3,4-Dihydro-2(1*H*)-quinolinone as a Novel Antidepressant Drug: Synthesis and Pharmacology of 1-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone and Its Derivatives

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To develop a novel antidepressant drug with central nervous system-stimulating activity, we prepared a series of 1-[*ω*-(4-substituted phenyl-1-piperazinyl)alkyl]-3,4-dihydro-2(1*H*)-quinolinone derivatives and examined their activities by their effects at 30 and 100 mg/kg po on the sleeping time of mice anesthetized with halothane and on the time required for recovery from coma induced in mice by cerebral concussion. We examined their binding affinities for *σ* receptors by evaluating their ability to inhibit [^{3}H]-1,3-di(*o*-tolyl)guanidine ([^{3}H]DTG) binding to the rat whole brain membrane in comparison with three putative *σ* receptor agonists: 1,3-di(*o*-tolyl)guanidine (DTG, **66**), (+)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazecin-8-ol (SKF10,047, **67**), and (+)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazecin-8-ol (pentazocine, **68**). Among the series of derivatives, 1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone hydrochloride **(34b)** and its mesylate **(34c)**, at a dose of 30 mg/kg po, reduced the sleeping time and the time for recovery from coma and they inhibited [^{3}H]DTG binding for *σ* receptors. The putative *σ* receptor agonists reduced the sleeping time and the time for recovery from coma whereas two *σ* receptor antagonists, α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol hydrochloride (BMY14802, **69)** and *cis*-9-[3-(3,5-dimethyl-1-piperazinyl)-propyl]carbazole dihydrochloride (rimcazole, **70),** were inactive in the two tests. Preadministration of the putative *σ* receptor antagonists **69** (3 mg/kg po) and **70** (30 mg/kg po) completely antagonized the actions of **34b** and the *σ* receptor agonists in the test for recovery from coma. These results suggested that **34b** and **34c** are *σ* receptor agonists. Furthermore, a single administration of 1 and 10 mg/kg po **34b** and **34c** showed antidepressant-like activity by reducing the immobility time in the forced-swimming test with mice, while a tricyclic antidepressant, 10,11-dihydro-*N*,*N*-dimethyl-5*H*-dibenz[*b*,*f*]azepine-5-propanamine hydrochloride (imipramine, **1)** (10 and 30 mg/kg po), did not reduce the time after a single administration. **1** reduced the time after repeated administration of 30 mg/kg po once a day for 4 days. The structure−activity relationship of the series of compounds is also discussed.

Introduction

A prototypic tricyclic antidepressant, 10,11-dihydro-*N*,*N*-dimethyl-5*H*-dibenz[*b*,*f*]azepine-5-propanamine (imipramine, **1**), inhibits the presynaptic reuptake of monoamines, especially 4-(2-amino-1-hydroxyethyl)-1,2-benzenediol (norepinephrine) and 5-hydroxytryptamine (serotonine, 5-HT) in the central nervous system, and the monoamine reuptake inhibitory effect is believed to account for its clinical efficacy.[1,2] A number of tricyclic antidepressants with the monoamine reuptake inhibitory effect have been developed and widely used. Those classical tricyclic antidepressants, however, show anticholinergic and cardiovascular side effects, and cases of fatal overdose with their use have been known.[3,4] Furthermore, they required at least several weeks until manifestation of therapeutic effect in depressive patients. The adverse effects, anticholinergic and cardiovascular toxicity in the classical tricyclic antidepressant treatments, have been reduced by the introduction of newer antidepressant drugs that are atypical in both structure and pharmacology, i.e., selective 5-HT reuptake inhibitors. However, none of them have a more rapid onset of action or a broader range of efficacy than the classical tricyclic antidepressants.[5] Thus, novel antidepressants with faster onset action, greater efficacy, and greater safety than the classical tricyclic antidepressants are demanded.[1,2,5] Such novel antidepressants will probably emerge from quite different approaches from those in traditional developments of tricyclic antidepressants.[1]

Depression is not a homogeneous entity, and many neurotransmitter systems, other than monoaminergic systems such as noradrenergic, serotonergic, and dopaminergic systems, neuroendocrinergic systems, and neuropeptides, have been suggested as being involved in the pathophysiology of depression.[1,2,5] Disturbance of circadian rhythm, sleep and wake cycle, in depressive patients has been reported, and sleep deprivation therapies for treatment of depressive patients have been known.[1,6]

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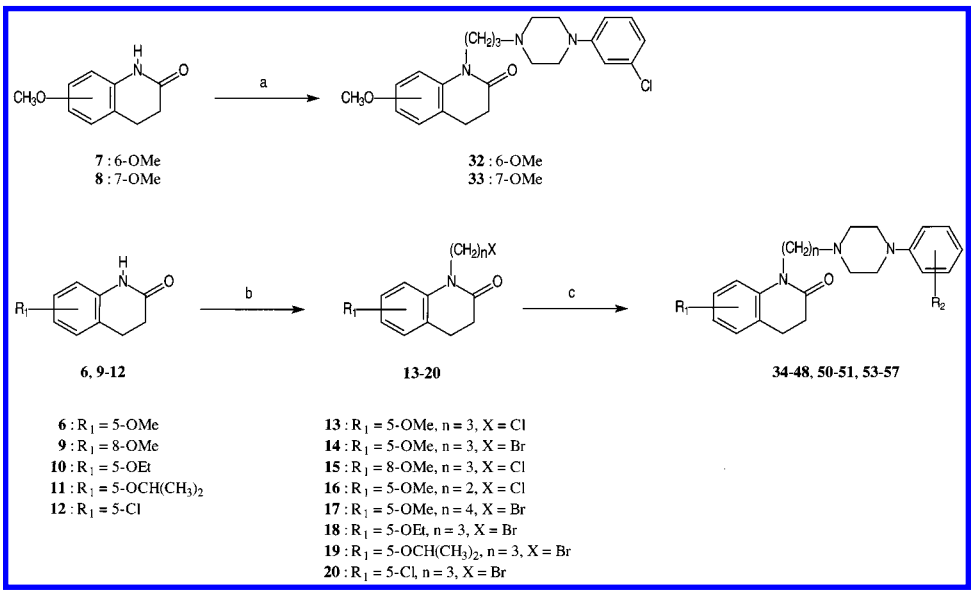
Scheme 1[a]



[a] Conditions: (a) (1) 60% NaH, DMF, (2) 1-chloro-3-[4-(3-chlorophenyl)-1-piperazinyl]propane hydrochloride in DMF; (b) (1) 60% NaH, DMF, (2) 1,ω-dihaloalkane in DMF; (c) NaI, K_2CO_3, phenylpiperazines in CH_3CN. n = 2, 3, or 4.

We are interested in the development of a central nervous system-activating agent, which accelerates awakening from 2-bromo-2-chloro-1,1,1-trifluoroethane (halothane)-induced anesthesia.[7,8] The γ-aminobutyric acid system is suggested to be involved in anesthesia[9,10] and also plays important roles in the pathophysiology of depression.[11−14] The central nervous system activator thyrotropin-releasing hormone, which accelerates awakening from anesthesia induced by halothane,[1,7,8] also modulates γ-aminobutyric acid system transmission[15] and potentiates the effects of **1** in the experimental model for depression.[16] We believe that a compound which affects sleep and wakefulness, as a central nervous system activator, might be an effective antidepressant. The belief led us to synthesize a novel series of 3,4-dihydro-2(1*H*)-quinolinone derivatives. We examined the central nervous system-activating potential of the synthesized compounds by their effects on the sleeping time induced by halothane and on the time required for recovery from coma induced by cerebral concussion in mice. We found that some 5-methoxy-3,4-dihydro-2(1*H*)-quinolinone derivatives had potent central nervous system-stimulating activity and also that the selected compound showed the antidepressant activity in the forced-swimming test.[17] In addition, we found that the derivatives examined showed binding affinity to σ receptors. σ Receptors modulate neurotransmission in monoaminergic and neuroendocrinergic systems and in neuropeptides.[18−20] Also, the possibility of involvement of the σ receptors in the pathophysiology of affective disorders has been suggested.[21,22] However, the involvement of σ receptors in sleep and wakefulness has not been reported.

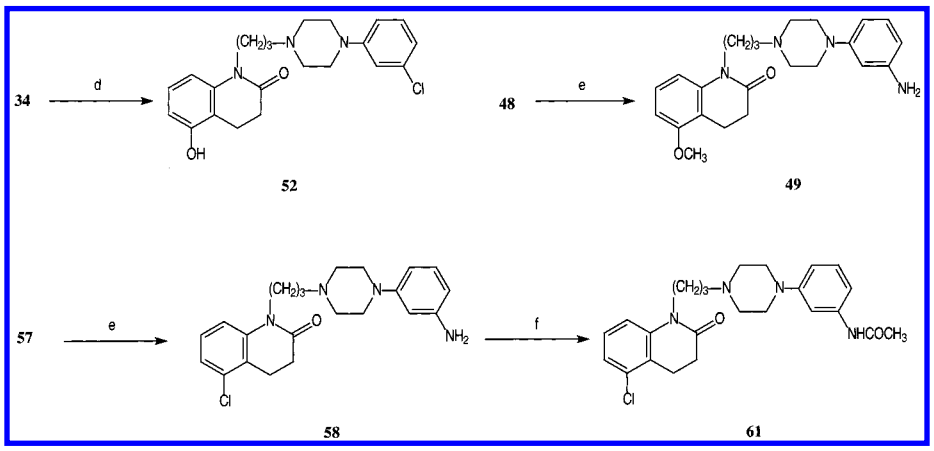
In this paper, we will describe (1) the synthesis of the novel series of 3,4-dihydro-2(1*H*)-quinolinones and their effects on the sleeping time induced by halothane, (2) their structure−activity relationships, (3) their effects on coma induced by concussion in mice, (4) their affinities for σ receptors, and (5) preliminary antidepressant effects of the selected compound.

Chemistry

Our target compounds, 1-[ω-[4-(substituted phenyl)-1-piperazinyl]alkyl]-2(1*H*)-quinolinone derivatives listed in Tables 1 and 2, were prepared as shown in Schemes 1−4.

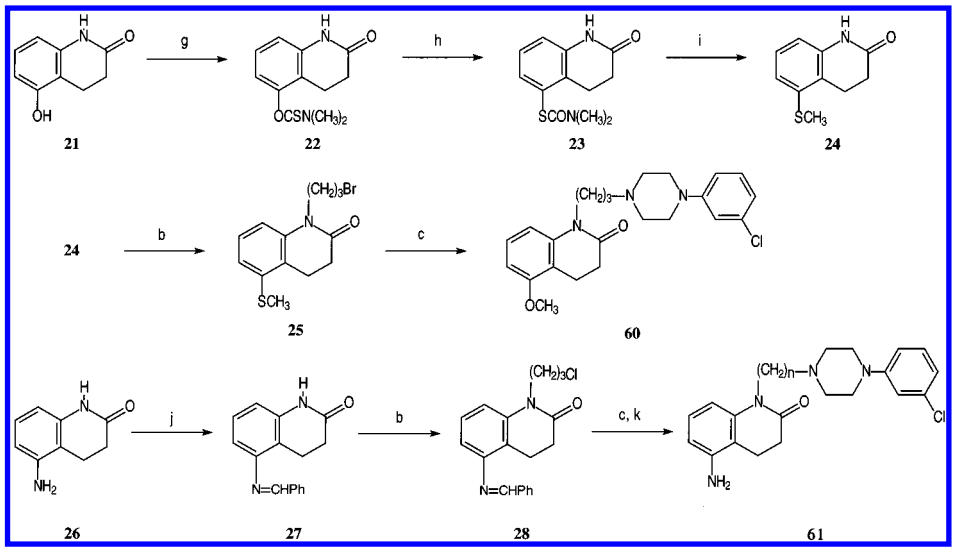
Scheme 1 shows two methods for the preparation of new target compounds **32**−**48, 50, 51**, and **53**−**57**. Starting materials, 5-, 6-, 7-, and 8-methoxy-3,4-dihydro-2(1*H*)-quinolinones (**6**,[23,24] **7**,[25] **8**,[26] and **9**[27]), 5-ethoxy- (**10**)[23] and 5-isopropoxy-3,4-dihydro-2(1*H*)-quinolinone (**11**),[23] and 5-chloro-3,4-dihydro-2(1*H*)-quinolinone (**12**),[28] were prepared according to the reported methods. Compounds with the 3-[4-(3-chlorophenyl)-1-piperazinyl]propyl moiety can be prepared by the method reported for the preparation of compounds **3**,[29−32] **4,** and **5**.[26,29] Thus, **7**[25] was converted to its sodium salt by the addition of NaH in DMF; subsequent alkylation with 1-chloro-3-[4-(3-chlorophenyl)-1-piperazinyl]propane hydrochloride, which is commercially available, produced 1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-6-methoxy-2(1*H*)-quinolinone (**32**). Analogously, 1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone (**33**) was prepared from **8**. A series of compounds with an ω-[4-(substituted phenyl)-1-piperazinyl]alkyl moiety was prepared by another method.[30] Thus, **6** was converted to its sodium salt with NaH in DMF followed by alkylation with 1-bromo-3-chloropropane to produce 1-(3-chloropropyl)-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (**13**). Conversion of **13** to 3,4-dihydro-1-(3-iodopropyl)-5-methoxy-2(1*H*)-quinolinone with NaI and subsequent amination by 4-(3-chlorophenyl)-1-piperazine led to 1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (**34**). Analogously, alkylation of a sodium salt of **9** with 1-bromo-3-chloropropane produced 1-(3-chloropropyl)-3,4-dihydro-8-methoxy-2(1*H*)-quinolinone (**15**) as an oil, which was reacted with 4-(3-chlorophenyl)-1-piperazine without isolation to give 1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-8-methoxy-2(1*H*)-quinolinone (**35**). Alkylation of **6** with

Scheme 2[a]



[a] Conditions: (d) 47% HBr reflux; (e) H_2, 3 kg/cm^2, 5% Pd−C in EtOH; (f) acetic anhydride.

Scheme 3[a]



[a] Conditions: (g) (1) 60% NaH, DMF, (2) $ClCSN(CH_3)_2$ in DMF; (h) 200 °C in diphenyl ether; (i) KOH in MeOH, reflux, then MeI; (j) benzaldehyde in EtOH, reflux; (k) 6 N HCl, reflux.

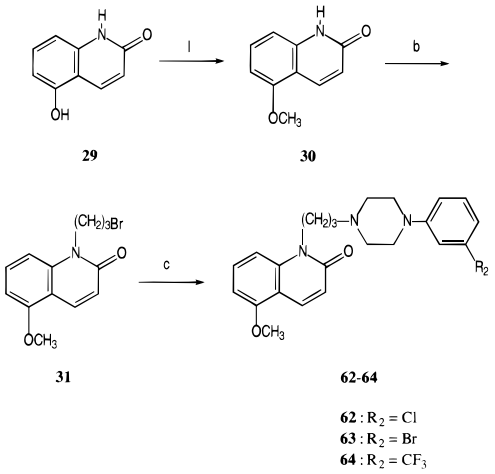
1,3-dibromopropane and 1,4-dibromobutane gave 1-(3-bromopropyl)- (**14**) and 1-(4-bromobutyl)-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (**17**), respectively. Alkylation of **6** with 1-bromo-2-chloroethane afforded 1-(2-chloroethyl)-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (**16**), whereas that with 1,2-dibromoethane did not give the intermediate. Reaction of **16** and **17** with 1-(3-chlorophenyl)piperazine gave 1-[2-[4-(3-chlorophenyl)-1-piperazinyl]ethyl]-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (**36**) and 1-[4-[4-(3-chlorophenyl)-1-piperazinyl]-butyl]-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (**37**), respectively. Analogously, compounds **38**−**48**, **50**, **51,** and **53**−**57** were prepared from **13, 18, 19,** and **20**, respectively, and the corresponding phenylpiperazines.

Scheme 2 shows preparation of compounds **49**, **52**, **58**, and **59**. Demethylation of **34** by refluxing with 47% HBr gave **52**. Catalytic hydrogenation of **48** afforded **49**. Analogously, compound **58** was obtained from **57**. Acetylation of **58** with acetic anhydride gave **59**.

Scheme 3 shows the preparation of the 5-methylthio- and 5-amino-3,4-dihydro-2(1*H*)-quinolinone derivatives (**60** and **61**). 3,4-Dihydro-5-methylthio-2(1*H*)-quinolinone (**24**) was prepared from 3,4-dihydro-5-hydroxy-2(1*H*)-quinolinone (**21**)[24] by applying the method reported for preparation of 6-butylthio-1(2*H*)-naphthalenone.[33] Thus, acylation of 3,4-dihydro-5-hydroxy-2(1*H*)-quinolinone (**21**) with *N*,*N*-dimethylthiocarbamoyl chloride in the presence of NaH in DMF gave the *N*,*N*-dimethylthiocarbamoyloxy derivative **22**. Rearrangement of **22** in diphenyl ether at 200 °C afforded *N*,*N*-dimethylcarbamoylthio derivative **23**. Hydrolysis of **23** in an alkaline solution and subsequent methylation with methyl iodide gave **24**. Alkylation of the sodium salt of **24** with 1,3-dibromopropane gave **25**, which was converted to the 3-iodopropyl derivative and followed by amination with 1-(3-chlorophenyl)piperazine to afford compound **60**. Compound **26**[34] was converted to the Shiff base with benzaldehyde (**27**). Alkylation of the sodium salt of **27** with 1-bromo-3-chloropropane gave **28**, which was converted to an iodide derivative with NaI, followed by amination with phenylpiperazine and subsequent hydrolysis in diluted hydrochloric acid to produce compound **61**.

Scheme 4 shows the preparation of 5-methoxy-2(1*H*)-quinolinone derivatives **62**−**64**. Starting compound, 5-methoxy-2(1*H*)-quinolinone (**30**),[36] was prepared from 5-hydroxy-2(1*H*)-quinolinone (**29**)[35] by reaction with methyl iodide in the presence of K_2CO_3 in DMF.

Scheme 4[a]



[a] Conditions: (l) K_2CO_3, MeI in DMF.

Alkylation of the sodium salt of **30** with 1,3-dibromopropane gave **31**, which was converted to the iodide derivative with NaI and followed by amination with phenylpiperazines to produce compounds **62**−**64**.

Pharmacology

To find target compounds which would possess the central nervous system-stimulating activity, we used the test for effects on sleeping time of anesthetized mice with halothane[37] as a primary screen (Table 3). The central nervous system stimulant 1-phenyl-2-aminopropane (amphetamine) reduces the sleeping time, but the central nervous system depressor sodium 5-ethyl-5-(1-methylbutyl)barbiturate (pentobarbital sodium) prolongs it.[37] The central nervous system-stimulating activities of several compounds were also confirmed by evaluating their effects on the time required for recovery of righting reflex from coma induced by cerebral concussion in mice (Table 3). This test has been reported as the experimental model for cerebral trauma, and the central nervous system activator pyroglutamylhistydylprolineamide tartarate (TRH-T, **65)**[38] and its γ-butyrolactone γ-carbonyl analogue[39] show promotional effects in this test. Binding affinities to σ receptors for all prepared compounds were evaluated by their abilities to inhibit the binding of [^{3}H]-1,3-di(*o*-tolyl)guanidine ([^{3}H]DTG) to rat whole brain membranes[40] (Table 3). The clinically available central nervous system activator **65**, the classical tricyclic antidepressant **1**, the putative σ receptor agonists 1,3-di(*o*-tolyl)guanidine (DTG, **66**), (+)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazecin-8-ol (SKF10,047, **67),** and (+)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazecin-8-ol (pentazocine, **68**), and the putative σ receptor antagonists α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol hydrochloride (BMY14802, **69)** and *cis*-9-[3-(3,5-dimethyl-1-piperazinyl)propyl]carbazole dihydrochloride (rimcazole, **70)** were also examined in the two tests as reference drugs.

The effects of the putative σ receptor antagonists on the activities of the selected compounds in the tests for acceleration recovery from coma were examined to clarify whether their central nervous system-stimulating activities are related to their σ receptor agonistic activities (Table 4). Finally, to assess the clinical potential for an antidepressant drug, we examined the effects of the selected compounds on the immobility time in a forced-swimming test.[17] This test is recognized for the valid test of antidepressant activity and is the only method reported to predict the potency of known antidepressants (Table 5). Classical tricyclic antidepressants shorten the time in this test only after repeated administration.[1−5]

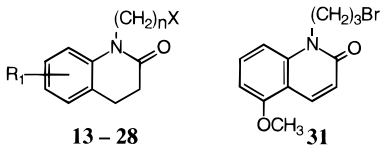
Results and Structure−Activity Relationships

As shown in Table 3, we confirmed that the central nervous system activator **65** (1 mg/kg ip) antagonized halothane by reducing sleeping time and the central nervous system depressor 7-chloro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one (diazepam, **71)** (10 mg/kg po) facilitated the effects of halothane by prolonging it. The putative σ receptor agonists **67** (3 mg/kg sc) and **68** (3 mg/kg sc) antagonized the action of halothane, whereas the putative σ receptor antagonist **70** (30 mg/kg po) showed no effect on the sleeping time.

In the search for a lead compound, we initially examined two types of 2(1*H*)-quinolinone derivatives **2**−**5** represented in Chart 1. The neuroleptic agent **2**,[41] an *O*-alkyl derivative, prolonged the sleeping time at 8 mg/kg po. With *N*-alkyl type compounds, the analgesic[29] and antihistamine[30] agent **3** without a substituent on the 3,4-dihydro-2(1*H*)-quinolinone nucleus did not affect the sleeping time at a dose of 100 mg/kg po. The analgesic agent **4**[26,29] with the hydrophobic benzyloxy substituent at the 6-position prolonged the sleeping time at 100 mg/kg po like **2,** whereas **5**[26,29] with the hydrophilic hydroxyl substituent at the 7-position did not affect sleeping time at a dose of 100 mg/kg po. Introduction of a methoxy group to the 6- and 7-positions in **3** resulted in the central nervous system depressors **32** and **33**, respectively. Positional changes of the methoxy substituent in **32** and **33** from the 6- and 7-positions, respectively, to the 5-position dramatically altered the action of the parent compounds to produce **34b**, the first 3,4-dihydro-2(1*H*)-quinolinone derivative with the central nervous system-stimulating activity. We made a variety of modifications on **34b** as a lead compound and examined the modification effects with respect to electronic and lipophilic factors of the substituents. Our purpose in this paper is to find the most potent oral administrated compound. Therefore, the structure−activity relationships are discussed below with the results obtained by oral administration at 30 or 100 mg/kg (Table 3).

First, we examined the effects of the length of the alkyl chain, positional change of the chloro substituent, introduction of another chlorine substituent at the 5-position, and replacement of the chloro substituent with a variety of substituents in **34b**. Change of the side chain from propyl to ethyl (**36**) and butyl (**37**), positional change in the chloro substituent from 3 to 2 and 4 (**38**, **39**), and introduction of another chlorine substituent to the 5-position (**40**) resulted in the inactive compounds. Replacement of the chlorine substituent in the 3-chlorophenyl-1-piperazinyl moiety in **34** with a more bulky bromine substituent (**42**) or with a more electron-withdrawing trifluoromethyl group **(43)** or a nitro group (**48**) retained the stimulating activity. On the other

Table 1. 1-(ω-Haloalkyl)-3,4-dihydro-2(1*H*)-quinolinones **13**−**28** and 2(1*H*)-Quinolinone **31**

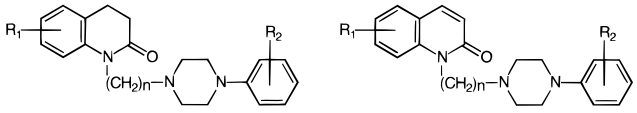


13 – 28 **31**

no.	R_1	*n*	X	yield (%)[a,b]	mp (°C)	formula	analysis[c]
13	5-OCH_3	3	Cl	39	103−105	$C_{13}H_{16}NO_2Br$	C, H, N
14	5-OCH_3	3	Br	8	106−107	$C_{13}H_{16}NO_2Br$	C,[d] H, N
15	8-OCH_3	3	Cl	27	oil[e]	$C_{13}H_{16}NO_2Cl$	
16	5-OCH_3	2	Cl	38	114−115	$C_{12}H_{14}NO_2Cl$	C, H, N
17	5-OCH_3	4	Br	47	69−70	$C_{14}H_{18}NO_2Br$	C, H, N
18	5-OCH_2CH_3	3	Br	64	90−91	$C_{14}H_{18}NO_2Br$	C, H, N
19	5-$OCH(CH_3)CH_3$	3	Br	70	54−55	$C_{15}H_{20}NO_2Br$	C, H, N
20	5-Cl	3	Br	54	oil[e]	$C_{12}H_{13}NO_2BrCl$	
25	5-SCH_3	3	Br	64	oil[e]	$C_{13}H_{16}NOSBr$	
28	5-N=CHPh	3	Cl	80	oil[e]	$C_{19}H_{19}NO_2Cl$	
31	5-OCH_3	3	Br	64	161−161.5	$C_{13}H_{14}NO_2Br$	C, H, N[f]

[a] Yields were not optimized in most cases. [b] EtOH was used as a solvent for recrystallization. [c] C, H, N analyses were within ±0.4% of the calculated value. [d] C: calcd 52.37, found 52.82. [e] Used in the next step without further purification. [f] N: calcd 4.73, found 4.24.

Table 2. Physical and Chemical Data of 3,4-Dihydro-2(1*H*)-quinolinone and 2(1*H*)-Quinolinone Derivatives



32 – 61 **62 – 64**

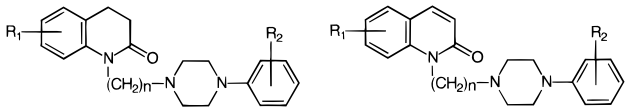
no.	R_1	R_2	*n*	yield[a] (%)	mp[b] (°C)	formula	analysis[c]
32	6-OMe	3-Cl	3	75	159−161	$C_{23}H_{28}N_3O_2Cl{\cdot}2HCl$	C, H, N
33	7-OMe	3-Cl	3	77	224−229 dec[d]	$C_{23}H_{28}N_3O_2Cl{\cdot}2HCl$	C, H, N
34b	5-OMe	3-Cl	3	46	224−226	$C_{23}H_{28}N_3O_2Cl{\cdot}HCl$	C, H, N
34c	5-OMe	3-Cl	3	75	192−194	$C_{23}H_{28}N_3O_2Cl{\cdot}CH_3SO_3H{\cdot}H_2O$	C, H, N
35	8-OMe	3-Cl	3	12	169−171	$C_{23}H_{28}N_3O_2Cl{\cdot}HCl$	C, H, N
36	5-OMe	3-Cl	2	29	132−132.5	$C_{22}H_{26}N_3O_2Cl$	C, H, N
37	5-OMe	3-Cl	4	60	128−129 dec	$C_{24}H_{30}N_3O_2Cl$	C, H, N
38	5-OMe	2-Cl	3	54	214−215 dec	$C_{23}H_{28}N_3O_2Cl{\cdot}HCl$	C, H, N
39	5-OMe	4-Cl	3	46	124−125	$C_{23}H_{28}N_3O_2Cl$	C, H, N
40	5-OMe	3,5-Cl_2	3	42	226−228 dec	$C_{23}H_{27}N_3O_2Cl_2{\cdot}HCl{\cdot}1/2H_2O$	C, H, N
41	5-OMe	3-F	3	46	236−240 dec	$C_{23}H_{28}N_3O_2F{\cdot}HCl$	C, H, N
42	5-OMe	3-Br	3	46	228−231 dec	$C_{23}H_{28}N_3O_2Br{\cdot}HCl$	C,[e] H, N
43	5-OMe	3-CF_3	3	42	207−208	$C_{24}H_{28}N_3O_2F_3{\cdot}HCl$	C, H, N
44	5-OMe	3-Me	3	63	217−228 dec	$C_{24}H_{31}N_3O_2{\cdot}2HCl$	C, H, N
45	5-OMe	3-OH	3	39	205−208 dec	$C_{23}H_{29}N_3O_3{\cdot}HCl{\cdot}3/2H_2O$	C, H, N
46	5-OMe	3-OMe	3	45	176−177	$C_{24}H_{31}N_3O_3{\cdot}2HCl$	C, H, N
47	5-OMe	3-CN	3	28	235−236	$C_{24}H_{28}N_4O_2{\cdot}HCl{\cdot}1/2H_2O$	C, H, N
48	5-OMe	3-NO_2	3	33	221−222 dec	$C_{23}H_{28}N_4O_4{\cdot}HCl{\cdot}2H_2O$	C, H, N
49	5-OMe	3-NH_2	3	69	132−133	$C_{23}H_{30}N_4O_2$	C, H, N
50	5-OEt	3-Cl	3	43	221−224 dec	$C_{24}H_{30}N_3O_2Cl{\cdot}HCl$	C, H, N
51	5-O^{i}Pr	3-Cl	3	51	218−229 dec	$C_{25}H_{32}N_3O_2Cl{\cdot}HCl$	C, H, N
52	5-OH	3-Cl	3	74	200−201.5 dec	$C_{22}H_{26}N_4O_2Cl$	C, H, N
53	5-Cl	3-Cl	3	40	217 dec	$C_{22}H_{29}N_3OCl_2{\cdot}2HCl$	C, H, N
54	5-Cl	3-OMe	3	40	212−213 dec	$C_{23}H_{28}N_3O_2Cl{\cdot}2HCl$	C, H, N
55	5-Cl	3-OPr	3	30	186−188	$C_{25}H_{32}N_3O_2Cl{\cdot}2HCl$	C, H, N
56	5-Cl	3-OH	3	36	236−239	$C_{22}H_{26}N_3O_2Cl{\cdot}HBr$	C, H, N
57	5-Cl	3-NO_2	3	65	204−211 dec	$C_{22}H_{25}N_4O_3Cl{\cdot}HCl{\cdot}1/2H_2O$	C, H, N
58	5-Cl	3-NH_2	3	89	161−163	$C_{22}H_{27}N_4OCl$	C, H, N
59	5-Cl	3-NHAc	3	75	177−178	$C_{24}H_{29}N_4O_2Cl$	C, H, N
60	5-SMe	3-Cl	3	54	221−224	$C_{23}H_{28}N_3OSCl{\cdot}2HCl$	C,[f] H, N
61	5-NH_2	3-Cl	3	61	218−240 dec	$C_{22}H_{27}N_4OCl{\cdot}2HCl{\cdot}H_2O$	C, H, N
62	5-OMe	3-Cl	3	65	232−236 dec	$C_{23}H_{26}N_3O_2Cl{\cdot}HCl$	C,[g] H, N
63	5-OMe	3-Br	3	20	222−232 dec	$C_{23}H_{26}N_3O_2Br{\cdot}HCl$	C,[h] H, N
64	5-OMe	3-CF_3	3	45	221−228 dec	$C_{24}H_{26}N_3O_2F_3{\cdot}HCl$	C, H, N

[a] Yields were not optimized in most cases. [b] EtOH was used for recrystallization solvent unless otherwise indicated. [c] C, H, N analyses were within ±0.4% of the calculated value unless otherwise indicated. [d] Decomposed. [e] C: calcd 55.82, found 56.30. [f] C: calcd 54.93, found 59.93. [g] C: calcd 61.61, found 62.14. [h] C: calcd 55.94, found 56.45.

hand, replacement of the chlorine substituent with a smaller fluorine substituent (**41**), with electron-donating methyl (**44**), hydroxy (**45**), and methoxy (**46**) groups, and with a nitrile group (**47**), which has greater electron-withdrawing nature but less lipophilicity than a chloro group, gave inactive compounds. The compound with the electron-donating amino group (**49**) facilitated the action of halothane.

Subsequently, we examined the effects of the methoxy group at the 5-position in the 3,4-dihydro-2(1*H*)-quino-

Table 3. Biological Activities of 3,4-Dihydro-2(1*H*)-quinolinone and 2(1*H*)-Quinolinone Derivatives



32-61 **62-64**

				ST[a] (mean ± SE, s)			RRT[b] (mean ± SE, s, $n = 10$)			
no.	R_1	R_2	n	control group	treated group	% of control	control group	treated group	% of control	inhibn of [^{3}H]DTG binding (nM)[c]
32	6-OMe	3-Cl	3	566 ± 32	770 ± 87*	136	nt[d]	nt	−	650
33	7-OMe	3-Cl	3	566 ± 32	1280 ± 201**	226	nt	nt	−	1130
34b	5-OMe	3-Cl	3	566 ± 32	294 ± 53**	52	180 ± 19	36 ± 13**[e]	20	340 ± 110
34c	5-OMe	3-Cl	3	613 ± 17	414 ± 34**	68	165 ± 90	49 ± 15**[e]	30	nt
35	8-OMe	3-Cl	3	nt	nt	−	128 ± 19	109 ± 21	85	600
36	5-OMe	3-Cl	2	498 ± 55	676 ± 204	136	nt	nt	−	nt
37	5-OMe	3-Cl	4	478 ± 41	549 ± 32	115	nt	nt	−	nt
38	5-OMe	2-Cl	3	465 ± 62	675 ± 82	145	nt	nt	−	260 ± 360
39	5-OMe	4-Cl	3	465 ± 62	496 ± 74	107	nt	nt	−	460 ± 40
40	5-OMe	3,5-Cl_2	3	363 ± 23	310 ± 27	85	133 ± 13	168 ± 18	126	nt
41	5-OMe	3-F	3	465 ± 62	600 ± 53	129	nt	nt	−	nt
42	5-OMe	3-Br	3	498 ± 55	267 ± 53**	54	136 ± 8	61 ± 12**	45	420
43	5-OMe	3-CF_3	3	379 ± 32	250 ± 29**	66	134 ± 12	48 ± 13**	36	490 ± 140
44	5-OMe	3-Me	3	353 ± 26	426 ± 75	121	nt	nt	−	nt
45	5-OMe	3-OH	3	483 ± 59	400 ± 25	83	nt	nt	−	810
46	5-OMe	3-OMe	3	478 ± 41	579 ± 77	121	nt	nt	−	nt
47	5-OMe	3-CN	3	553 ± 35	465 ± 45	84	nt	nt	−	2470
48	5-OMe	3-NO_2	3	553 ± 35	339 ± 37**	61	141 ± 22	74 ± 12*	52	870 ± 140
49	5-OMe	3-NH_2	3	553 ± 35	1380 ± 128**	250	nt	nt	−	1210 ± 100
50	5-OEt	3-Cl	3	353 ± 26	238 ± 25**	67	113 ± 10	31 ± 11**	27	870
51	5-O^{i}Pr	3-Cl	3	353 ± 26	304 ± 28	86	nt	nt	−	nt
52	5-OH	3-Cl	3	585 ± 46	516 ± 55	88	nt	nt	−	nt
53	5-Cl	3-Cl	3	548 ± 33	677 ± 93	124	nt	nt	−	nt
54	5-Cl	3-OMe	3	548 ± 33	277 ± 48**	51	132 ± 8	36 ± 12**	27	130 ± 110
55	5-Cl	3-OPr	3	465 ± 44	393 ± 35	85	nt	nt	−	370
56	5-Cl	3-OH	3	564 ± 35	529 ± 55	94	nt	nt	−	240
57	5-Cl	3-NO_2	3	nt	nt	−	152 ± 21	110 ± 13	72	390
58	5-Cl	3-NH_2	3	504 ± 46	646 ± 70	128	nt	nt	−	710
59	5-Cl	3-NHAc	3	565 ± 35	778 ± 60**	138	nt	nt	−	670
60	5-SMe	3-Cl	3	363 ± 23	439 ± 42	121	nt	nt	−	nt
61	5-NH_2	3-Cl	3	nt	nt	−	128 ± 19	129 ± 15	101	nt
62	5-OMe	3-Cl	3	nt	nt	−	122 ± 13	131 ± 21	108	980 ± 130
63	5-OMe	3-Br	3	nt	nt	−	122 ± 13	70 ± 17*	57	150
64	5-OMe	3-CF_3	3	nt	nt	−	128 ± 19	65 ± 14*	51	820 ± 110
1[f]				nt	nt	−	177 ± 47	290 ± 29	164	nt
2[g]				311 ± 37	956 ± 82***	307	nt	nt	−	nt
3	H	3-Cl	3	616 ± 83	704 ± 109	114	138 ± 17	111 ± 8	80	620
4	6-OBz	H	3	561 ± 96	1097 ± 167**	196	nt	nt	−	>10000
5	7-OH	4-F	3	561 ± 96	582 ± 72	104	nt	nt	−	1320
65[h]				663 ± 74	377 ± 29**	57	173 ± 8	44 ± 13**	25	nt
66[i]				nt	nt	−	153 ± 9	101 ± 13*	66	400 ± 40
67[j]				581 ± 28	270 ± 32**	46	138 ± 29	34 ± 17**	25	H: 50 ± 17 L: 8940 ± 1520
68[k]				549 ± 23	370 ± 36*	67	170 ± 12	72 ± 19**	42	170 ± 7
69[l]				nt	nt	−	87 ± 27	111 ± 11	128	860 ± 30
70[m]				482 ± 38	490 ± 42	102	131 ± 9	115 ± 7	88	2503 ± 1033[n]
71[o]				245 ± 19	709 ± 67*	289	nt	nt	−	nt
72				625 ± 30	373 ± 40*	60	210 ± 14	54 ± 13**	26	>15000

[a] ST: sleeping time. Test compounds (100 mg/kg po) and reference drugs (po, ip, and sc as indicated by parentheses) were administered to 10 mice as a treated group ($n = 10$) at 30 min (ip and sc) and 1 h (po) before halothane load. The values for ST for treated and control groups are presented as mean ± SE (in seconds); significance was determined by two-tailed *t*-test, *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$ vs control group. [b] RRT: time required for recovery of righting reflex from coma induced by concussion (in seconds). Test compounds were administered 100 mg/kg po unless otherwise indicated to 10 mice ($n = 10$) as a treated group 1 h before concussion load. Reference agents were administered at doses as indicated at 30 min for ip and sc and 1 h for po, respectively, before concussion load. The values of RRT for treated and control groups are presented as mean ± SE (in seconds, $n = 10$); significance was determined by two-tailed *t*-test, *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$ vs control group. [c] Binding affinity for σ receptors was evaluated by the inhibitory effect of test compounds on [^{3}H]DTG to rat whole brain membrane. The IC_{50} values were calculated by computer analysis using the nonlinear least-squares method and are presented as mean ± SE after three experiments ($n = 3$) with three concentrations (100, 1000, and 10000 nM). The values without SE were after an experiment ($n = 1$) with three concentrations (100, 1000, and 10000 nM). [d] nt: not tested. [e] 30 mg/kg po. [f] Imipramine (30 mg/kg po). [g] 1 mg/kg ip. [h] TRH-T (1 mg/kg ip). [i] DTG (10 mg/kg ip). [j] (+)-SKF10,047 (3 mg/kg sc). [k] (+)-pentazocine (1 mg/kg sc). [l] BMY-14802 (3 mg/kg po). [m] Rimcazole (30 mg/kg po). [n] From ref 40. [o] Diazepam (10 mg/kg po).

linone nucleus in **34b**. Replacement of the methoxy group with an ethoxy group (**50**), which has a similar electron-donating nature and lipophilicity, retained the stimulating activity. On the other hand, replacement of the methoxy group with the higher lipophilic isopropoxy group (**51**), with the hydrophilic hydroxy group (**52**), and with a chloro (**53**) or a methylmercapto (**60**) group resulted in inactive compounds. Compound **54,**

Table 4. Effects of Several Antagonists on RRT of the σ Receptor Agonists and Compounds **34b**, **54,** and **72**

compound (dose) + antagonist (dose)	RRT[a] (mean ± SE, s, $n = 10$)	% of control
control	126 ± 11	100
34b (10 mg/kg po)	26 ± 10***	21
34b (10 mg/kg po) + **73** (0.3 mg/kg ip)	94 ± 15##	75
control	162 ± 11	100
34b (10 mg/kg po)	54 ± 22***	33
34b (10 mg/kg po) + **69** (3 mg/kg po)	155 ± 26###	96
control	149 ± 11	100
34b (10 mg/kg po)	72 ± 13***	48
34b (10 mg/kg po) + **70** (30 mg/kg po)	136 ± 15##	91
control	113 ± 10	100
54 (30 mg/kg po)	21 ± 6**	19
54 (30 mg/kg po) + **69** (3 mg/kg po)	106 ± 12##	94
control	168 ± 16	100
72 (30 mg/kg po)	54 ± 15***	32
72 (30 mg/kg po) + **73** (0.15 mg/kg ip)	162 ± 11##	96
control	162 ± 11	100
72 (10 mg/kg po)	87 ± 13**	54
72 (10 mg/kg po) + **69** (3 mg/kg po)	57 ± 20	35
control	151 ± 11	100
66 (DTG) (10 mg/kg po)	81 ± 11***	54
66 (DTG) (10 mg/kg po) + **69** (3 mg/kg po)	210 ± 31##	139
control	122 ± 12	100
67 (SKF10,047) (3 mg/kg po)	39 ± 7***	32
67 (SKF10,047) (3 mg/kg po) + **69** (3 mg/kg po)	169 ± 19###	94

[a] RRT: time for required recovery of righting reflex from coma induced by concussion (in seconds). Test compounds were administered at a dose of 10 mg/kg po unless otherwise indicated to 10 mice ($n = 10$) as a treated group at 1 h before concussion load. **73** (scopolamine, 0.15 or 0.3 mg/kg ip), **69** (BMY-14802, 3 mg/kg po), and **70** (rimcazole, 30 mg/kg, po) were administered at 15 min, 30 min, and 1 h, respectively, before test compounds were administered. The values of RRT for treated and control groups are presented as mean ± SE (in seconds, $n = 10$); significance was determined by two-tailed *t*-test, $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$ vs control group ($n = 10$), and by one-way ANOVA followed by two-tailed Dunnett's test, $\#p < 0.05$, $\#\#p < 0.01$, and $\#\#\#p < 0.001$ vs treated group ($n = 10$).

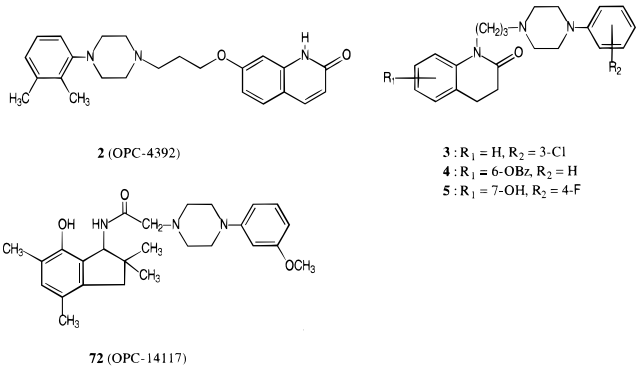
Table 5. Effects on Immobility Time in the Forced-Swimming Test in Mice

compd	dose (mg/kg po)	immobility time[a] ($n = 8$, mean ± SE, s)	% of control
1 (imipramine)[b]	0	198 ± 8	100
(single administration)	10	158 ± 10	80
	30	160 ± 9	81
1 (imipramine)[c]	0	178 ± 8	100
(repeated administration)	10	122 ± 24	68
	30	109 ± 22*	61
72[b]	0	120 ± 13	100
(single administration)	10	119 ± 14	99
	30	123 ± 10	102
34b[b]	0	115 ± 15	100
(single administration)	1	56 ± 9**	49
	10	61 ± 5**	53
34c[b]	0	199 ± 5	100
(single administration)	1	140 ± 14**	70
	10	138 ± 15**	69

[a] Eight mice were used in each group ($n = 8$), and immobility time is represented as mean ± SE (in seconds). [b] Single administration. [c] Repeated administration of 10 or 30 mg/kg po/day for 4 days; significance was calculated by one-way ANOVA followed by two-tailed Dunnett's test, $*p < 0.05$, $**p < 0.01$ vs control group.

in which the chloro group at the 3-position in the phenylpiperazinyl moiety in **53** is replaced with a methoxy group, showed stimulating activity equipotent to that of **34b**. Again, we examined the effects of the methoxy group on the phenylpiperazinyl moiety in compound **54** by replacing it with other groups. Replacement of the methoxy group with the more hydrophobic *n*-propoxy group (**55**), with the more hydrophilic hydroxy group (**56**), and with the more electron-donating amino (**58**) and acetoamido (**59**) groups resulted in inactive compounds. We could not find any active compound derived by those modifications on **54** and found strict structural requirements for showing the central nervous system-stimulating activity in these series of compounds.

Chart 1



Findings for the structure−activity relationships on the reduction of sleeping time induced by halothane in the series of compounds were: (1) a structure of 5-substituted-3,4-dihydro-2(1*H*)-quinolinone with the 3-[4-(3-substituted phenyl-1-piperazinyl)propyl] side chain at the 1-position was essential for showing the central nervous system-stimulating activity; (2) one of three methoxy, ethoxy, and chloro substituents on the 3,4-dihydro-2(1*H*)-quinolinone nucleus was required for showing the stimulating activity and it should be located at the 5-position on the 3,4-dihydro-2(1*H*)-quinolinone nucleus; (3) as a substituent at the 3-position in the 3-(4-phenyl-1-piperazinyl)propyl side chain, Cl, Br, and CF_3 groups were suitable for the 5-methoxy-3,4-dihydro-2(1*H*)-quinolinone derivatives and a methoxy group for 5-chloro-3,4-dihydro-2(1*H*)-quinolinone derivatives.

We selected the compounds which reduced the sleeping time and confirmed their central nervous system-stimulating activity in the test for promotional effects on the time required for recovery from coma induced by cerebral concussion in mice. Furthermore, we prepared and examined several structurally interesting compounds, 8-methoxy (**35**), 5-amino (**61**), and 2(1*H*)-quinolinone analogues (**62**−**64**) of **34b** for comparisons.

Test for Promotional Effects of Recovery from Coma Induced by Cerebral Concussion. Table 3 also shows results in the test for promotional effect on recovery from coma induced by cerebral concussion in mice. This test is well-recognized as an animal model which mimics the most prevalent clinical head injury.[38,39] The central nervous system-stimulating activity of **65**, a clinical effective central nervous system-activating drug, was confirmed in the test. Putative σ receptor agonists, **66**−**68**, promoted recovery from coma, but putative σ receptor antagonists, **69** and **70,** did not show the promotional effect. Compounds **34b**, **34c**, **42**, **43**, **48**, **50**, and **53**, which reduced sleeping time in the

test for halothane-induced anesthesia, accelerated recovery from coma, whereas compounds **3** and **40,** which were inactive in the test for halothane-induced anesthesia, were also inactive in this test. The 8-methoxy (**35**) and the 5-amino (**61**) analogues of **34b** and the 5-chloro (**57**) isomer of **48** were inactive in the test. The 2(1*H*)-quinolinone analogues (**63** and **64**) of **42** and **43** accelerated recovery from coma, whereas the 2(1*H*)-quinolinone analogue (**62**) of **34b** did not promote the recovery at 30 mg/kg po.

Binding Affinity for σ Receptors. A clinical effective central nervous system-activating drug, **65**, promotes recovery from coma induced by concussion as shown in Table 3. This action has been suggested to be mediated via cholinergic and/or monoaminergic systems.[38] The σ receptor has been suggested to modulate those systems.[18] The putative σ receptor agonists **66**−**68** also showed promotional effect. Therefore, we examined the affinity of the series of compounds synthesized for σ receptors and found that they inhibited [^{3}H]DTG binding to the σ receptor in rat whole brain membrane. To confirm whether the central nervous system-stimulating activity of the series of compounds was mediated by their σ receptor agonistic activity, we examined the effect of putative σ receptor antagonists on the acceleration of recovery from coma of the selected compounds.

As seen in Table 4, preadministration of putative σ receptor antagonists, **69** and **70,** antagonized the action of putative σ receptor agonists, **67** and **70**. Compounds **34b**, **34c** (10 mg/kg po), and **54** (30 mg/kg po) accelerated recovery from coma. Preadministration of **69** and **70**, also, completely antagonized the actions of **34b** and **54**. These results strongly suggested that **34b** and **54** are σ receptor agonists. On the other hand, the action of **72**[8] (Chart 1) was antagonized not by the putative σ receptor antagonist **70** but by the muscarinic antagonist α-(hydroxymethyl)benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]non-7-yl ester (scopolamine, **73**) suggesting its cholinomimetic action. Furthermore, the muscarinic antagonist **73** also antagonized the **34b** and the results suggested that **34b** had no anticholinergic action. The classical antidepressant **1** was inactive in the test up to 30 mg/kg po; this negative result of **1** may be attributable to its intrinsic anticholinergic activity[3,4] and to its σ receptor antagonistic activity.[42]

These results suggested that the central nervous system-stimulating activity of the series of **34b** and **34c** may be attributable to their σ receptor agonistic activity.

Porsolt's Forced-Swimming Test. Table 5 shows that **34b** and **34c** reduced the immobility time after a single administration of 1 and 10 mg/kg po. The classical antidepressant **1**, however, did not reduce the immobility time after single administration up to 30 mg/kg po. Classical tricyclic antidepressants have been reported to reduce immobility time in the forced-swimming test only after repeated administration.[1−3] In our experiment, **1**, also, reduced immobility time after repeated administration (once a day 30 mg/kg po) for 4 days. **1** has been reported to be a σ receptor antagonist.[42] These results suggested that the fast onset action of **34b** and **34c** in the forced-swimming test may be attributable to their σ receptor agonistic activity.

The central nervous system-activating agent **72**, which promotes arousal from coma, also did not reduce the immobility time. Compound **72** did not inhibit [^{3}H]-DTG binding for σ receptors up to 15 μM, and its promotional effect on recovery from coma was not antagonized by the putative σ receptor antagonist **69** but by muscarinic antagonist **73** indicating its cholinomimetic action. There are interesting reports related to the cholinergic systems and affective disorder that cholinergic systems exaggerate the symptoms of affective disorder.[43] Therefore, **34b** and **34c** might be useful drugs in the treatment of depressive patients because of their more potent and faster onset action in the forced-swimming test and less anticholinergic action than those of the classical tricyclic antidepressant **1**.

Compound **34c** showed better solubility in water than **34b** (0.5 w/v % vs 0.02 w/v %), and the better solubility of **34c** in water may allow a variety of formulations other than tablet form, such as injectable formulations. Because of its attractive profile and its minimal adverse effects after toxicological studies, compound **34c** was selected for further preclinical investigations.

In the preclinical studies, **34c** was examined to clarify the mechanism of its antidepressant activity by biochemical and pharmacological studies. Interestingly, **34c** also showed binding affinity to serotonine 1A (5-HT$_{1A}$) receptors in rat brain membrane using [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetraline (8-OH-DPAT) as a ligand with an IC$_{50}$ value of 2.3 nM,[44] and its 5-HT$_{1A}$ agonistic activity was confirmed by behavioral studies with rat.[44] The compound also inhibited [^{3}H]serotonine reuptake into the rat brain synaptosomes with an IC$_{50}$ value of 27 nM, which was similar to that of **1** (63 nM),[44] and elicited a very weak inhibitory effect on [^{3}H]-norepinephrine and [^{3}H]-4-(2-aminoethyl)-1,2-benzenediol (dopamine) reuptake, with an IC$_{50}$ value of 2900 and 9700 nM, respectively.[44] **34c** at a high dose of 100 mg/kg po did not inhibit (3a*S*-*cis*)-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethylpyrrolo[2,3-*b*]indol-5-ol methylcarbamate (physostigmine)-induced lethality, indicating that **34c** has no anticholinergic action. On the other hand, **1** (30, 60, 90 mg/kg po) dose-dependently inhibits lethality, with an ED$_{50}$ value of 55.3 mg/kg po.[44] Although the results from this work and preclinical investigations suggest that the antidepressant activity of **34c** after a single oral administration may be due to its σ receptor agonistic action, the interaction between the σ receptor agonistic effect and 5-HT$_{1A}$ receptor agonistic action of **34c** has not yet been clarified. Further investigations to clarify the mechanism of action of **34c** are necessary.

Clinical trials with **34c**, OPC-14523 mesylate, as an antidepressant drug are in progress.

Conclusion

We prepared a novel series of 3,4-dihydro-2(1*H*)-quinolinone derivatives to find a novel antidepressant drug with faster onset action, greater efficacy, and greater safety than the classical tricyclic antidepressants. And, we tested their central nervous system-activating potential by evaluation of their effects on anesthesia in mice induced by halothane and on coma in mice induced by concussion. According to our hypothesis that a compound which affects sleep and wakefulness, as a central nervous system activator, might be useful for treating depressive disorder, we found **34b**

and **34c** as our target compounds which were active in the two tests. Furthermore, the compounds showed antidepressant activities in the forced-swimming test with faster onset action than **1** and lack of anticholinergic action. Moreover, the compounds were found to exhibit affinity to σ receptors and σ receptor agonistic activity.

Experimental Section

Melting points were determined by a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-250 NMR spectrometer in the presence of tetramethylsilane (TMS) as an internal standard. Elementary analyses for carbon, hydrogen, and nitrogen were carried out on a Yanaco MT-5 CHN recorder. Where analyses are indicated only as symbols of elements, analytical results obtained are within ±0.4% of theoretical value. All compounds were routinely checked by TLC with Merck silica gel 60 F254 precoated plates. $MgSO_4$ anhydrous was used as drying agent for an extract solution. Abbreviations used are NaH, sodium hydride 60% dispersion in mineral oil; AcOEt, ethyl acetate; DMF, *N*,*N*-dimethylformamide; Et_3N, triethylamine; MeI, methyl iodide; dec, decomposed. Starting materials that were not commercially available were prepared according to procedures reported.[45−47]

Preparations of the Intermediates 13−31 in Table 1. 1-(3-Chloropropyl)-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (13) and 1-(3-Bromopropyl)-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (14). NaH (16.0 g, 0.4 mol) was added in portions to a solution of 3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (**6**)[23] (53.0 g, 0.3 mol) in DMF (200 mL) at room temperature and the resultant mixture was stirred for 30 min; then 1-bromo-3-chloropropane (94.5 g, 0.6 mol) was added. The mixture was stirred for 8 h at 60 °C, concentrated in vacuo, and extracted with AcOEt (1 L). The extract was washed, dried, and evaporated to dryness in vacuo to give a crude **13**, which was used as a precursor for the next step without further purification. An analytical sample was obtained after purification by flash column chromatography (SiO_2, CH_2Cl_2−AcOEt) and recrystallization. Thus, the fractions eluted with 1% AcOEt in CH_2Cl_2 were combined and concentrated in vacuo to give a colorless oil, which was crystallized by allowing to stand at room temperature overnight. Recrystallization from EtOH to give **14** as colorless needles (8% yield): mp 106−107 °C; ^{1}H NMR ($CDCl_3$) δ 2.21 (2H, m, J = 6 Hz), 2.58 (2H, t, J = 7 Hz), 2.88 (2H, t, J = 7 Hz), 3.46 (2H, t, J = 6 Hz), 3.84 (3H, s), 4.06 (2H, t, J = 7 Hz), 6.63 (1H, d, J = 8 Hz), 6.72 (1H, d, J = 8 Hz), 7.21 (1H, t, J = 8 Hz). Anal. ($C_{13}H_{16}NO_2Br$) H, N; C: calcd 52.37, found 52.82.

Next fractions eluted with 20% AcOEt in CH_2Cl_2 were combined and evaporated to dryness in vacuo and the residue was recrystallized from EtOH to afford **13** as colorless needles (39% yield): mp 103−105 °C; ^{1}H NMR ($CDCl_3$) δ 2.13 (2H, m, J = 6 Hz), 2.60 (2H, t, J = 7 Hz), 2.88 (2H, t, J = 7 Hz), 3.62 (2H, t, J = 6 Hz), 3.85 (3H, s), 4.08 (2H, t, J = 6 Hz), 6.64 (1H, d, J = 8 Hz), 6.73 (1H, d, J = 8 Hz), 7.21 (1H, t, J = 8 Hz). Anal. ($C_{13}H_{16}NO_2Cl$) C, H, N.

1-(3-Chloropropyl)-3,4-dihydro-8-methoxy-2(1*H*)-quinolinone (15). This compound was prepared from 3,4-dihydro-8-methoxy-2(1*H*)-quinolinone (**9**)[27] (6.0 g, 34 mmol), NaH (2.0 g, 50 mmol), and 1-bromo-3-chloropropane (18.8 g, 120 mmol) in DMF (100 mL) and obtained as pale yellow oil in 27% yield: mass calcd for $C_{13}H_{16}NO_2Cl$ (MW 253.72), found M^+ = 255, 253, 202, 218, 162; ^{1}H NMR ($CDCl_3$) δ 2.15 (2H, m), 2.58 (2H, t, J = 7 Hz), 2.77 (2H, t, J = 7 Hz), 3.54 (2H, t, J = 7 Hz), 3.68 (3H, s), 4.10 (2H, t, J = 7 Hz), 6.81 (1H, d, J = 8 Hz), 6.83 (1H, d, J = 8 Hz), 7.04 (1H, t, J = 8 Hz).

1-(2-Chloroethyl)-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (16). NaH (1.6 g, 40 mmol) was added in portions to a solution of **6** (5.3 g, 30 mmol) in DMF (200 mL) at room temperature and the resultant mixture was stirred for 1 h until the mixture was turned to a clear solution. The clear solution was then added dropwise to a solution of 1-bromo-2-chloroethane (8.6 g, 60 mmol) in DMF (50 mL) with stirring at room temperature. The resultant mixture was stirred for 8 h at room temperature and poured into water (200 mL). The organic layer was extracted with AcOEt (300 mL) and the extract was washed, dried, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, AcOEt−hexane) to give a colorless oil, which was crystallized by standing at room temperature for overnight. Recrystallization from AcOEt−hexane gave **16** as colorless leaflets (38% yield): mp 114−115 °C; ^{1}H NMR ($CDCl_3$) δ 2.59 (2H, t, J = 7 Hz), 2.89 (2H, t, J = 7 Hz), 3.67 (2H, t, J = 6 Hz), 3.83 (3H, s), 4.24 (2H, t, J = 7 Hz), 6.63 (1H, d, J = 8 Hz), 6.67 (1H, d, J = 8 Hz), 7.21 (1H, t, J = 8 Hz). Anal. ($C_{12}H_{14}NO_2Cl$) C, H, N.

1-(4-Bromobutyl)-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (17). This compound was prepared from **6** (5.3 g, 30 mmol), NaH (1.6 g, 40 mmol), and 1,4-dibromobutane (25.9 g, 120 mmol) in DMF (100 mL) and obtained as colorless needles (EtOH) in 47% yield: mp 69−70 °C; ^{1}H NMR ($CDCl_3$) δ 1.75 (2H, m), 1.89 (2H, m), 2.58 (2H, t, J = 7 Hz), 2.87 (2H, t, J = 7 Hz), 3.43 (2H, t, J = 7 Hz), 3.83 (3H, s), 3.95 (2H, t, J = 7 Hz), 6.63 (1H, d, J = 8 Hz), 6.65 (1H, d, J = 8 Hz), 7.20 (1H, t, J = 8 Hz). Anal. ($C_{14}H_{18}NO_2Br$) C, H, N.

1-(3-Bromopropyl)-5-ethoxy-3,4-dihydro-2(1*H*)-quinolinone (18). This compound was prepared from 5-ethoxy-3,4-dihydro-2(1*H*)-quinolinone (**10**)[23] (6.0 g, 34 mmol), NaH (2.0 g, 50 mmol), and 1,3-dibromopropane (18.8 g, 93 mmol) in DMF (100 mL) and obtained as colorless needles (AcOEt−hexane) in 64% yield: mp 90−91 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, t, J = 7 Hz), 2.21 (2H, m), 2.58 (2H, t, J = 7 Hz), 2.89 (2H, t, J = 7 Hz), 3.46 (2H, t, J = 6 Hz), 4.06 (4H, m), 6.61 (1H, d, J = 8 Hz), 6.70 (1H, d, J = 8 Hz), 7.18 (1H, t, J = 8 Hz). Anal. ($C_{14}H_{18}NO_2Br$) C, H, N.

1-(3-Bromopropyl)-3,4-dihydro-5-(2-propoxy)-2(1*H*)-quinolinone (19). This compound was prepared from 3,4-dihydro-5-(2-propoxy)-2(1*H*)-quinolinone (**11**)[23] (2.1 g, 10 mmol), NaH (0.5 g, 15 mmol), and 1,3-dibromopropane (4.0 g, 20 mmol) in DMF (100 mL) and obtained as colorless fibrous crystals (petroleum ether) in 70% yield: mp 54−55 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (6H, d, J = 6 Hz), 2.21 (2H, m), 2.58 (2H, d, J = 7 Hz), 2.88 (2H, d, J = 7 Hz), 3.46 (2H, t, J = 7 Hz), 4.05 (2H, t, J = 7 Hz), 4.53 (1H, m), 6.40 (1H, d, J = 8 Hz), 6.67 (1H, d, J = 8 Hz), 7.17 (1H, t, J = 8 Hz). Anal. ($C_{15}H_{20}NO_2Br$) C, H, N.

1-(3-Bromopropyl)-5-chloro-3,4-dihydro-2(1*H*)-quinolinone (20). This compound was prepared from 5-chloro-3,4-dihydro-2(1*H*)-quinolinone (**12**)[28] (6.0 g, 34 mmol), NaH (2.0 g, 50 mmol), and 1,3-dibromopropane (18.8 g, 93 mmol) in DMF (100 mL) and obtained as a pale yellow oil in 54% yield: ^{1}H NMR ($CDCl_3$) δ 2.24 (2H, m), 2.65 (2H, t, J = 7 Hz), 3.04 (2H, t, J = 7 Hz), 3.48 (2H, t, J = 7 Hz), 4.08 (2H, t, J = 7 Hz), 6.99 (1H, d, J = 8 Hz), 7.10 (1H, d, J = 8 Hz), 7.20 (1H, t, J = 8 Hz).

Preparation of 1-(3-Bromopropyl)-3,4-dihydro-5-methylthio-2(1*H*)-quinolinone (25). 3,4-Dihydro-5-(dimethylthiocarbamoyloxy)-2(1*H*)-quinolinone (22). NaH (4.4 g, 110 mmol) was added in portions to a solution of 3,4-dihydro-5-hydroxy-2(1*H*)-quinolinone (**21**)[23] (16.3 g, 100 mmol) in DMF (200 mL) at room temperature and the mixture was stirred until evolution of hydrogen ceased; then *N*,*N*-dimethylthiocarbamoyl chloride (13.6 g, 110 mmol) was added. The resultant mixture was stirred for 1 h at 60 °C and poured into water and the organic layer was extracted with CH_2Cl_2. The extract was washed, dried, and evaporated to dryness in vacuo. Recrystallization from MeOH gave **22** as pale yellow needles (68% yield): mp 222−224 °C; ^{1}H NMR ($CDCl_3$) δ 2.62 (2H, t, J = 7 Hz), 2.86 (2H, t, J = 7 Hz), 3.37 (3H, s), 3.47 (3H, s), 6.72 (2H, m, J = 8 Hz), 7.20 (1H, t, J = 8 Hz), 9.09 (1H, br). Anal. ($C_{12}H_{14}N_2O_2S$) C, H, N.

3,4-Dihydro-5-(dimethylcarbamoylthio)-2(1*H*)-quinolinone (23). A solution of **22** (10.0 g, 40 mmol) in phenyl ether (60 mL) was refluxed for 2 h, cooled to room temperature, and diluted with *n*-hexane (200 mL). The precipitated crystals were filtered, washed with hexane, and purified by column chromatography (SiO_2, 2% MeOH in CH_2Cl_2). Recrystallization

from EtOH gave **23** as pale yellow granules (81% yield): mp 212−215 °C; ^{1}H NMR ($CDCl_3$) δ 2.59 (2H, t, J = 7 Hz), 3.09 (8H, m), 6.82 (1H, dd, J = 3, 8 Hz), 7.14 (1H, t, J = 8 Hz), 7.19 (1H, dd, J = 3, 8 Hz), 8.82 (1H, br). Anal. ($C_{12}H_{14}N_2O_2S$) C, H, N.

3,4-Dihydro-5-methylthio-2(1*H*)-quinolinone (24). A solution of **23** (8.0 g, 32 mmol) and KOH (3.6 g, 64 mmol) in MeOH (200 mL) was refluxed for 2 h and cooled to room temperature; then MeI (6.8 g, 50 mmol) was added. The resultant mixture was stirring for 4 h at 60 °C, neutralized with HCl, concentrated in vacuo, and extracted with CH_2Cl_2. The extract was washed, dried, and evaporated in vacuo. The residue was purified by column chromatography (SiO_2, CH_2Cl_2) and recrystallized from EtOH to give **24** as colorless needles (52% yield): mp 182−183 °C; ^{1}H NMR ($CDCl_3$) δ 2.47 (3H, s), 2.64 (2H, t, J = 7 Hz), 3.00 (2H, t, J = 7 Hz), 6.62 (1H, d, J = 8 Hz), 6.89 (1H, d, J = 8 Hz), 7.15 (1H, t, J = 8 Hz), 8.71 (1H, br). Anal. ($C_{10}H_{11}NOS$) C, H, N.

1-(3-Bromopropyl)-3,4-dihydro-5-methylthio-2(1*H*)-quinolinone (25). This compound was prepared from **24** (3.3 g, 17 mmol), NaH (1.0 g, 25 mmol), and 1,3-dibromopropane (8.0 g, 40 mmol) in DMF (100 mL) and obtained as an oil in 64% yield: ^{1}H NMR ($CDCl_3$) δ 2.17 (2H, m, J = 7 Hz), 2.47 (3H, s), 2.64 (2H, t, J = 7 Hz), 2.95 (2H, t, J = 7 Hz), 3.36 (2H, t, J = 7 Hz), 4.08 (2H, t, J = 7 Hz), 6.90 (1H, d, J = 8 Hz), 6.94 (1H, d, J = 8 Hz), 7.24 (1H, t, J = 8 Hz); mass calcd for $C_{13}H_{16}NOSBr$ (MW 314.18), found M^+ = 315, 313.

Preparation of 5-Benzylideneamino-1-(3-chloropropyl)-3,4-dihydro-2(1*H*)-quinolinone (28). 5-Benzylideneamino-3,4-dihydro-2(1*H*)-quinolinone (27). A mixture of 5-amino-3,4-dihydro-2(1*H*)-quinolinone (**26**)[34] (6.0 g, 37 mmol) and benzaldehyde (6.5 g, 40 mmol) in EtOH (200 mL) was refluxed for 1 h and cooled to room temperature. The precipitated crystals were filtered, washed with EtOH, and recrystallized from EtOH to give **27** as yellow needles (90% yield): mp 194−196 °C; ^{1}H NMR ($CDCl_3$) δ 2.66 (2H, t, J = 7 Hz), 3.10 (2H, t, J = 7 Hz), 6.70 (2H, d, J = 8 Hz), 7.19 (1H, t, J = 8 Hz), 7.48 (3H, m), 7.91 (2H, dd, J = 3, 8 Hz), 8.40 (1H, d, J = 8 Hz), 8.73 (1H, br). Anal. ($C_{16}H_{14}N_2O$) C, H, N.

5-Benzylideneamino-1-(3-chloropropyl)-3,4-dihydro-2(1*H*)-quinolinone (28). This compound was obtained from **27** (5.0 g, 20 mmol) by reaction with 1-bromo-3-chloropropane (9.4 g, 60 mmol) in DMF (100 mL) in the presence of NaH (0.9 g, 25 mmol) as a crude oil in 80% yield and was used in the next step without purification.

Preparation of 1-(3-Bromopropyl)-5-methoxy-2(1*H*)-quinolinone (31). 5-Methoxy-2(1*H*)-quinolinone (30). MeI (5.7 g, 40 mmol) was added dropwise with stirring to a solution of 5-hydroxy-2(1*H*)-quinolinone (**29**) (4.8 g, 30 mmol) and KOH (2.4 g, 36 mmol) in 50% MeOH (80 mL) and the resultant mixture was stirred for 10 h at 50 °C, and then concentrated in vacuo. The residue was extracted with $CHCl_3$ and the extract was washed with a 10% KOH solution and water and concentrated in vacuo. Recrystallization from *i*-PrOH gave **30** as colorless needles (38% yield): mp 243−250 °C (lit. mp 240 °C).[36]

1-(3-Bromopropyl)-5-methoxy-2(1*H*)-quinolinone (31). This compound was prepared from **30** (6.0 g, 34 mmol), NaH (2.0 g, 50 mmol), and 1,3-dibromopropane (18.8 g, 93 mmol) in DMF (100 mL), and obtained as colorless needles (AcOEt−hexane) in 64% yield: mp 161−161.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.29 (2H, m), 3.55 (2H, t, J = 6 Hz), 4.01 (3H, s), 4.42 (2H, t, J = 7 Hz), 6.61 (1H, d, J = 9 Hz), 6.68 (1H, d, J = 8 Hz), 7.05 (1H, d, J = 8 Hz), 7.49 (1H, t, J = 8 Hz), 8.14 (1H, d, J = 9 Hz). Anal. ($C_{13}H_{14}NO_2Br$) C, H; N: calcd 4.73, found 4.24.

Preparation of 1-[3-[4-(3-Chlorophenyl)-1-piperazinyl]-propyl]-3,4-dihydro-6-methoxy-2(1*H*)-quinolinone (32). NaH (0.8 g, 20 mmol) was added in portions to a solution of 3,4-dihydro-6-methoxy-2(1*H*)-quinolinone (**7**)[25] (1.77 g, 10 mmol) in DMF (50 mL) at room temperature. The mixture was stirred for 30 min until evolution of hydrogen ceased, and then 1-(3-chloropropyl)-4-(3-chlorophenyl)piperazine hydrochloride (3.1 g, 10 mmol) was added. The resultant mixture was stirred for 8 h at room temperature and poured into water (200 mL). The organic layer was extracted with AcOEt (200 mL) and the extract was washed, dried, and concentrated in vacuo and purified by flash column chromatography (SiO_2, 5% MeOH in CH_2Cl_2) to give a pale yellow oil, which was dissolved in EtOH. The solution was acidified with HCl and evaporated to dryness in vacuo. Recrystallization from EtOH afforded **32** (75% yield) as colorless needles: mp 159−161 °C; ^{1}H NMR (DMSO-d_6) δ 2.02 (2H, m), 2.50 (2H, m), 2.86 (2H, t, J = 7 Hz), 3.14 (6H, m), 3.50 (2H, m), 3.74 (3H, s), 3.93 (2H, m), 6.82 (3H, m), 6.95 (1H, dd, J = 3, 8 Hz), 7.03 (1H, d, J = 3 Hz), 7.14 (1H, d, J = 8 Hz), 7.25 (1H, t, J = 8 Hz), 11.11 (1H, br). Anal. ($C_{23}H_{28}N_3O_2Cl$·2HCl) C, H, N.

1-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone (33). This compound was prepared in a similar procedure to that for **32** from 3,4-dihydro-7-methoxy-2(1*H*)-quinolinone (**8**)[26] (1.77 g, 10 mmol), NaH (0.8 g, 20 mmol), and 1-(3-chloropropyl)-4-(3-chlorophenyl)piperazine hydrochloride (3.1 g, 10 mmol) in DMF (50 mL) and obtained as colorless needles in 77% yield: mp 224−229 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.04 (2H, m), 2.52 (2H, m), 2.80 (2H, t, J = 7 Hz), 3.20 (6H, m), 3.51 (2H, m), 3.79 (3H, s), 3.85 (2H, m), 3.95 (2H, t, J = 7 Hz), 6.60 (1H, dd, J = 3, 8 Hz), 6.72 (1H, d, J = 3 Hz), 6.85 (1H, d, J = 8 Hz), 6.95 (1H, d, J = 8 Hz), 7.03 (1H, d, J = 3 Hz), 7.13 (1H, d, J = 3 Hz), 7.25 (1H, t, J = 8 Hz), 11.24 (1H, br). Anal. ($C_{23}H_{28}N_3O_2Cl$·2HCl) C, H, N.

General Procedure for Preparations of Compounds 34−57 Listed in Table 2. 1-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (34). A solution of **13** (3.6 g, 14 mmol) and NaI (2.3 g, 15 mmol) in CH_3CN (100 mL) was refluxed for 30 min and cooled to room temperature; then 1-(3-chlorophenyl)piperazine (2.4 g, 15 mmol) and K_2CO_3 (2.1 g, 15 mmol) were added. The resultant mixture was stirred for 2 h at 80 °C and cooled to room temperature. The precipitates were filtered off and the filtrate was concentrated in vacuo and extracted with AcOEt. The extract was washed, dried, and concentrated in vacuo and the residue was purified by column chromatography (SiO_2, CH_2Cl_2) and recrystallized from EtOH to afford **34** free base (**34a**) as colorless needles (83% yield): 92−93 °C; ^{1}H NMR (DMSO-d_6) δ 1.70 (2H, m), 2.35 (2H, t, J = 7 Hz), 2.47 (6H, m), 2.78 (2H, t, J = 7 Hz), 3.15 (4H, m), 3.79 (3H, s), 3.91 (2H, d, J = 7 Hz), 6.73 (2H, d, J = 8 Hz), 6.87 (3H, m), 7.20 (1H, t, J = 8 Hz), 7.22 (1H, t, J = 8 Hz). Anal. ($C_{23}H_{28}N_3O_2Cl$) C, H, N.

Hydrochloride of 34 (34b). A solution of the free base **34a** (4.1 g, 10 mmol) in EtOH (50 mL) was acidified with HCl and evaporated to dryness. The residue was recrystallized from EtOH to give **34b** as colorless leaflets (46% yield): mp 239−241 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.37 (2H, t, J = 7 Hz), 2.58 (2H, t, J = 7 Hz), 3.02 (6H, m), 3.55 (6H, m), 3.84 (3H, s), 4.04 (2H, t, J = 6 Hz), 6.65 (1H, d, J = 8 Hz), 6.78 (3H, m), 6.87 (1H, d, J = 2 Hz), 6.90 (1H, dd, J = 2 Hz, 8 Hz), 7.19 (1H, t, J = 8 Hz). Anal. ($C_{23}H_{28}N_3O_2Cl$·HCl) C, H, N.

Methanesulfonate of 34 (34c). A solution of the free base of **34a** (4.1 g, 10 mmol) in EtOH (50 mL) was acidified with methanesulfonic acid and evaporated to dryness. The residue was recrystallized from EtOH to give **34c** as colorless needles (75%): mp 192−194 °C; ^{1}H NMR (DMSO-d_6) δ 1.97 (2H, m), 2.32 (3H, s), 2.51 (2H, m), 2.86 (2H, t, J = 7 Hz), 2.89−3.20 (6H, m), 3.55 (2H, m), 3.81 (3H, s), 3.85 (2H, m), 3.95 (2H, t, J = 7 Hz), 6.77 (1H, d, J = 8 Hz), 6.86 (1H, t, J = 8 Hz), 6.96 (1H, dd, J = 3, 8 Hz), 7.04 (1H, d, J = 3 Hz), 7.28 (2H, m), 9.48 (1H, br). Anal. ($C_{23}H_{28}N_3O_2Cl$·CH_3SO_3H·H_2O) C, H, N.

Analogously, compounds **38**−**49** were prepared from **13** (14 mmol) and 2 molar equiv of the corresponding phenylpiperazines and Na_2CO_3. Yield, mp, and formulas are listed in Table 2. ^{1}H NMR spectra for these compounds are presented in the Supporting Information.

1-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-8-methoxy-2(1*H*)-quinolinone Hydrochloride (35). This compound was prepared in a similar procedure to that for **34b** from **15** (10 mmol), NaI (15 mmol), 1-(3-chlorophenyl)-piperazine (20 mmol), and Na_2CO_3 (20 mmol) and obtained as

colorless needles (EtOH) in 12% yield: mp 169−171 °C; ^{1}H NMR (DMSO-d_6) δ 2.05 (2H, m), 2.44 (2H, m), 2.82 (2H, t, J = 7 Hz), 3.17 (6H, m), 3.52 (2H, m), 3.86 (2H, m), 3.89 (5H, m), 6.86 (1H, d, J = 8 Hz), 7.04 (4H, m), 10.83 (1H, br). Anal. ($C_{23}H_{28}N_3O_2Cl$·HCl) C, H, N.

1-[2-[4-(3-Chlorophenyl)-1-piperazinyl]ethyl]-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (36). This compound was prepared in a similar procedure to that for **34a** from **16** (10 mmol), NaI (15 mmol), 1-(3-chlorophenyl)piperazine (20 mmol), and Na_2CO_3 (20 mmol) and obtained as colorless needles (EtOH) in 29% yield: mp 132−132.5 °C; ^{1}H NMR (DMSO-d_6) δ 2.04 (2H, m), 2.52 (2H, m), 2.80 (2H, t, J = 7 Hz), 3.20 (6H, m), 3.51 (2H, m), 3.79 (3H, s), 4.11 (2H, t, J = 7 Hz), 6.64 (1H, d, J = 8 Hz), 6.80 (4H, m), 7.20 (2H, m). Anal. ($C_{22}H_{26}N_3O_2Cl$) C, H, N.

1-[4-[4-(3-Chlorophenyl)-1-piperazinyl]butyl]-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (37). This compound was prepared in a similar procedure to that for **34a** from **17** (10 mmol), NaI (15 mmol), 1-(3-chlorophenyl)piperazine (20 mmol), and Na_2CO_3 (20 mmol) and obtained as a white powder (EtOH) in 60% yield: mp 128−129 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.70 (4H, m), 2.46 (2H, t, J = 7 Hz), 2.60 (6H, m), 2.91 (2H, t, J = 7 Hz), 3.22 (4H, m), 3.87 (3H, s), 3.99 (2H, t, J = 7 Hz), 6.66 (1H, d, J = 8 Hz), 6.76 (1H, d, J = 8 Hz), 6.83 (2H, m), 6.90 (1H, d, J = 3 Hz), 7.18 (1H, t, J = 8 Hz), 7.22 (1H, t, J = 8 Hz). Anal. ($C_{24}H_{30}N_3O_2Cl$) C, H, N.

Preparation of 1-[3-[4-(3-Aminophenyl)-1-piperazinyl]-propyl]-3,4-dihydro-5-methoxy-2(1*H*)-quinolinone (49). A mixture of 3,4-dihydro-5-methoxy-1-[3-[4-(3-nitrophenyl)-1-piperazinyl]propyl]-2(1*H*)-quinolinone (**48**) (2.5 g, 10 mmol) and 5% Pd−C (200 mg) in EtOH (200 mL) was hydrogenated with a Parr apparatus under 3 kg/cm^2 hydrogen pressure at room temperature. Catalyst was filtered off and the filtrate was evaporated to dryness in vacuo. The residue was purified by column chromatography (SiO_2, 1% MeOH in CH_2Cl_2) and recrystallized from EtOH to give **49** as a white powder (46% yield): mp 132−133 °C; ^{1}H NMR ($CDCl_3$) δ 1.85 (2H, m), 2.45 (2H, t, J = 7 Hz), 2.57 (6H, m), 2.86 (2H, t, J = 7 Hz), 3.16 (2H, m), 3.63 (2H, br), 3.83 (3H, s), 3.99 (2H, m), 6.19 (1H, dd, J = 3, 8 Hz), 6.21 (1H, d, J = 3 Hz), 6.34 (1H, dd, J = 3, 8 H z), 6.61 (1H, d, J = 8 Hz), 6.75 (1H, d, J = 8 Hz), 7.02 (1H, t, J = 8 Hz), 7.18 (1H, t, J = 8 Hz). Anal. ($C_{23}H_{30}N_4O_2$) C, H, N.

1-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-5-ethoxy-3,4-dihydro-2(1*H*)-quinolinone Hydrochloride (50). This compound was prepared in a similar procedure to that for **34b** from **18** (10 mmol), NaI (15 mmol), 1-(3-chlorophenyl)piperazine (20 mmol), and Na_2CO_3 (20 mmol) and obtained as colorless needles (EtOH) in 43% yield: mp 221−224 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.34 (3H, t, J = 7 Hz), 2.02 (2H, m), 2.51 (2H, m), 2.82 (2H, t, J = 7 Hz), 3.14 (6H, m), 3.94 (4H, m), 4.04 (2H, q, J = 7 Hz), 6.75 (1H, d, J = 8 Hz), 6.85 (2H, m), 6.95 (1H, dd, J = 3 and 8 Hz), 7.04 (1H, d, J = 3 Hz), 7.22 (2H, m), 11.09 (1H, br). Anal. ($C_{24}H_{30}N_3O_2Cl$·HCl) C, H, N.

1-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-5-(2-propoxy)-2(1*H*)-quinolinone Hydrochloride (51). This compound was prepared in a similar procedure to that for **34b** from **19** (10 mmol), NaI (15 mmol), 1-(3-chlorophenyl)piperazine (20 mmol), and Na_2CO_3 (20 mmol) and obtained as colorless needles (EtOH) in 51% yield: mp 218−229 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.27 (6H, d, J = 6 Hz), 2.03 (2H, m), 2.51 (2H, m), 2.81 (2H, t, J = 7 Hz), 3.14 (6H, m), 3.49 (2H, m), 3.92 (4H, m), 4.59 (1H, m), 6.76 (1H, d, J = 8 Hz), 6.81 (1H, d, J = 8 Hz), 6.86 (1H, dd, J = 3, 8 Hz), 6.95 (1H, dd, J = 3, 8 Hz), 7.04 (1H, d, J = 3 Hz), 7.20 (1H, t, J = 8 Hz), 7.26 (1H, t, J = 8 Hz), 11.07 (1H, br). Anal. ($C_{25}H_{32}N_3O_2$-Cl·HCl) C, H, N.

Preparation of 1-[3-[4-(3-Chlorophenyl)-1-piperazinyl]-propyl]-3,4-dihydro-5-hydroxy-2(1*H*)-quinolinone (52). A solution of the free base of **34a** (4.1 g, 10 mmol) in 47% HBr (50 mL) was refluxed for 4 h, concentrated in vacuo, and made basic with a 37% NH_4OH solution. The precipitated crystals were filtered, washed, dried, dissolved in EtOH, and evaporated to dryness. Recrystallization from EtOH gave **52** as a white powder (74% yield): mp 200−201.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.88 (2H, m), 2.46 (2H, t, J = 7 Hz), 2.62 (8H, m), 2.88 (2H, t, J = 7 Hz), 3.21 (4H, m), 4.00 (2H, t, J = 7 Hz), 6.45 (1H, d, J = 8 Hz), 6.65 (1H, d, J = 8 Hz), 6.79 (2H, m), 6.87 (1H, d, J = 3 Hz), 7.05 (1H, t, J = 8 Hz), 7.16 (1H, t, J = 8 Hz), 10.01 (1H, br). Anal. ($C_{22}H_{26}N_4O_2Cl$) C, H, N.

5-Chloro-1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-2(1*H*)-quinolinone Hydrochloride (53). This compound was prepared in a similar procedure to that for **34b** from **20** (10 mmol), NaI (15 mmol), 1-(3-chlorophenyl)piperazine (20 mmol), and Na_2CO_3 (20 mmol) and obtained as colorless needles (EtOH) in 40% yield: mp 217 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.03 (2H, m), 2.60 (2H, m), 3.00 (2H, t, J = 7 Hz), 3.14 (6H, m), 3.51 (2H, m), 3.86 (2H, m), 3.98 (2H, t, J = 7 Hz), 6.87 (1H, dd, J = 3, 8 Hz), 6.95 (1H, d, J = 3 Hz), 7.04 (1H, dd, J = 3, 8 Hz), 7.26 (4H, m), 11.04 (1H, br). Anal. ($C_{22}H_{29}N_3OCl_2$·2HCl) C, H, N.

Analogously, compounds **54**−**57** were prepared from **20** (10 mmol) and 2 molar equiv of the corresponding phenylpiperazines and Na_2CO_3. Their yield, mp, and formulas are listed in Table 2. ^{1}H NMR spectra for these compounds are presented in the Supporting Information.

1-[3-[4-(3-Aminophenyl)-1-piperazinyl]propyl]-5-chloro-3,4-dihydro-2(1*H*)-quinolinone (58). This compound was prepared by catalytic hydrogenation of 5-chloro-3,4-dihydro-1-[3-[4-(3-nitrophenyl)-1-piperazinyl]propyl]-2(1*H*)-quinolinone (**57**) (10 mmol) in the presence of 5% Pd−C (200 mg) in EtOH (200 mL) and obtained as a white powder in 89% yield: mp 161−163 °C; ^{1}H NMR (DMSO-d_6) δ 1.72 (2H, m), 2.36 (2H, t, J = 7 Hz), 2.51 (6H, m), 2.59 (2H, t, J = 7 Hz), 3.02 (6H, m), 3.95 (2H, t, J = 7 Hz), 4.85 (2H, br), 6.04 (1H, dd, J = 3, 8 Hz), 6.15 (2H, m), 6.85 (1H, t, J = 8 Hz), 7.16 (1H, d, J = 8 Hz), 7.23 (1H, d, J = 8 Hz), 7.30 (1H, t, J = 8 Hz). Anal. ($C_{22}H_{27}N_4OCl$) C, H, N.

Preparation of 1-[3-[4-(3-Acetylaminophenyl)-1-piperazinyl]propyl]-5-chloro-3,4-dihydro-2(1*H*)-quinolinone (59). A mixture of **58** (2.5 g, 10 mmol), acetic anhydride (50 mL), and a catalytic amount of 4-(dimethylamino)pyridine (100 mg) was stirred for 2 h and evaporated to dryness. Recrystallization from EtOH afforded **59** as a white powder (75% yield): mp 177−178 °C; ^{1}H NMR (DMSO-d_6) δ 1.72 (2H, m), 2.02 (3H, s), 2.34 (2H, t, J = 7 Hz), 2.51 (6H, m), 2.59 (2H, t, J = 7 Hz), 3.09 (4H, m), 3.93 (2H, t, J = 7 Hz), 6.62 (1H, dd, J = 3, 8 Hz), 7.01 (1H, dd, J = 3, 8 Hz), 7.21 (5H, m), 9.78 (1H, br). Anal. ($C_{24}H_{29}N_4O_2Cl$) C, H, N.

Preparation of 1-[3-[4-(3-Chlorophenyl)-1-piperazinyl]-propyl]-3,4-dihydro-5-methylthio-2(1*H*)-quinolinone Hydrochloride (60). This compound was prepared in a similar procedure to that for compound **34b** by reacting 1-(3-chlorophenyl)piperazine (2.5 g, 21 mmol), Et_3N (3 mL, 21.5 mmol), and NaI (2.5 g, 16.7 mmol) with **25** (2.7 g, 10 mmol) and obtained as colorless leaflets (EtOH) in 51% yield: mp 221−224 °C; ^{1}H NMR (DMSO-d_6) δ 2.01 (2H, m), 2.48 (3H, s), 2.57 (2H, m), 2.88 (2H, t, J = 7 Hz), 3.14 (6H, m), 3.53 (2H, m), 3.88 (2H, m), 3.97 (2H, t, J = 7 Hz), 6.87 (1H, dd, J = 3, 8 Hz), 6.96 (1H, dd, J = 3, 8 Hz), 7.04 (3H, m), 7.26 (1H, t, J = 8 Hz), 7.29 (1H, t, J = 8 Hz), 10.65 (1H, br). Anal. ($C_{23}H_{28}N_3$-OSCl·2HCl) H, N; C: calcd 54.93, found 59.93.

Preparation of 5-Amino-1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-2(1*H*)-quinolinone Dihydrochloride (61). Crude **28** (3.3 g, 10 mmol) and NaI (2.5 g, 16.7 mmol) were dissolved in CH_3CN (100 mL) and the solution was refluxed for 30 min; then 1-(3-chlorophenyl)piperazine (3.0 g, 15 mmol) and Et_3N (3 mL, 21.5 mmol) were added. The resultant mixture was refluxed for a further 2 h and cooled to room temperature. The precipitates were filtered off and the filtrate was concentrated in vacuo. The residue was extracted with AcOEt and the extract was washed, dried, concentrated in vacuo, purified by column chromatography (SiO_2, 2% MeOH in CH_2Cl_2), and dissolved in 50% EtOH. The solution was acidified with concentrated HCl. After being stirred for 1 h at 80 °C, the solution was evaporated to dryness in vacuo. The residue was recrystallized from EtOH to give **61** as a white powder (61% yield): mp 218−240 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.03 (2H, m), 2.56 (2H, m), 2.92 (2H, t, J = 7 Hz), 3.21

(6H, m), 3.50 (2H, m), 3.86 (2H, m), 2.80−4.40 (3H, br), 3.94 (2H, t, J = 7 Hz), 6.88 (1H, dd, J = 3, 8 Hz), 6.97 (1H, dd, J = 3, 8 Hz), 7.11(3H, m), 7.29 (1H, t, J = 8 Hz), 7.30 (1H, t, J = 8 Hz), 10.89 (1H, br). Anal. ($C_{22}H_{27}N_4OCl\cdot 2HCl\cdot H_2O$) C, H, N.

Preparation of 1-[3-[4-(3-Chlorophenyl)-1-piperazinyl]-propyl]-5-methoxy-2(1*H*)-quinolinone Hydrochloride (62). This compound was prepared in a similar procedure to that for **34b** by reacting 1-(3-chlorophenyl)piperazine (3.0 g, 15 mmol), NaI (2.5 g, 16.7 mmol), and Et_3N (3 mL, 21.5 mmol) with 1-(3-bromopropyl)-5-methoxy-2(1*H*)-quinolinone (**31**) (2.7 g, 10 mmol) and obtained as a white powder (EtOH) in 65% yield: mp 232−236 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.00 (2H, m), 3.21 (6H, m), 3.53 (2H, m), 3.85 (2H, m), 4.00 (3H, s), 4.30 (2H, t, J = 7 Hz), 6.56 (1H, d, J = 9 Hz), 6.97 (3H, m), 7.03 (1H, d, J = 3 Hz), 7.25 (2H, m), 7.58 (1H, t, J = 8 Hz), 8.10 (1H, d, J = 9 Hz), 11.21 (1H, br). Anal. ($C_{23}H_{26}N_3O_2Cl\cdot HCl$) H, N; C: calcd 61.61, found 62.14.

Analogously, compounds **63** and **64** were prepared from **31** (10 mmol) and 2 molar equiv of the corresponding phenylpiperazines and Et_3N. Their yield, mp, and formulas are presented in Table 2. ^{1}H NMR spectra for these compounds are presented in the Supporting Information.

Pharmacology. Male ICR mice weighing 20−30 (purchased from Clea Japan) and male Wistar rats weighing 148−250 g (purchased from Japan SLC Inc.) were starved for 18−20 h and used. Test compounds were suspended or dissolved in a gum arabic solution and administered to a group of 10 mice 0.25 h (iv, sc, or ip injection) or 1 h (oral administration) before the test. The control group of 10 mice received the same amount of gum arabic solution. Following abbreviations were used: gum arabic solution, 0.5% gum arabic solution in 0.9% saline; Tris buffer, 5 mM Tris hydrochloride buffer (pH 7.4).

Test for Effect on Halothane Anesthesia. The test was performed with mice according to the method reported.[37] Mice were placed in a chamber supplied with air containing 4% halothane at a rate of 2 L/min and they immediately lost righting reflex in the chamber. Even after they were taken out from the chamber the mice continued to show loss of righting reflex for awhile and then regained the reflex. The time from loss to recovery of the reflex was measured and used as the sleeping time in halothane-induced anesthesia (ST, mean ± SE, seconds). The test compound was administered orally 1 h before anesthesia loading. The recovery accelerating effect of the test compound was expressed in the ratio of the sleeping time in the mice given the test compound to that in the control mice (% of control). The results are shown in Table 3, in which the sleeping time in mice treated with each test compound is shown with the sleeping time of halothane-induced anesthesia in the control mice being taken as 100%. Significance was determined by two-tailed t-test (n = 10) versus control group as shown Table 3.

Test for Effects on Recovery from Coma. The procedure used was similar to that reported as the experimental model for the head injury.[38,39] The head of the test mouse was fixed on a pillow made of foamed polystyrene resin by holding the neck of the mouse. A plastic tube (22-mm internal diameter) was placed vertically over the head and the mouse received a concussion by dropping an acrylate cylindrical rod (weighing 20 g) through the tube from a 40-cm height to strike the vertex. Chronic convulsion occurred for 1−10 s, followed by loss of consciousness (righting reflex); the mouse then remained motionless in a crouching or prone portion for a period. The time required for the reappearance of the righting reflex after concussion (RRT, mean ± SE in seconds) was used as indicators of the promoting effect on recovery from coma. Each of the test compounds was administered orally 1 h before concussion loading. Activity of the compound in the test was defined as the ratio of RRT of the test compound to that of the control group being taken as 100%. To examine the effects of antagonists, **69**, **70**, and **73** were administered 30 min, 1 h, and 15 min, respectively, before the administration of test compound. The results are shown in Tables 3 and 4. Statistical analysis was performed by the two-tailed t-test (n = 10) versus control group. In Table 4, one-way ANOVA followed by Dunnett's test was used.

Binding Affinity for the σ Receptor. Preparation of a membrane fraction and a [^{3}H]-1,3-di(*o*-tolyl)guanidine binding test were performed according to the reported method.[40]

Preparation of a membrane fraction: A Wistar strain male rat was decapitated and the whole brain was excised and homogenized in 30 volumes of an ice-cooled Tris buffer. The homogenate was then centrifuged at 4 °C and 50000*g* for 15 min to give the first sediment, which was suspended in 1 volume of the buffer. The suspension was centrifuged again after 45 min of incubation at 37 °C and the second sediment obtained was suspended in 1 volume of the buffer. The suspension was stored frozen at −80 °C until used. The frozen tissue preparation was thawed and centrifuged at 4 °C and 50000*g* for 15 min and the sediment obtained was suspended in 10 volumes of Tris buffer. This suspension was used as the membrane preparation.

Binding test: The test compound (50 mL, final concentration 0.1, 1, and 10 mM), [^{3}H]-1,3-di(*o*-tolyl)guanidine (50 mL, final concentration 3 nM), and the membrane preparation (150 mL) were placed in a test tube (total volume 250 mL per tube). The reaction started on addition of the membrane preparation. The tubes were incubated at 25 °C for 60 min in a cell harvester, the reaction was stopped by suction filtration through a Whatman GF/B filter saturated in advance with 0.5% poly(ethylenimine), and the filter was immediately washed with 3-mL portions of an ice-cooled Tris buffer. The filter was transferred to a vial and then 5 mL of a liquid scintillation cocktail (Aquasol 2) was added; the vial was allowed to stand in the dark for a predetermined time. The radioactivity was then measured by a scintillation counter. The specific binding was determined by subtracting the binding in the presence of 10 mM haloperidol from the total binding. The IC_{50} values were calculated by computer analysis using the nonlinear least-squares method.[48]

Forced-Swimming Test. The immobility time was measured by the behavioral despair test with mice.[17] Each mouse was placed individually in a glass cylinder (height 21 cm, diameter 12 cm) containing 6 cm of water at 22−23 °C and the immobility time was recorded for the last 4 min of a 6-min forced-swimming test. Each mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water making only those movements necessary to keep its head above water. To assess the effects of a single administration of **1**, **34b**, **34c,** and **72**, these agents were administered orally 1 h before the experiment on day 2. Statistical analysis were performed by one-way ANOVA followed by two-tailed Dunnett's test (n = 8). Results are summarized in Table 5.

Supporting Information Available: Additional ^{1}H NMR data on final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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