.3 ± 0.4
11	4-Et	O	8.2 ± 0.3	**17**	4-Br	O	2.6 ± 0.3
12	4-OMe	O	11.8 ± 1.2	**18**	4-Cl	O	2.2 ± 0.3
13	4-OH	O	46.7 ± 4.9	**19**	3-Cl	O	20.4 ± 2.9
14	4-NH_2	O	82.4 ± 6.5	**20**	2-Cl	O	13.2 ± 1.8

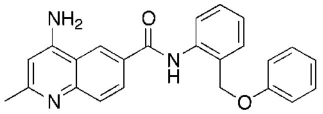
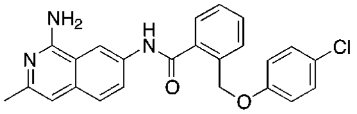
[a] Displacement of [^{3}H]nociceptin (0.5 nM) binding from human ORL$_1$ receptors expressed in HeLa cells. Data are given as mean ± SE (n = 3−6).

that of the lead compound **1**. Compounds **4** and **5**, with a two-atom linker between the terminal benzene ring and the benzamide ring, showed the highest binding among the compounds listed in Table 1. Therefore, the phenethyl group and the phenoxymethyl group were selected as the substituents on the benzamide ring for further investigation. Moving the phenethyl group to the *meta* or *para* position on the benzamide ring caused loss of binding, indicating that the *ortho* position was specific.

Subsequently, the effect of introduction of various substituents on the terminal benzene ring of compound **4** or **5** was examined (Table 2). Although introduction of a methyl group at the *para* position of the terminal benzene ring could not enhance binding (**9**), introduction of a methyl group at the *para* position of the terminal phenoxy ring caused an 7-fold increase in the binding affinity of compound **5** (**10**). Therefore, further investigation was performed using compound **5**. An ethyl, methoxy, trifluoromethyl, nitro, bromo, or chloro group was introduced at the *para* position of the terminal phenoxy ring (**11**, **12** and **15**−**18**). These compounds showed increased binding affinity regardless of the electronic properties of the substituent introduced, although the effect of the electron-withdrawing groups was stronger than that of the electron-donating groups. On the other hand, introduction of an amino group at the *para* position (**14**) decreased the affinity, and introduction of a hydroxy group at the *para* position (**13**) could not enhance the affinity. These results indicated that lipophilic, but not hydrophilic, substituents at the *para* position of the terminal phenoxy ring played an important role in the enhancement of binding. The influence of substituent position was examined using a chloro group. Enhancement of binding by a chloro group at the *meta* or *ortho* position (**19** and **20**) was weaker than when the group was located at the *para* position (**18**).

Table 3. Roles of Quinoline Ring Substituents and the Nitrogen Atom in the Quinoline Ring



compd	R$_1$	R$_2$	R$_3$	R$_4$	K_i (nM)[a]
21	−Me	−H	−H	−H	ND[b]
22	−Me	−NHMe	−H	−H	ND[b]
23	−H	−NH_2	−H	−Cl	85.6 ± 13.9
24	−Et	−NH_2	−H	−Cl	1.8 ± 0.3
25	−Pr	−NH_2	−H	−Cl	6.5 ± 1.1
26	−Me	−NH_2	−Me	−Cl	ND[b]
27	 NH2 O N H N O				ND[b]
28	 NH2 H N Cl N O O				37.3 ± 3.4

[a] Displacement of [^{3}H]nociceptin (0.5 nM) binding to human ORL$_1$ receptors expressed in HeLa cells. Data are given as mean ± SE (n = 3−6). [b]ND, not determined.

Next, the roles of substituents on the quinoline ring and the nitrogen atom of this ring were examined (Table 3). Removal of the amino group at the 4-position of the quinoline ring (**21**) caused loss of affinity, and introduction of a methyl group into the amino group at the 4-position (**22**) also extinguished binding. These results indicated that the primary amino group at the 4-position was necessary for binding. Removal of the methyl group at the 2-position of the quinoline ring (**23**) caused a decrease in affinity. Although changing the methyl group to an ethyl group (**24**) maintained binding affinity, changing it to a propyl group (**25**) caused a decrease of binding. Accordingly, a small alkyl group at the 2-position of the quinoline ring was essential for high affinity, while the ethyl and methyl groups were optimum. Introduction of a methyl group at the nitrogen atom in the amide moiety (**26**) caused loss of binding, and the reversed amide compound **27** also showed loss of affinity. These results indicated that the amide moiety was important for binding. The isoquinoline **28** showed decreased binding but did not completely lose its affinity, indicating that the nitrogen atom in the quinoline ring was important but was not directly related to binding. Compound **15** and **24** showed the strongest binding among a series of quinoline derivatives, and the binding was 205-fold higher than that of the lead compound **1**.

We selected compound **11** for further in vivo studies, because this compound showed the best bioavailability (data not shown). Before in vivo studies, we examined the effect of compound **11** on forskolin-stimulated cyclic AMP accumulation and its affinity for human opioid μ-,

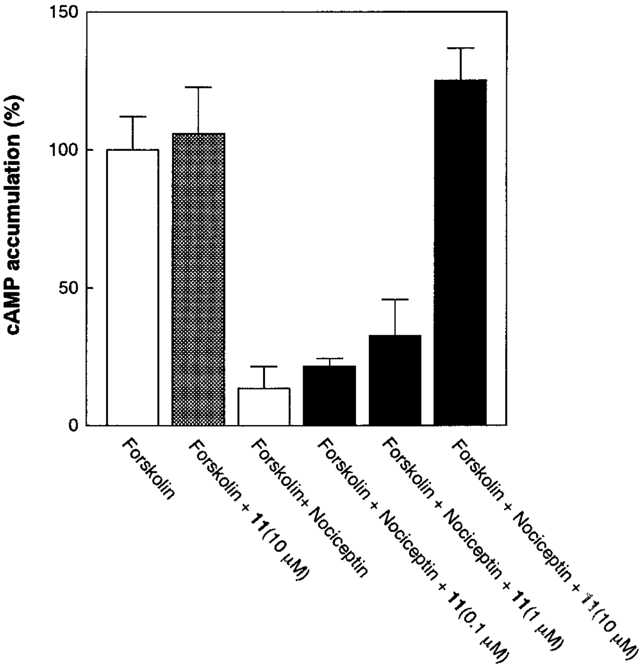


Figure 1. Effect of compound **11** on nociceptin-induced inhibition of forskolin-stimulated cyclic AMP accumulation in human ORL$_1$ receptor-expressing HeLa cells. Values are the mean ± SE ($n = 3$).

Table 4. Opioid Receptor Binding of Compound **11**

	K_i (nM)			
compd	ORL$_1$[a]	μ[b]	κ[c]	δ[d]
11	8.2 ± 0.3	102.9 ± 5.9	1057.5 ± 128.9	8647.2 ± 557.5

Displacement of [a][^{3}H]nociceptin (0.5 nM) binding from human ORL$_1$ receptors expressed in HeLa cells, [b][^{3}H]diprenorphine (0.33 nM) binding from human opioid μ-receptors expressed in CHO-K1 cells, [c][^{3}H]naltrindole (0.55 nM) binding from human opioid δ-receptors expressed in CHO-K1 cells. Data are given as mean ± SE ($n = 3$).

Table 5. Effect of Compound **11** on Nociceptin-Induced Allodynia

compd	score[b]
nociceptin	7.11 ± 0.26
nociceptin + **11**[a]	3.11 ± 1.23*

[a] Compound **11** (0.3 mg/kg) was administered orally. [b]Values are the mean ± SE of allodynia score at 20 min ($n = 9$). *$p < 0.05$, significantly different from control (nociceptin alone) by the Mann–Whitney U-test.

κ-, and δ-receptors. Compound **11** did not inhibit forskolin-stimulated cyclic AMP accumulation in human ORL$_1$ receptor-expressing HeLa cells, but it prevented nociceptin-induced inhibition of cyclic AMP accumulation (Figure 1), indicating that the compound possessed full antagonistic activity. The affinity of compound **11** for human opioid μ-, κ-, and δ-receptors is shown in Table 4. Compound **11** displayed about 12.5-, 129-, and 1055-fold selectivity for ORL$_1$ receptor over μ-, κ-, and δ-receptors, respectively. The effect of compound **11** on nociceptin-induced allodynia (pain evoked by an innocuous tactile stimulus) was examined in mice (Table 5). Injection of nociceptin into the subarachnoid space of the spinal cord (i.e., intrathecally) is known to induce hyperalgesia (enhancement of pain sensation) and allodynia in mice.[4] Oral administration of compound **11** decreased allodynia induced by the intrathecal injection of nociceptin, and the antagonistic effect of compound **11** was also confirmed in vivo. Next, the analgesic effect of compound **11** was evaluated from the time on a hot plate (55–56 °C) until mice showed an avoidance response.[22] This compound delayed the response when administered orally (Figure 2). Furthermore, the effect of compound **11** on the biphasic paw-licking response (first phase, 0–5 min; second phase, 15–45 min) induced by injection of formalin was examined in rats.[23] Oral administration of this compound decreased both phases of the response, and this analgesic action was not blocked by naloxone (a narcotic antagonist) (Figure 3A). Since the analgesic action of morphine (a μ-agonist) was blocked by naloxone (Figure 3B), compound **11** did not act through the opioid μ-receptor. Accordingly, this 4-aminoquinoline-based nociceptin antagonist seemed to have potential as a novel type of analgesic agent differing from μ-agonists such as morphine. It was recently reported that a peptidic nociceptin antagonist has a naloxone-resistant antinociceptive action and potentiates morphine-induced analgesia.[14] These findings are consistent with our results.

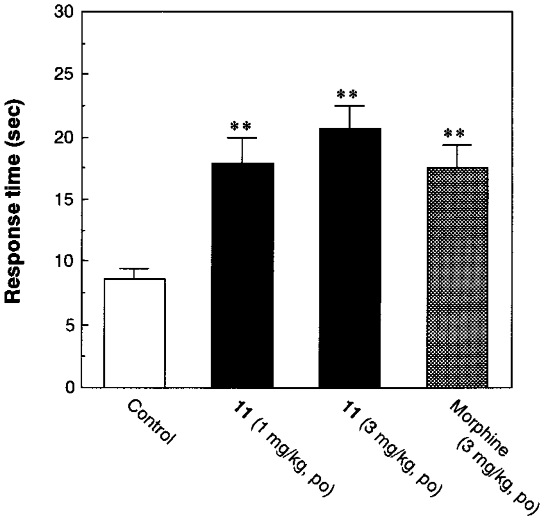


Figure 2. Analgesic effect of compound **11** and morphine in the hot-plate test. The time until the mice showed the first avoidance responses to the hot plate (55–56 °C) is shown. Values are the mean ± SE ($n = 12$). **$p < 0.01$, significantly different from control by Dunnett's two-tailed test.

In conclusion, we succeeded in synthesizing 4-aminoquinoline-based nociceptin antagonists, and SAR studies on a series of these compounds disclosed the structural requirements for binding and activity. One of the optimum compounds (**11**), which was confirmed to be a selective small-molecule ORL$_1$ antagonist by in vitro studies, antagonized nociceptin-induced allodynia and showed an analgesic effect that was not prevented by the specific opioid antagonist naloxone. These findings suggested the therapeutic potential of nociceptin antagonists as a novel class of analgesics, so we have subsequently started clinical trials of the 4-aminoquinoline-based nociceptin antagonist **11**.

Experimental Section

Chemistry. Melting points were obtained with a Yanagimoto micro melting point apparatus or a Mettler-Toledo FP62 melting point instrument and are uncorrected. Elemental analysis was performed with a Perkin-Elmer 2400 series II CHNS/O analyzer, and all values were within ±0.4% of the

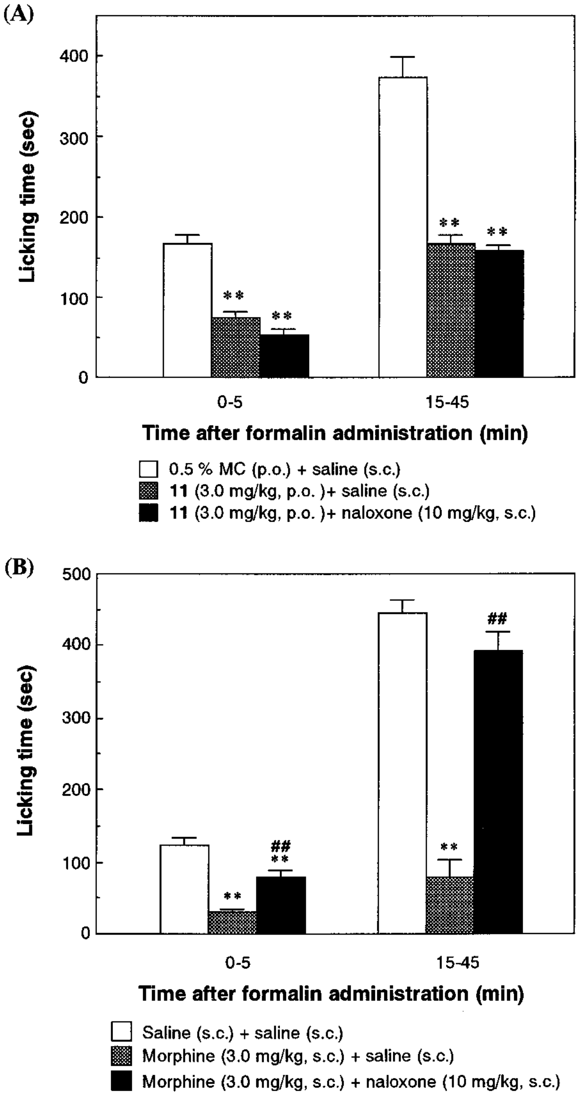


Figure 3. Effect of naloxone on the analgesic action of compound **11** (A) or morphine (B) in the formalin test using normal rats. Values are the mean ± SE ($n = 7$ or 8). $^{**}p < 0.01$, significantly different from control at the same time by Tukey's compromise test; $^{\#\#}p < 0.01$, significantly different from the morphine group at the same time by Tukey's compromise test.

calculated values. The water content of the compounds calculated by microanalysis was consistent with that measured by the Karl Fischer method. ^{1}H NMR spectra were recorded on a JEOL JNM-A300W, Bruker AMX 300, or Bruker ARX 400 spectrometer in a solution of DMSO-d_6, using tetramethylsilane as the internal standard. Chemical shifts are expressed as δ (ppm) values for protons relative to the internal standard, and all compounds gave spectra consistent with their assigned structures.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-(4-methylphenethyl)benzamide Hydrochloride (9).** A solution of 4-aminoacetanilide **29** (150.2 g, 1 mol) and methyl acetoacetate **30a** (136.8 g, 1.1 mol) in methanol (450 mL) was refluxed for 17 h. After cooling to 0 °C, the precipitate was collected by filtration to give methyl 3-(4-acetylaminophenylamino)crotonate **31a** as a colorless solid (231.5 g, 93%). The powder form of **31a** (231.5 g, 0.93 mol) was added to Dowtherm A (600 mL) while heating at 280 °C. After heating for 10 min, the mixture was cooled to room temperature. The resulting precipitate was collected by filtration and was washed with ethyl acetate and methanol to give 6-acetamide-4-hydroxy-2-methylquinoline **32a** as a deep yellow solid (187.3 g, 88%). Dimethyl sulfate (75 mL, 0.79 mol) was added dropwise to a suspension of **32a** (100 g, 0.46 mol) in toluene (490 mL), and the mixture was refluxed for 8 h. After cooling to room temperature, the precipitate was collected by filtration. The product was dissolved in water (1.35 L) and the solution was alkalinized with 35% aqueous sodium hydroxide solution (100 mL). The resulting precipitate was collected by filtration to give 6-acetamide-4-methoxy-2-methylquinoline **33a** as a brown solid (55.3 g, 52%). A mixture of **33a** (55.3 g, 0.24 mol) and ammonium acetate (279.4 g, 3.62 mol) was heated at 135 °C for 4 h. Water (280 mL) and 37% hydrochloric acid (450 mL) were added to the reaction mixture, which was heated at 90 °C for 5 h. After cooling to 0 °C, the precipitate was collected by filtration. Then the crude product was dissolved in hot water, and charcoal (3 g) was added to the solution. After removal of the charcoal by filtration, the filtrate was alkalinized with 35% aqueous hydroxide while cooling at 0 °C. The resulting precipitate was collected by filtration, washed with water, and dried under a vacuum at 100 °C to give 4,6-diamino-2-methylquinoline **34a** as a slightly yellow solid (28.4 g, 68%). *N*-Bromosuccinimide (18.7 g, 0.1 mol) was added to a solution of methyl 2-toluate **50a** (15.0 g, 0.1 mol) in carbon tetrachloride (200 mL), and the mixture was refluxed with a catalytic amount of benzoyl peroxide for 2 h. After cooling to room temperature, the precipitate was removed by filtration and the filtrate was concentrated under a vacuum to give methyl α-bromo-2-toluate **51a** as a yellow oil (24.4 g, 100%). Triphenylphosphine (28.8 g, 0.11 mol) was added to a solution of **51a** (24.4 g, 0.11 mol) in toluene (400 mL), and the mixture was refluxed for 2 h. After cooling to room temperature, the precipitate was collected by filtration and washed with ethyl acetate to give (2-(methylcarbonyl)-benzyl)triphenylphosphonium bromide **52a** as a colorless solid (37.0 g, 76%). Potassium *tert*-butoxide (404 mg, 3.6 mmol) was added to a solution of **52a** (1.47 g, 3 mmol) in tetrahydrofuran (3 mL), and the mixture was heated at 80 °C for 1 h. Next, a solution of 4-tolualdehyde (396 mg, 3.3 mmol) in tetrahydrofuran (3 mL) was added to the mixture, which was heated at 80 °C for 30 min. After cooling to room temperature, the mixture was diluted with ethyl acetate. The organic solution was washed with water (50 mL) and brine (50 mL), dried over sodium sulfate, and concentrated. Then the residue was chromatographed on a silica gel column eluted with hexane/ethyl acetate (9:1) to give methyl 2-(4-methylstyryl)benzoate **53a** as a colorless oil (640 mg, 85%). A solution of **53a** (630 mg, 2.5 mmol) in a mixture of ethanol (5 mL) and ethyl acetate (5 mL) was stirred in the presence of 5% palladium carbon (630 mg) under 2.5 kg/cm^2 of hydrogen at room temperature for 40 min. The solution was filtered through Celite, and the filtrate was evaporated under a vacuum to give methyl 2-(4-methylphenethyl)benzoate as a colorless oil (478 mg, 74%). Next, 4 N aqueous sodium hydroxide (1.8 mL, 7.2 mmol) was added to a solution of the oil (457 mg, 1.8 mmol) in methanol (5 mL), and the mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with ethyl ether (50 mL) and water (50 mL) and was acidified with 2 N hydrochloric acid. Then the mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over sodium sulfate, and concentrated to give 2-(4-methylphenthyl)benzoic acid **59** as a colorless solid (359 mg, 83%). Oxalyl chloride (105 μL, 1.2 mmol) and a catalytic amount of dimethylformamide were added to a solution of **59** (240 mg, 1 mmol) in dichloromethane (5 mL). The mixture was stirred at room temperature for 1 h and concentrated under a vacuum, after which a solution of the residue in dichloromethane (3 mL) was added dropwise to a solution of **34a** (208 mg, 1.2 mmol) in pyridine (5 mL). Then the mixture was stirred at room temperature and concentrated under a vacuum. The residual solvent was diluted with ethyl acetate (50 mL), washed with saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL), dried over sodium sulfate, and concentrated. Next, a 4.0 M solution of hydrogen chloride in 1,4-dioxane (0.5 mL) was added to a solution of the residue in a mixture of methanol (0.5 mL) and ethyl acetate (20 mL). The resulting precipitate was collected by filtration and dried under a vacuum to give **9** as a slightly yellow solid

(280 mg, 70%): mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.21 (3H, s), 2.60 (3H, s), 2.82−2.87 (2H, m), 3.01−3.06 (2H, m), 6.62 (1H, s), 7.02 (2H, d, J = 8.15 Hz), 7.06 (2H, d, J = 8.15 Hz), 7.35−7.55 (4H, m), 7.96 (2H, s), 8.70 (2H, br s), 8.79 (1H, s), 10.80 (1H, s), 13.98 (1H, s). Anal. ($C_{26}H_{25}N_3O{\cdot}HCl{\cdot}0.4H_2O$) C, H, N.

***N*-(4-Aminoquinolin-6-yl)-2-(4-chlorophenoxymethyl)benzamide Hydrochloride (23).** A suspension of 4-nitroquinoline *N*-oxide **36** (10 g, 52.5 mmol) and iron powder (26.4 g, 0.47 mol) in acetic acid (500 mL) was stirred at 110 °C for 3 h. After removal of the precipitate by filtration, the filtrate was concentrated under a vacuum. 35% Aqueous sodium hydroxide (100 mL) was added to the residue, and the solution was extracted with chloroform (50 mL × 6). The organic layer was washed with water (100 mL) and brine (100 mL), dried over sodium sulfate, and concentrated to give 4-aminoquinoline **37** as a brown solid (6.0 g, 79%). Bromine (2.78 g, 17.4 mmol) was added dropwise to a solution of **37** (2.28 g, 15.8 mmol) in acetic acid (30 mL) at 0 °C, and the mixture was stirred at room temperature for 30 min. Diethyl ether (100 mL) was added to the mixture, and the precipitate was collected by filtration. The product was dissolved in water (50 mL), and the solution was alkalinized with 1 N aqueous sodium hydroxide (50 mL). The resulting precipitate was collected by filtration, washed with water (50 mL), and dried under a vacuum to give 4-amino-3-bromoquinoline **38** as an off-white solid (2.91 g, 82%). Then 60% nitric acid (1.5 mL, 20 mmol) was added dropwise to a solution of **38** (2.90 g, 13 mmol) in sulfuric acid (25 mL) at 0 °C, and the mixture was stirred for 1 h. Sodium hydroxide (40 g) was carefully added to the mixture while cooling in an ice bath, and the precipitate was collected by filtration. The crude product was dissolved in acetone (50 mL), and charcoal (200 mg) was added to the solution. After removal of the charcoal by filtration, the filtrate was concentrated under a vacuum. Then the crude solid was crystallized from acetone to give 4-amino-3-bromo-6-nitroquinoline **39** as a yellow solid (1.65 g, 47%). A 25% solution of hydrogen bromide in acetic acid (0.7 mL, 3.05 mmol) was added to a solution of **39** (0.82 g, 3.05 mmol) in ethanol (30 mL) and was stirred in the presence of 10% palladium carbon (200 mg) under a hydrogen atmosphere at room temperature for 6 h. The solution was filtered through Celite, and the filtrate was evaporated under a vacuum. The residue was crystallized from water/ethanol (1:1) to give 4,6-diaminoquinoline dihydrobromide **40** as a brown solid (0.92 g, 94%). A suspension of α-bromo-2-toluate **51a** (2.29 g, 10 mmol), 4-chlorophenol (1.29 g, 10 mmol), and potassium carbonate (6.91 g, 50 mmol) in dimethylformamide (50 mL) was heated at 100 °C for 13 h. After cooling to room temperature, the precipitate was removed by filtration. Then the filtrate was diluted with water (200 mL) and extracted with ethyl acetate (200 mL). The organic solution was washed with saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL), dried over magnesium sulfate, and concentrated. Next, 4 N aqueous sodium hydroxide (6 mL, 24 mmol) was added to a solution of the residual oil in a mixture of tetrahydrofuran (5 mL) and methanol (5 mL). The mixture was refluxed for 24 h, the solvent was evaporated under a vacuum, 2 N hydrochloric acid (50 mL) was added to the residue, and the aqueous solution was extracted with ethyl acetate (50 mL). Then the organic layer was washed with brine (50 mL), dried over magnesium sulfate, and concentrated to give 2-(4-methylphenoxymethyl)benzoic acid **70** as a colorless solid (2.19 g, 83%). Oxalyl chloride (148 mL, 1.7 mmol) and a catalytic amount of dimethylformamide were added to a solution of **70** (250 mg, 1.1 mmol) in chloroform (10 mL), after which the mixture was stirred for 12 h and concentrated under a vacuum. A solution of the residue and **40** (107 mg, 0.67 mmol) in pyridine (10 mL) was stirred at room temperature for 3 h. The reaction mixture was alkalinized with 2 N aqueous potassium hydroxide and extracted with ethyl acetate (50 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over sodium sulfate, and concentrated, after which the residue was chromatographed on a silica gel column eluted with chloroform/methanol (9:1). Next, a 4.0 M solution of hydrogen chloride in 1,4-dioxane (0.5 mL) was added to a solution of the product in a mixture of methanol (0.5 mL) and ethyl acetate (20 mL). The resulting precipitate was collected by filtration and dried under a vacuum to give **23** as an off-white solid (223 mg, 75%): mp 231 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.34 (2H, s), 6.79 (1H, d, J = 6.8 Hz), 6.96 (2H, d, J = 6.9 Hz), 7.26 (2H, d, J = 6.9 Hz), 7.50−7.71 (4H, m), 7.93−8.00 (2H, m), 8.35 (1H, d, J = 6.8 Hz), 8.78 (1H, s), 8.88 (2H, br s), 10.90 (1H, s), 14.03 (1H, s). Anal. ($C_{23}H_{18}N_3O_2{\cdot}HCl{\cdot}1.5H_2O$) C, H, N.

The following compounds (**1**−**8**, **10**−**21**, and **24**−**25**) were prepared using the above procedures.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-phenylbenzamide (1):** mp 161 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.37 (3H, s), 6.36 (2H, s), 6.42 (1H, s), 7.29−7.61 (1H, m), 8.25 (1H, d, J = 2.0 Hz), 10.33 (1H, s). Anal. ($C_{23}H_{19}N_3O{\cdot}1.2H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)benzamide (2):** mp 251 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.40 (3H, s), 6.43 (2H, br s), 6.45 (1H, s), 7.53−7.75 (5H, m), 8.00 (1H, s), 8.03 (1H, s), 8.38 (1H, d, J = 2.1 Hz), 10.35 (1H, s). Anal. ($C_{17}H_{15}N_3O{\cdot}0.5H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-benzylbenzamide (3):** mp 131 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.38 (3H, s), 4.18 (2H, s), 6.41 (2H, s), 6.45 (1H, s), 7.14−7.63 (11H, m), 8.42 (1H, s), 10.44 (1H, s). Anal. ($C_{24}H_{21}N_3O{\cdot}0.3H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-phenethylbenzamide (4):** mp 153 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.38 (3H, s), 2.88−2.93 (2H, m), 3.03−3.09 (2H, m), 6.43 (2H, s), 6.45 (1H, s), 7.14−7.71(11H, m), 8.43 (1H, s), 10.46 (1H, s). Anal. ($C_{25}H_{23}N_3O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-(phenoxymethyl-)benzamide hydrochloride (5):** mp 245−246 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.59 (3H, s), 5.33 (2H, s), 6.60 (1H, s), 6.87−6.95 (3H, m), 7.21−7.26 (2H, m), 7.51−7.70 (4H, m), 7.93 (2H, s), 8.66 (2H, br s), 8.75 (1H, s). Anal. ($C_{24}H_{21}N_3O_2{\cdot}1.5HCl$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-(3-phenylpropyl)benzamide hydrochloride (6):** mp 252.0−254.0 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.88−1.96 (2H, m), 2.59 (2H, t, J = 7.4 Hz), 2.61 (3H, s), 2.81 (2H, t, J = 7.4 Hz), 6.63 (1H, s), 7.08−7.20 (5H, m), 7.32−7.52 (4H, m), 7.90 (1H, d, J = 9.0 Hz), 7.98 (1H, d, J = 9.0 Hz), 8.75 (2H, br s), 8.76 (1H, s), 10.78 (1H, s), 14.03 (1H, s). Anal. ($C_{26}H_{25}N_3O{\cdot}HCl{\cdot}0.3H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-3-phenethylbenzamide hydrochloride (7):** mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.61 (3H, s), 2.90−3.06 (4H, m), 6.66 (1H, s), 7.16−7.29 (5H, m), 7.42−7.47 (2H, m), 7.90 (1H, d, J = 6.52 Hz), 8.01 (1H, s), 8.07 (1H, d, J = 9.10 Hz), 8.14 (1H, dd, J = 9.10 and 1.87 Hz), 8.63 (2H, br s), 8.78 (1H, s), 8.90 (1H, s). Anal. ($C_{25}H_{23}N_3O{\cdot}HCl$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-4-phenethylbenzamide benzamide (8):** mp 183.0−184.0 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.40 (3H, s), 2.92−3.01 (4H, m), 6.43 (2H, br s), 6.44 (1H, s), 7.16−7.38 (7H, m), 7.65 (1H, d, J = 8.9 Hz), 7.73 (1H, dd, J = 2.1 and 8.9 Hz), 7.94 (2H, d, J = 8.1 Hz), 8.37 (1H, d, J = 2.1 Hz), 10.28 (1H, s). Anal. ($C_{25}H_{23}N_3O{\cdot}0.1H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-(4-methylphenoxymethyl)benzamide hydrochloride (10):** mp 255 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18 (3H, s), 2.59 (3H, s), 5.29 (2H, s), 6.60 (1H, s), 6.82 (2H, d, J = 8.4 Hz), 7.02 (2H, d, J = 8.4 Hz), 7.48−7.88 (6H, m), 8.66 (2H, br s), 8.74 (1H, s), 10.85 (1H, s), 13.81 (1H, s). Anal. ($C_{25}H_{23}N_3O_2{\cdot}HCl{\cdot}0.6H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-(4-ethylphenoxymethyl)benzamide hydrochloride (11):** mp 235 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10 (3H, t, J = 7.7 Hz, CH_2*CH_3*), 2.48 (2H, q, J = 7.7 Hz, *CH_2*CH_3), 2.59 (3H, s, 2-CH_3 on quinoline), 5.30 (2H, s, CH_2O), 6.61 (1H, s, 3-H on quinoline), 6.84 (2H, d, J = 8.6 Hz, 3,5-H on OAr), 7.05 (2H, d, J = 8.6 Hz, 2,6-H on OAr), 7.48−7.69 (4H, m, NHCO*Ar*), 7.94 (2H, s, 7,8-H on quinoline), 8.66 (2H, br s, 4-NH$_2$ on quinoline), 8.74 (1H, s, 5-H on quinoline), 10.86 (1H, s, NHCO), 13.93 (1H, br s, HCl). Anal. ($C_{26}H_{25}N_3O_2 \cdot HCl \cdot H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-(4-methoxyphenoxymethyl)benzamide hydrochloride (12):** mp 276 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.59 (3H, s), 3.65 (3H, s), 5.27 (2H, s), 6.60 (1H, s), 6.77−6.89 (4H, m), 7.48−7.68 (4H, m), 7.88−7.96 (2H, m), 8.70 (2H, br s), 8.74 (1H, s), 10.85 (1H, s), 13.78 (1H, s). Anal. ($C_{25}H_{23}N_3O_3 \cdot HCl$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-(4-hydroxyphenoxymethyl)benzamide hydrochloride (13):** mp 183.0−184.0 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.58 (3H, s), 5.22 (2H, s), 6.59 (1H, s), 6.61 (2H, d, J = 9.6 Hz), 6.76 (2H, d, J = 9.6 Hz), 7.50−7.65 (4H, m), 7.89−7.99 (2H, m), 8.59 (2H, br s), 8.74 (1H, s), 8.94 (1H, s), 10.83 (1H, s), 13.78 (1H, br s). Anal. ($C_{24}H_{21}N_3O_3 \cdot HCl \cdot 2H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-(4-aminophenoxymethyl)benzamide dihydrochloride (14):** mp 237 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (3H, s), 5.36 (2H, s), 6.61 (1H, s), 7.05 (2H, d, J = 9.2 Hz), 7.28 (2H, d, J = 9.2 Hz), 7.52−7.71 (4H, m), 7.96 (1H, s), 8.70 (2H, br s), 8.73 (1H, s), 10.24 (3H, br s), 10.89 (1H, s), 14.01 (1H, s). Anal. ($C_{24}H_{22}N_4O_2 \cdot 2HCl \cdot H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-(4-trifluoromethylphenoxymethyl)benzamide dihydrochloride (15):** mp 220 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (3H, s), 5.44 (2H, s), 6.61 (1H, s), 7.13 (2H, d, J = 8.7 Hz), 7.53−7.72 (6H, m), 7.95 (2H, s), 8.69 (2H, br s), 8.72 (1H, s). Anal. ($C_{25}H_{20}F_3N_3O_2 \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-(4-nitrophenoxymethyl)benzamide hydrochloride (16):** mp 238 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.59 (3H, s), 5.50 (2H, s), 6.60 (1H, s), 7.16 (2H, d, J = 9.15 Hz), 7.55−7.73 (4H, m), 7.93 (2H, s), 8.14 (2H, d, J = 9.15 Hz), 8.69 (2H, br s), 8.71 (1H, s), 10.91 (1H, s), 13.95 (1H, s). Anal. ($C_{24}H_{20}N_4O_4 \cdot HCl \cdot H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-(4-bromophenoxymethyl)benzamide hydrochloride (17):** mp 252 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (3H, s), 5.34 (2H, s), 6.61 (1H, s), 6.91 (2H, d, J = 8.9 Hz), 7.39 (2H, d, J = 8.9 Hz), 7.52−7.70 (4H, m), 7.95 (2H, s), 8.66 (2H, br s), 8.72 (1H, s), 10.89 (1H, s), 14.01 (1H, s). Anal. ($C_{24}H_{20}BrN_3O_2 \cdot HCl \cdot 1.5H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-(4-chlorophenoxymethyl)benzamide hydrochloride (18):** mp 245 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.59 (3H, s), 5.33 (2H, s), 6.59 (3H, s), 6.95 (2H, d, J = 8.9 Hz), 7.27 (2H, d, J = 8.9 Hz), 7.49−7.70 (4H, m), 7.85−7.95 (2H, m), 8.67 (2H, br s), 8.73 (1H, s). Anal. ($C_{24}H_{20}ClN_3O_2 \cdot HCl \cdot 0.7H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-(3-chlorophenoxymethyl)benzamide hydrochloride (19):** mp 147−149 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.59 (3H, s), 5.36 (2H, s), 6.60 (1H, s), 6.90−6.99 (3H, m), 7.22−7.28 (1H, m), 7.50−7.71 (4H, m), 7.89−7.92 (2H, m), 8.61 (2H, br s), 8.73 (1H, s), 10.86 (1H, s), 13.85 (1H, br s). Anal. ($C_{24}H_{20}Cl_3O_2 \cdot HCl \cdot 0.5H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-2-(2-chlorophenoxymethyl)benzamide hydrochloride (20):** mp 165 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (3H, s), 5.44 (2H, s), 6.61 (1H, s), 6.93 (2H, d, J = 8.9 Hz), 7.24−7.40 (3H, m), 7.54−7.74 (4H, m), 7.96 (2H, s), 8.70 (2H, br s), 8.76 (1H, s), 10.90 (1H, s), 13.98 (1H, s). Anal. ($C_{24}H_{20}ClN_3O_2 \cdot HCl \cdot 0.6H_2O$) C, H, N.

***N*-(2-Methylquinolin-6-yl)-2-(phenoxymethyl)benzamide hydrochloride (21):** mp 209 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.91 (3H, s), 5.33 (2H, s), 6.87−6.92 (3H, m), 7.18−7.23 (2H, m), 7.52−7.68 (4H, m), 7.87 (1H, d, J = 8.7 Hz), 8.18−8.25 (2H, m), 8.79 (1H, s), 8.92 (1H, d, J = 8.7 Hz), 11.05 (1H, s). Anal. ($C_{24}H_{20}N_2O_2 \cdot HCl$) C, H, N.

***N*-(4-Amino-2-ethylquinolin-6-yl)-2-(4-chlorophenoxymethyl)benzamide hydrochloride (24):** mp 247−249 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 7.7 Hz), 2.89 (2H, q, J = 7.7 Hz), 5.34 (2H, s), 6.66 (1H, s), 6.96 (2H, d, J = 9.2 Hz), 7.26 (2H, d, J = 8.8 Hz), 7.49−7.71 (4H, m), 7.95 (1H, d, J = 8.8 Hz), 7.99 (1H, d, J = 9.2 Hz), 8.72 (2H, br s), 8.73 (1H, s), 10.87 (1H, s), 13.91 (1H, s). Anal. ($C_{25}H_{22}ClN_3O_2 \cdot HCl \cdot 0.2H_2O$) C, H, N.

***N*-(4-Amino-2-propylquinolin-6-yl)-2-(4-chlorophenoxymethyl)benzamide hydrochloride (25):** mp 232−233 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (3H, t, J = 7.4 Hz), 1.73−1.80 (2H, m), 2.85 (2H, t, J = 7.4 Hz), 5.34 (2H, s), 6.65 (1H, s), 6.96 (2H, d, J = 8.8 Hz), 7.26 (2H, d, J = 8.8 Hz), 7.50−7.71 (4H, m), 7.94 (1H, d, J = 9.2 Hz), 8.00 (1H, d, J = 9.2 Hz), 8.73 (2H, br s), 8.74 (1H, s), 10.87 (1H, s), 13.93 (1H, s). Anal. ($C_{26}H_{24}ClN_3O_2 \cdot HCl \cdot 0.3H_2O$) C, H, N.

***N*-(2-Methyl-4-methylaminoquinolin-6-yl)-2-(phenoxymethyl)benzamide Hydrochloride (22).** A mixture of **32a** (4.32 g, 20 mmol) and phosphoryl chloride (9.32 mL, 100 mmol) was heated at 100 °C for 30 min. After cooling to room temperature, the mixture was poured into ice water (50 mL). The aqueous solution was alkalinized with 28% ammonium hydroxide. Then the precipitate was collected by filtration, washed with ethyl ether (30 mL), and dried under a vacuum to give 6-acetamide-4-chloro-2-methylquinoline **41** as a slightly yellow solid (4.69 g, 100%). A solution of **41** (2.74 g, 11.7 mmol) in *N*-methylformamide (5 mL) was heated at 170 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with chloroform (50 mL). The organic solution was washed with saturated aqueous sodium bicarbonate (50 mL), water (50 mL), and brine (50 mL), dried over sodium sulfate, and concentrated. Then the crude product was chromatographed on silica gel eluted with chlorofrom/methanol/ammonium hydroxide (85:15:0.1) to give 6-acetamide-2-methyl-4-methylaminoquinoline **42** as a slightly brown solid (255 mg, 9.4%). A solution of **42** (248 mg, 1.08 mmol) in 6 N hydrochloric acid (10 mL) was refluxed for 2 h. After cooling to room temperature, the mixture was alkalinized with 4 N aqueous sodium hydroxide. The resulting precipitate was collected by filtration and dried under a vacuum to give 6-amino-2-methyl-4-methylaminoquinoline **43** as a slightly brown solid (202 mg, 100%). 2-(4-Chlorophenoxymethyl)benzoyl chloride (258 mg, 1.05 mmol) was added to a solution of **43** (187 mg, 1 mmol) in pyridine (5 mL), after which the mixture was stirred at room temperature for 12 h and concentrated under a vacuum. The residue was dissolved in ethyl acetate (30 mL), which was washed with saturated aqueous sodium bicarbonate (30 mL), water (30 mL), and brine (30 mL), dried over sodium sulfate, and concentrated. Next, a 4 N solution of hydrogen chloride in ethyl acetate (0.5 mL) was added to a solution of the product in ethyl acetate (10 mL). The precipitate was collected by filtration and dried under a vacuum to give **22** as a slightly yellow solid (216 mg, 50%): mp 284 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.66 (3H, s), 3.06 (3H, d, J = 4.8 Hz), 5.34 (2H, s), 6.65 (1H, s), 6.87−6.95 (3H, m), 7.21−7.26 (2H, m), 7.49−7.70 (4H, m), 7.90 (2H, dd, J = 9.2 and 1.8 Hz), 7.97 (1H, d, J = 9.2 Hz), 8.83 (1H, s), 9.02 (1H, br s), 10.89 (1H, s), 14.15 (1H, s).. Anal. ($C_{25}H_{23}N_3O_2 \cdot HCl \cdot 0.2H_2O$) C, H, N.

***N*-(4-Amino-2-methylquinolin-6-yl)-*N*-methyl-2-(4-chlorophenoxymethyl)benzamide Hydrochloride (26).** **33a** (2.3 g, 10 mmol) was added to a suspension of sodium hydride (440 mg, 11 mmol) in dimethylformamide (20 mL) at room temperature, and the mixture was stirred for 30 min. Next, iodomethane (747 μL, 12 mmol) was added dropwise to the mixture, which was stirred for 2 h. The reaction mixture was subsequently poured into water (100 mL), and the aqueous solution was extracted with chloroform (100 mL). The organic layer was washed with brine (50 mL), dried over sodium sulfate, and concentrated under a vacuum. Then the residue was chromatographed on silica gel eluted with chloroform to give 4-methoxy-2-methyl-6-(*N*-methylacetamide)quinoline **44** as a pink solid (744 mg, 31%). A mixture of **44** (740 mg, 3.03 mmol) and ammonium acetate (3.5 g, 45.44 mmol) was heated at 135 °C for 3.5 h. Water (3.5 mL) and 37% hydrochloric acid (6 mL) were added to the mixture, which was heated at 90 °C for 18 h. After cooling to room temperature, the mixture was alkalinized with 4 N aqueous sodium hydroxide. The precipitate was collected by filtration and washed with water to give 4-amino-2-methyl-6-methylaminoquinoline **45** as a slightly brown solid (420 mg, 74%). 2-(4-Chlorophenoxymethyl)benzoyl chloride (258 mg, 1.05 mmol) was added to a solution of **45** (187 mg, 1 mmol) in pyridine (10 mL), and the mixture was stirred at room temperature for 16 h. Saturated aqueous sodium bicarbonate (50 mL) was added to the mixture, and the aqueous solution was extracted with ethyl acetate (50 mL). Then the organic layer was washed with brine (50 mL) and concentrated, after which a 4 N solution of hydrogen chloride (0.5 mL) in dioxane was added to a solution of the residue in ethyl acetate (20 mL). The resulting precipitate was collected by filtration and dried under a vacuum to give **26** as a slightly yellow solid (447 mg, 95%): mp 155 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.44 (3H, s), 5.20 (2H, s), 6.50 (1H, s), 6.89−6.99 (5H, m), 7.23−7.40 (4H, m), 7.53 (1H, s), 7.56 (1H, s), 7.72 (1H, d, $J = 8.8$ Hz), 8.05 (1H, dd, $J = 8.8$ and 1.7 Hz), 8.78 (1H, d, $J = 1.7$ Hz), 10.03 (1H, s). Anal. ($C_{25}H_{22}ClN_3O_2{\cdot}HCl{\cdot}H_2O$) C, H, N.

***N*-(1-Amino-3-methylisoquinolin-7-yl)-2-(4-chlorophenoxymethyl)benzamide Hydrochloride (28).** Acetyl acetone (5.1 mL, 50 mmol) was added in aliquots to a suspension of sodium hydride (2.1 g, 5.25 mmol, 60% dispersion) in dimethyl sulfoxide (20 mL), and the mixture was stirred at room temperature for 1.5 h. Next, 2-chloro-5-nitrobenzonitrile **46** (4.58 g, 25 mmol) was added to the mixture, which was heated at 100 °C for 1 h. After cooling to room temperature, the mixture was poured into water (50 mL). Saturated aqueous ammonium chloride (10 mL) was added to the aqueous solution, which was extracted with ethyl acetate (50 mL). Then the organic layer was washed with water (30 mL) and brine (30 mL), dried over sodium sulfate, and concentrated under a vacuum. The crude product was crystallized from hexane/ethyl acetate (4:1) to give 2-acetylacetonyl-5-nitrobenzonitrile **47** as a brown solid (3.38 g, 55%). A suspension of **47** (3.25 g, 13.2 mmol) in 28% ammonium solution was stirred at room temperature for 16 h. The mixture was acidified with 2 N hydrochloric acid (150 mL), and the aqueous solution was washed with ethyl acetate (50 mL). Then the aqueous layer was alkalinized with 4 N aqueous sodium hydroxide (80 mL). The resulting precipitate was collected by filtration and dried under a vacuum at 100 °C to give 1-amino-3-methyl-7-nitroisoquinoline **48** as a yellow solid (1.794 g, 67%). A solution of **48** (1.72 g, 8.47 mmol) in a mixture of tetrahydrofuran (50 mL) and ethanol (50 mL) was stirred in the presence of 5% palladium carbon (1.5 g) under an atmosphere of hydrogen at room temperature for 6.5 h. The solution was filtered through Celite, and the filtrate was evaporated under a vacuum to give 2,7-diamino-3-methylisoquinoline **49** as a yellow solid (1.30 g, 89%). 2-(4-Chlorophenoxymethyl)benzoyl chloride (206 mg, 0.84 mmol) was added to a solution of **49** (121 mg. 0.7 mmol) in pyridine (5 mL). The mixture was stirred at room temperature for 3 h and concentrated. Saturated aqueous sodium bicarbonate (50 mL) was added to the residue, and the aqueous solution was extracted with ethyl acetate (50 mL). Then the organic layer was washed with water (30 mL) and brine (30 mL), dried over sodium sulfate, and concentrated under a vacuum. Next, a 4 N solution of hydrogen chloride in 1,4-dioxane (0.5 mL) was added to a solution of the residue in a mixture of methanol (0.5 mL) and ethyl acetate (20 mL). The resulting precipitate was collected by filtration and dried under a vacuum to give **28** as a brown solid (178 mg, 56%): mp 239 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.45 (3H, s), 5.34 (2H, s), 6.95 (2H, d, $J = 9.0$ Hz), 6.99 (1H, s), 7.26 (2H, d, $J = 9.0$ Hz), 7.52−7.70 (4H, m), 7.81 (1H, d, $J = 8.8$ Hz), 7.92 (1H, d, $J = 8.8$ Hz), 8.81 (2H, br s), 8.87 (1H, s), 10.68 (1H, s), 13.79 (1H, s). Anal. ($C_{24}H_{20}ClN_3O_2{\cdot}HCl{\cdot}1.3H_2O$) C, H, N.

***N*-(2-Phenoxymethylphenyl)-4-amino-2-methylquinoline-6-carboxamide (27).** A solution of ethyl 4-aminobenzoate **75** (16.5 g, 0.1 mol) and ethyl acetoacetate (15 mL, 0.12 mol) in dichloromethane (50 mL) was stirred at room temperature for 4 h and concentrated under a vacuum. The residue was chromatographed on silica gel eluted with hexane/ethyl acetate (9:1) to give ethyl 3-(4-(ethoxycarbonyl)phenylamino)crotonate **76** as a slightly yellow solid (19.4 g, 70%). The powder form of **76** (8.13 g, 29.3 mmol) was added in aliquots to Dowtherm A at 280 °C, and the mixture was stirred for 4 h. After cooling to room temperature, the precipitate was collected by filtration and washed with hexane (100 mL). Then 1 N aqueous sodium hydroxide (31 mL, 31 mmol) was added to a solution of the product in ethanol (500 mL), and the mixture was refluxed for 8 h. After removal of the solvent under a vacuum, the residue was diluted with water (100 mL), and the aqueous solution was acidified with 37% hydrochloric acid. The resulting precipitate was collected by filtration and washed with water (30 mL) to give 4-hydroxy-2-methylquinoline-6-carboxylic acid **77** as a pink solid (4.42 g, 80%). A solution of diethyl azodicarboxylate (4.7 mL, 45 mmol) in dichloromethane (50 mL) was added dropwise to a solution of 2-nitrobenzyl alcohol **78** (6.89 g, 45 mmol), phenol (2.82 g, 30 mmol), and triphenylphosphine (11.8 g, 45 mmol) in tetrahydrofuran (50 mL). The mixture was stirred at room temperature for 20 h and concentrated under a vacuum. Ethyl ether (100 mL) was added to the residue, and the precipitate was removed by filtration. The filtrate was evaporated under a vacuum, and the crude product was chromatographed on silica gel eluted with hexane/ethyl acetate (6:1) to give 1-nitro-2-(phenoxymethyl)benzene **79** as a slightly brown oil (7.54 g, 81%). Tin(II) chloride dihydrate (9.1 g, 40.4 mmol) was added to a solution of **79** (1.85 g, 8.07 mmol) in ethyl acetate (16 mL), and the mixture was heated at 50 °C for 3.5 h. The reaction mixture was alkalinized to pH 8−9 with saturated aqueous sodium bicarbonate and the solution was filtered through Celite to remove the precipitate. Then the filtrate was washed with water (20 mL) and brine (20 mL), dried over sodium sulfate, and concentrated. The crude product was chromatographed on silica gel eluted with hexane/ethyl acetate (6:1) to give 2-(phenoxymethyl)aniline **80** as a slightly yellow solid (852 mg, 53%). 1-Ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (761 mg, 3.97 mmol) and (dimethylamino)pyridine (42 mg, 0.34 mmol) were added to a solution of **77** (647 mg, 3.42 mmol) and **80** (852 mg, 4.28 mmol) in dimethylformamide (14 mL), and the mixture was stirred at room temperature for 3 h. Saturated aqueous sodium bicarbonate (100 mL) was added to the reaction mixture, and the aqueous solution was extracted with ethyl acetate (100 mL). The organic layer was washed with water (50 mL), dried over magnesium sulfate, and concentrated. Toluene (20 mL) was added to the residual oil, and the resulting precipitate was collected by filtration to give the 4-hydroxyquinoline-6-carboxamide derivative **81** as a slightly yellow solid (260 mg, 20%). A suspension of **81** (260 mg, 0.68 mmol) and dimethyl sulfate (0.1 mL, 1.16 mmol) in toluene (5 mL) was stirred at 100 °C for 3 h. After cooling to room temperature, the solvent was removed by decantation and the residual oil was dissolved in water (5 mL). Then the aqueous solution was alkalinized with 35% aqueous sodium hydroxide and extracted with chloroform (10 mL), after which the organic layer was washed with brine (10 mL), dried over magnesium sulfate, and concentrated. The crude product was chromatographed on silica gel eluted with chloroform/methanol (19:1) to give 4-methoxyquinoline-6-carboxamide derivative **82** as a slightly yellow solid (207 mg, 76%). A mixture of **82** (207 mg, 0.52 mmol) and ammonium acetate (601 mg, 7.8 mmol) was heated at 135 °C for 1 h. After cooling to room temperature, saturated aqueous sodium bicarbonate (10 mL) was added to the reaction mixture. Then the precipitate was collected by filtration and washed with water (10 mL). The crude product was chromatographed on silica gel eluted with chloroform/methanol/ammonium hydroxide (9:1:0.1) to give **27** as a colorless solid (51 mg, 26%): mp 198 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.57 (3H, s), 3.45 (3H, s), 5.17 (2H, s), 6.60 (1H, s), 7.06 (2H, d, $J = 8.9$ Hz), 7.34 (2H, d, $J = 8.9$ Hz), 7.01−7.51 (4H, m), 7.64−7.81 (2H, m), 8.56 (1H, s), 8.88 (1H, s), 8.97 (1H, s). Anal. ($C_{24}H_{21}N_3O_2{\cdot}0.3H_2O$) C, H, N.

Biological Studies. 1. ORL$_1$ Receptor Binding Assay. A suspension of membranes from human ORL$_1$-expressing HeLa cells in 50 mM Tris buffer (pH 8.5) containing 2 mM ethylenediaminetetraacetic acid, 0.1 mM *p*-aminophenylmethanesulfonyl fluoride, and 2 mg/mL bovine serum albumin

(25 μg protein/mL) was incubated at room temperature for 30 min with 0.5 nM ^{3}H-labeled nociceptin and various concentrations of test compounds. The membranes were collected by filtration using Unifilter 96GF/B (Packard), and radioactivity was counted with a TopCount A9912V scintillation counter (Packard). Nonspecific binding (6.0%) was determined by adding 1 μM unlabeled nociceptin to the reaction mixture, and specific binding was calculated by subtracting nonspecific binding from the total binding. Data are the mean ± SE ($n = 3-6$).

2. Inhibition of Cyclic AMP Accumulation. Human ORL$_1$ receptor-expressing HeLa cells were incubated in 1 mL of Eagle's MEM buffer containing bovine serum albumin (0.1%), forskolin (10 μM), 3-isobutyl-1-methylxanthine (2 mM), and various concentrations of compound **11** in the presence or absence of nociceptin (0.1 nM). After 15 min at 37 °C, the buffer was removed and the residual cells were frozen with dry ice in methanol. Cyclic AMP was measured using an EIA kit (Amersham Pharmacia Biotech). Data are the mean ± SE ($n = 3$).

3. μ-Opioid Receptor Binding Assay. A suspension of membranes from human μ-opioid receptor-expressing CHO-K1 cells in 50 mM Tris-HCl buffer (pH 7.4) containing 5 mM $MgCl_2$ and 10% sucrose was incubated at room temperature for 2.5 h with 0.33 nM ^{3}H-labeled diprenorphine and various concentrations of compound **11**. The membranes were collected by filtration using Whatman 934-AH (Whatman), and radioactivity was counted with a TopCount A9912V scintillation counter (Packard). Nonspecific binding (6.4%) was determined with 10 μM naloxone. Specific binding was calculated by subtracting nonspecific binding from the total binding. Data are the mean ± SE ($n = 3$).

4. κ-Opioid Receptor Binding Assay. A suspension of membranes from human κ-opioid receptor-expressing HEK 293 cells in 50 mM Tris buffer (pH 7.4) containing 5 mM $MgCl_2$, 1 mM EDTA, and 10% sucrose was incubated at room temperature for 1 h with 0.41 nM ^{3}H-labeled diprenorphine and various concentrations of compound **11**. The membranes were collected by filtration using Whatman 934-AH (Whatman), and radioactivity was counted with a TopCount A9912V scintillation counter (Packard). Nonspecific binding (2.3%) was determined with 100 μM naloxone. Specific binding was calculated by subtracting nonspecific binding from the total binding. Data are the mean ± SE ($n = 3$).

5. δ-Opioid Receptor Binding Assay. A suspension of membranes from human δ-opioid receptor-expressing CHO-K1 cells in 50 mM Tris-HCl buffer (pH 7.4) containing 5 mM $MgCl_2$ and 10% sucrose was incubated at room temperature for 1 h with 0.55 nM ^{3}H-labeled naltrindole and various concentrations of compound **11**. The membranes were collected by filtration using Whatman 934-AH (Whatman), and radioactivity was counted with a TopCount A9912V scintillation counter (Packard). Nonspecific binding (4.0%) was determined with 10 μM naloxone. Specific binding was calculated by subtracting nonspecific binding from the total binding. Data are the mean ± SE ($n = 3$).

6. In Vivo Allodynia Test. Unanesthetized 4-week-old male ICR mice (Charles River Japan, Tokyo) were injected intrathecally with nociceptin (50 pg/5 μL). A test compound (0.3 mg/kg) suspended in 0.5% methyl cellulose solution or the vehicle (control) was administered orally at 60 min before nociceptin injection. Mechanical allodynia was assessed once every 5 min over a 20-min period after intrathecal injection of nociceptin by stroking the flank of each mouse with a paintbrush. The allodynic response was ranked as follows: (0) no response; (1) mild squeaking with attempts to move away from the brush; (2) vigorous squeaking evoked by stroking, biting at the brush, or strong efforts to escape. Results are shown as the mean ± SE ($n = 9$). Statistical evaluation of the results was done with the Mann–Whitney U-test ($^*p < 0.05$).

7. In Vivo Hot Plate Test. Four-week-old male ICR mice (Charles River Japan, Tokyo) were placed on a hot plate (55–56 °C), and the time until the mice showed the first avoidance response (jumping or escaping) was recorded. A test compound suspended in 0.5% methyl cellulose or vehicle (control) was administered orally at 60 min before the start of the hot plate test. Results are shown as the mean ± SE ($n = 12$). Statistical evaluation of the results was done with Dunnett's two-tailed test ($^{**}p < 0.01$).

8. In Vivo Formalin-Induced Paw-Licking Response. Eight-week-old male SD rats (Charles River Japan, Tokyo) were injected with 50 μL of 5.0% formalin solution into the dorsal surface of the left hindpaw. A solution of compound **11** (3.0 mg/kg) in saline or vehicle was administered orally at 60 min before formalin injection, or a solution of morphine (3.0 mg/kg) in saline or vehicle was administered subcutaneously at 20 min before formalin injection. A solution of naloxone hydrochloride (10 mg/kg) in saline or vehicle was administered subcutaneously 30 min before formalin injection. Licking times were recorded for 5 min from 0–5 min after formalin injection (first-phase response) and for 30 min from 15–45 min after formalin injection (second-phase response). Results are shown as the mean ± SE ($n = 7$ or 8). Statistical evaluation of the results was done with Tukey's compromise test ($^{**}p$ or $^{\#\#}p < 0.01$).

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