Synthesis and Muscarinic Activity of a Series of Quinolines and Naphthalenes with a 1-Azabicyclo[3.3.0]octane Moiety

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In order to discover a medicine effective against Alzheimer's disease, we synthesized a series of quinoline derivatives having a characteristic 1-azabicyclo[3.3.0]octane amine ring, and performed pharmacological evaluation of them. Acetylcholine esterase inhibitory activities of these derivatives were unexpectedly weak. Tests for central nervous muscarinic cholinergic receptor binding affinity indicated that these compounds had higher affinities to muscarinic M1 receptors than to M2 receptors.

A series of naphthalene derivatives substituted with the 1-azabicyclo[3.3.0]octane ring were also synthesized and muscarinic M1 and M2 receptor binding affinity determined. These compounds had much higher affinity for M1 receptors than the quinoline derivatives, and 1-[*N*-(1-azabicyclo[3.3.0]octan-5-yl)methyl-*N*-methylamino]-4-nitronaphthalene showed the highest affinity and selectivity. The ability of this compound to improve cognitive function was assessed using the passive avoidance test in scopolamine-induced mice.

Key words Alzheimer's disease; 1-azabicyclo[3.3.0]octane; central nervous muscarinic cholinergic receptor binding affinity; acetylcholine esterase inhibitor

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive loss of memory, judgment, language, and motor functions. Approximately 12 million people are estimated to suffer from AD in Japan, Europe and the U.S.A., and a steady increase in the number of AD patients can be predicted with increased life expectancy.[1] It has become very important to develop a medicine effective against AD.

Some of the important biochemical changes observed in brains of AD patients are significant deficits in presynaptic cholinergic markers.[2] The cholinergic hypothesis triggered many research efforts aimed at restoring defective cholinergic transmission. There are three strategies for activating acetylcholinic nervous conducting functions. The first is inhibition of acetylcholine esterase, in order to increase acetylcholine concentration in the brain. Tacrine[3] is an inhibitor of acetylcholine esterase. The second is acceleration of acetylcholine discharge in the synapse, and the third is activation of acetylcholine receptors by an agonist. YM796[4] and SR46559[5] were developed as receptor agonists.

Muscarinic M1 receptors are abundant in the cerebral cortex and hippocampus, and M1 receptor activation is important for learning and memory.[6] On the other hand, M2 receptors are widely distributed in peripheral tissues, and M2 receptor activation causes cholinergic side effects such as salivation.[5] Therefore, selective muscarinic M1 receptor agonists are expected to be cognition activators.

We have been studying cognition activators in order to develop a new medicine for AD, and recently found a new compound, SK-946, exhibiting much higher affinity for the M1 receptor than the M2 receptor. This compound, which is an aniline derivative, increased inositol phosphate production in primary cultured rat fetal hippocampal neuronal cells, and improved scopolamine induced dementia in mice.[7]

We planned to prepare a series of quinoline and naphthalene derivatives, which are modified structures based on the acridine framework of tacrine. This paper describes the synthesis and biological evaluation, from the viewpoint of acetylcholine esterase inhibitory activities (first strategy), and central muscarinic cholinergic receptor binding affinity (third strategy) of this novel series of compounds.

Chemistry 5-Substituted 1-azabicyclo[3.3.0]octanes can be readily prepared from 1-azoniabicyclo[3.3.0]oct-1(5)-ene salt (**2**) and nucleophiles.[8] Our group developed new methods for preparation of 5-cyano derivatives (**3a, b**) using 1,7-dichloroheptan-4-one (**1**). The syntheses of the 1-azabicyclo[3.3.0]octane derivatives are outlined in Chart 2. (1-azabicyclo[3.3.0]octan-5-yl)carbonitrile (**3a**) was synthesized from 1,7-dichloroheptan-4-one (**1**) and 2-amino-2-cyanopropane in NH_3–MeOH–water in good yield.[9] (1-azabicyclo[3.3.0]octan-5-yl)acetonitrile (**3b**) was synthesized from 1,7-dichloroheptan-4-one (**1**) and cyanoacetic

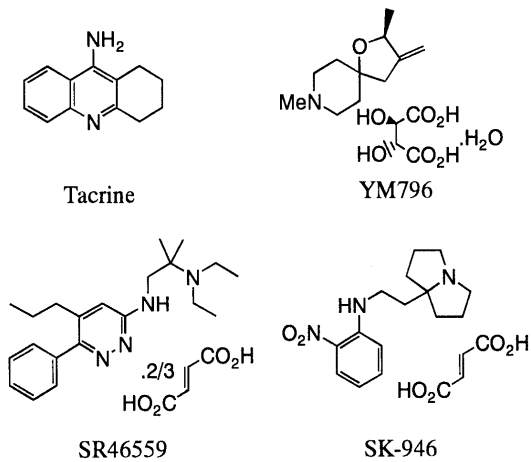

Chart 1

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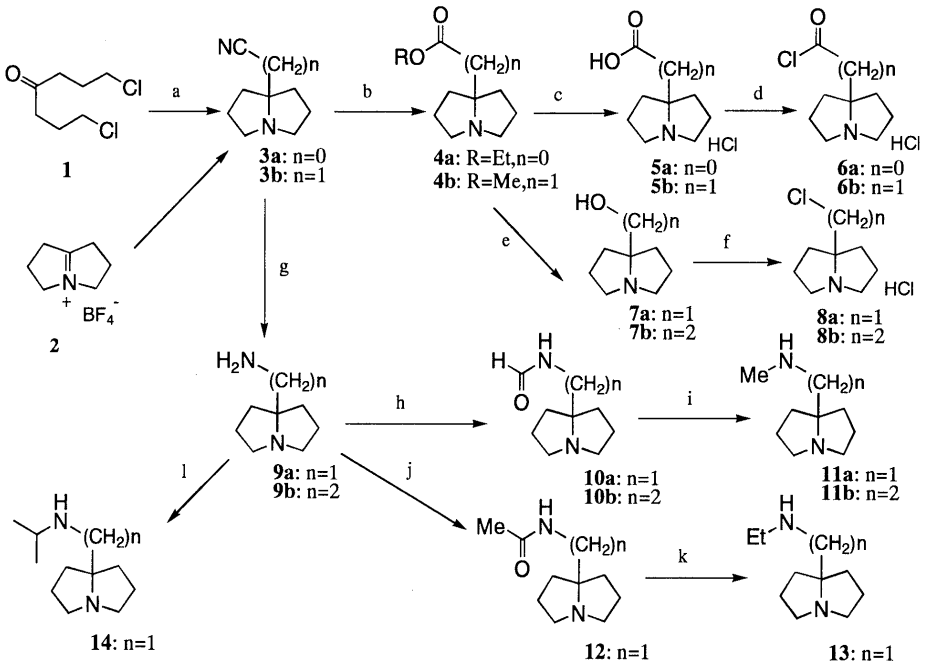


a)2-Amino-2-cyanopropane,NH_3-MeOH(for **3a**), cyanoacetic acid,NH_3/*n*-hexane-H_2O(for **3b**). b)HCl,EtOH(for **4a**),H_2SO_4, MeOH (for **4b**). c)NaOH/EtOH. d)$SOCl_2$. e)$LiAlH_4$/ether. f)$SOCl_2$/benzene. g)$LiAlH_4$/ether(for **9a**),Raney-Ni/H_2/NaOH-MeOH(for **9b**). h)Formic acid. i)$LiAlH_4$/ether. j)AcCl,triethylamine/CH_2Cl_2. k)$LiAlH_4$/THF. l)Acetone,BH_3/THF.

Chart 2

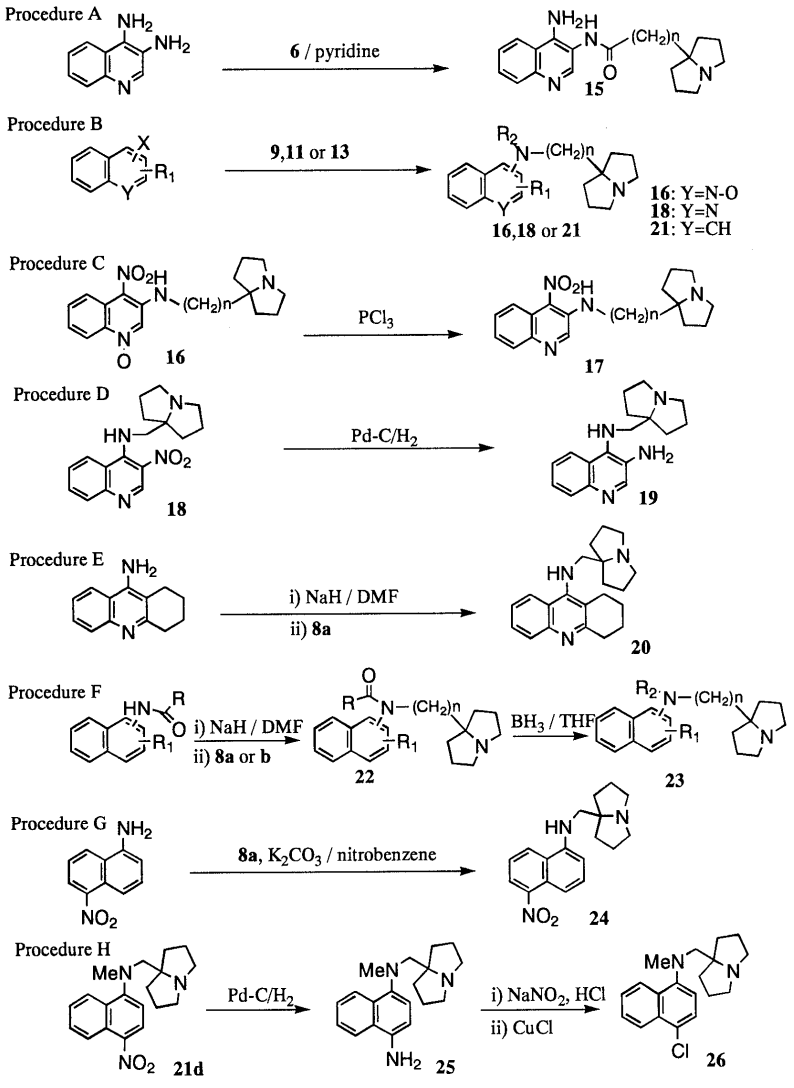


Chart 3

acid in hexane–ammonia water.[10] Cyano compound **3a** was converted to 5-ethoxycarbonyl-1-azabicyclo[3.3.0]-octane (**4a**) by treatment with HCl–EtOH at room temperature. 5-Methoxycarbonylmethyl-1-azabicyclo-[3.3.0]octane (**4b**) was available from **3b** by refluxing in H_2SO_4–MeOH. Treatment of the esters **4a, b** with NaOH and successive chlorination with $SOCl_2$ afforded 5-chlorocarbonyl substituted 1-azabicyclo[3.3.0]octanes (**6a, b**) in good yields. 5-Hydroxyalkyl-1-azabicyclo[3.3.0]octanes (**7a, b**), prepared by reduction of **4a, b** with $LiAlH_4$ in anhydrous ethyl ether, were chlorinated with $SOCl_2$ in benzene to give 5-chloroalkyl-1-azabicyclo[3.3.0]octanes (**8a, b**). Reduction of cyano compounds **3a, b** with $LiAlH_4$ affords 5-aminoalkyl-1-azabicyclo[3.3.0]octanes (**9a, b**). We developed a new method for [2-(1-azabicyclo[3.3.0]-octan-5-yl)ethyl]amine (**9b**) using hydrogenation with H_2–Raney-Ni in good yield.[11] Alkylamino compounds **11a, b** and **13** were derived from amines **9a, b**, *via* acylation and reduction with $LiAlH_4$. 5-(*N*-Isopropyl)aminomethyl-1-azabicyclo[3.3.0]octane (**14**) was prepared by reductive amination of **9a** with acetone and BH_3.

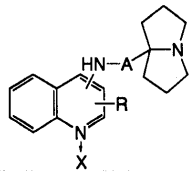
The general synthetic procedures for the final compounds are summarized in Chart 3. The quinoline derivatives were prepared from the corresponding amines and halides (Table 1). 3-Substituted amino-4-aminoquinolines (**15a, b**) were prepared by acylation of 3,4-diaminoquinoline with acyl chlorides **6a, b** in pyridine (procedure A). 3-Substituted amino-4-nitroquinoline *N*-oxides (**16a, b**) were prepared from 3-bromo-4-nitroquinoline *N*-oxide with diamines **9a, b** (procedure B), and 3-substituted amino-4-nitroquinolines (**17a, b**) were produced by the reduction of **16a, b** (procedure C). 4-(1-Azabicyclo[3.3.0]octan-5-yl)methylamino-3-nitroquinoline (**18**) was prepared from the corresponding halide and **9a**, and converted to 3-amino-4-(1-azabicyclo[3.3.0]-octan-5-yl)methylaminoquinoline (**19**) by catalytic reduction (procedure D). 9-(1-Azabicyclo[3.3.0]octan-5-yl)methylamino-1,2,3,4-tetrahydroacridine (**20**) was prepared from the corresponding amine and halide **8a** (procedure E).

The naphthyl amine derivatives were prepared from the corresponding halides, alkoxides, amines and amides (Table 2). 1-Substituted amino-2- or 4-nitronaphthalenes **21a—e** and 2-substituted amino-1-nitronaphthalene **21g** were prepared from the corresponding halonaphthalenes using procedure B. The attempted reaction of 1-chloro-4-nitronaphthalene with **14** failed to give the *N*-isopropylamino derivative, probably due to the steric hindrance of the *N*-isopropyl group. The *N*-(1-azabicyclo[3.3.0]octan-5-yl)methyl-*N*-methylamino derivatives **23a—d** were prepared from the corresponding aminonaphthalenes, and converted to *N*-formyl derivatives by acylation followed by alkylation with **8** and reduction with BH_3–tetrahydrofuran (THF) (procedure F) in high yields. 1-[2-(1-Azabicyclo[3.3.0]octan-5-yl)ethyl]aminonaphthalene (**23c**) was produced as a by-product in the alkylation of *N*-formamide with chloride **8b** in *N*,*N*-dimethylformamide (DMF). 1-(1-Azabicyclo[3.3.0]octan-5-yl)methylamino-4-methoxynaphthalene (**23e**) was obtained by $LiAlH_4$ reduction of 1-[*N*-(1-azabicyclo[3.3.0]octan-5-yl)methyl-*N*-formylamino]-4-methoxynaphthalene (**22d**). 1-(1-Azabicyclo[3.3.0]octan-5-yl)methylamino-5-nitronaphthalene (**24**) was prepared from the corresponding aminonaphthalene and **8a** in low yield. 1-Amino-4-[*N*-(1-azabicyclo[3.3.0]octan-5-yl)methyl-*N*-methylamino]-naphthalene (**25**) was prepared by catalytic reduction of **21d** with 10% palladium-on-carbon, followed by Sandmeyer reaction leading to 1-[*N*-(1-azabicyclo[3.3.0]octan-5-yl)methyl-*N*-methylamino]-4-chloronaphthalene (**26**).

Pharmacology The present compounds were tested for the ability to inhibit acetyl cholinesterase (AcChE) and for binding affinity to muscarinic M1 and M2 receptors *in vitro*, and behavioral efficacy in scopolamine-induced dementia models *in vivo*.

The inhibitory effects of the compounds on AcChE activity *in vitro* were determined according to the method

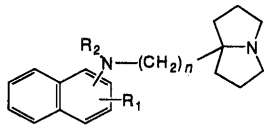
Table 1. Quinoline Derivatives



Compd.	Amino group		R	X	Salt	Procedure[b]	mp (°C)	Recrystn. solvent	Yield (%)	Analysis (%)					
	Position[a]	A								Calcd			Found		
										C	H	N	C	H	N
15a	3	CO	4-NH_2	—	—	A	182—184	EtOH–ether	29.7	68.89	6.80	18.19	68.75	6.81	18.06
15b	3	$COCH_2$	4-NH_2	—	—	A	205—209	EtOH–ether	44.8	69.65	7.14	18.05	69.86	7.09	17.88
16a	3	CH_2	4-NO_2	O	—	B	90—92	$CHCl_3$–ether	88.4	62.18	6.14	17.06	61.95	6.05	16.79
16b	3	CH_2CH_2	4-NO_2	O	—	B	103—106	$CHCl_3$–ether	87.9	63.14	6.48	16.36	62.94	6.42	16.17
17a	3	CH_2	4-NO_2	—	—	C	95—99	$CHCl_3$–hexane	65.4	65.37	6.45	17.94	65.19	6.31	17.87
17b	3	CH_2CH_2	4-NO_2	—	—	C	106—108	$CHCl_3$–hexane	66.3	66.24	6.79	17.17	66.07	6.80	17.13
18	4	CH_2	3-NO_2	—	—	B	155—158	—[c]	92.2	65.37	6.45	17.94	65.31	6.41	17.82
19	4	CH_2	3-NH_2	—	2HCl	D	231—235	EtOH–ether	70.5	57.47	6.81	15.77	57.21	6.95	15.39
20	4	CH_2	$CH_2CH_2CH_2CH_2$[d]	—	2HCl	E	250—255	EtOH–ether	82.9	63.95	7.41	10.65	63.66	7.43	10.36

a) Linking position of amino group. *b*) Refer to the procedures in Chart 3 and experimental section. *c*) Washed with water. *d*) Tetrahydroacridine ring.

Table 2. Naphthalene Derivatives



Compd.	R_1	Amino substituents			Procedure[b]	mp (°C)	Recrystn. solvent	Yield (%)	Analysis (%)					
		Position[a]	n	R_2					Calcd			Found		
									C	H	N	C	H	N
21a	2-NO_2	1	1	H	B	88—89	EtOH	84.1	69.43	6.80	13.49	69.20	6.74	13.58
21b	2-NO_2	1	1	Me	B	Oil	—	85.9	70.13	7.12	12.91	70.26	6.88	12.85
21c	4-NO_2	1	1	H	B	143—144	EtOH–hexane	50.9	69.43	6.80	13.49	69.21	6.70	13.21
21d	4-NO_2	1	1	Me	B	Oil	—	78.2	70.13	7.12	12.91	69.98	7.10	12.94
21e	4-NO_2	1	1	Et	B	Oil	—	30.6	70.77	7.42	12.38	71.13	7.32	12.61
21f	4-NO_2	1	2	H	B	90—91	EtOH–hexane	65.6	70.13	7.12	12.91	70.09	7.08	12.87
21g	1-NO_2	2	1	H	B	86—87	EtOH–hexane	39.1	69.43	6.80	13.49	69.38	6.67	13.44
23a	H	1	1	Me	F	Oil	—	86.7[d]	81.38	8.63	9.99	81.26	8.41	9.82
23b	H	1	2	Me	F	Oil	—	49.0[d]	81.59	8.90	9.51	81.29	8.76	9.37
23c	H	1	2	H	F	Oil	—	33.8	81.38	8.63	9.99	81.16	8.61	9.88
23d	4-MeO	1	1	Me	F	Oil	—	87.4[d]	77.38	8.44	9.02	77.12	8.39	9.08
23e	4-MeO	1	1	H	F[c]	Oil	—	63.0[d]	76.99	8.16	9.45	76.62	8.14	9.59
23f	4-F	1	1	Me	F	Oil	—	89.1[d]	76.48	7.77	9.39	76.51	7.70	9.33
24	5-NO_2	1	1	H	G	95—97	Hexane	36.3	69.43	6.80	13.49	69.19	6.54	13.46
26	4-Cl	1	1	Me	H	Oil	—	14.1[d]	72.48	7.36	8.90	72.41	7.26	8.85

a, *b*) See footnotes *a*), *b*), respectively, in Table 1. *c*) **23e** was obtained by reduction of **22d** with $LiAlH_4$. *d*) Total yield (%) of the compounds based on the formyl naphthylamine derivatives.

Table 3. AcChE Inhibitory Effect and Affinities of Quinoline Derivatives for M1 and M2 Receptors

Compd.	Inhibition of AcChE IC_{50} (μM)	Muscarinic receptor affinities K_i (μM)[a]		M2/M1 index
		[^{3}H]Pirenzepine (M1 receptors)	[^{3}H]QNB (M2 receptors)	
15a	830	2.8	>50	—
15b	350	2.0	5.0	2.5
16a	870	1.4	>50	—
17a	310	1.4	1.3	0.93
19	380	1.7	2.1	1.2
20	69	0.48	0.72	1.5
9a	n.e.	n.e.	n.e.	—
Tacrine	0.37	—	—	—

a) K_i value (μM) calculated from the respective IC_{50} using the Cheng–Prusoff equation, $K_i = IC_{50}/1 + [L]/K_d$, where [L] and K_d are respectively ligand concentration and dissociation constant. K_d values: [^{3}H] pirenzepine, cortex, 7.1 nM; [^{3}H] QNB, cortex, 0.029 nM. n.e.: no effect.

of Ellman *et al.*[12]

The affinities of compounds for muscarinic M1 and M2 receptors were evaluated from the abilities of the compounds to displace [^{3}H]pirenzepine, an M1-selective ligand and [^{3}H]quinuclidinyl benzilate ([^{3}H]QNB) from rat cerebral cortex, according to the method of Flynn and Mash.[13]

The abilities of compounds to improve cognitive function were assessed using passive avoidance tests in scopolamine-induced mice.

Results and Discussion

Initially, the inhibitory effects of quinoline derivatives (**15a**, **b**, **16a**, **17a**, **19**, and **20**) on acetylcholine esterase were compared with those of tacrine, a known acetylcholine esterase inhibitor (Table 3). Results indicated that these compounds had lower activity than tacrine. Compound **20**, which is a tetrahydroacridine derivative, had the highest activity, however, it was still two orders of magnitude weaker than tacrine. There was only a small difference in the activity of the other compounds (**15a**, **b**, **16a**, **17a**, and **19**).

On the other hand, compound **17a** ameliorated scopolamine-induced impairment in passive avoidance tasks at 1.0 mg/kg (i.p.) (Table 5). This indicated that these compounds had other activity, in addition to acetylcholine esterase inhibition. Therefore, affinity for the muscarinic receptor was examined (Table 3). These compounds had strong, essentially equipotent, affinities for muscarinic M1 receptors. Moreover, affinities were not affected by groups linking the aromatic ring and 1-azabicyclo[3.3.0]-octane ring, or by the substituents on the quinoline ring. Since, aminomethylazabicyclic compound **9a** was inactive, both the aromatic ring and the azabicyclic moiety were judged to be necessary for muscarinic activity.

Next, we examined the pharmacological activities of the

Table 4. Affinities of Naphthalene Derivatives for M1 and M2 Receptors

Compd.	Muscarinic receptor affinities K_i (μM)[a]		M2/M1 index
	[^{3}H]Pirenzepine (M1 receptors)	[^{3}H]QNB (M2 receptors)	
21a	1.8	1.4	0.78
21b	0.48	1.8	3.8
21c	1.1	2.4	2.2
21d	0.048	1.1	22.9
21e	0.24	2.3	9.6
21f	0.36	1.05	2.9
21g	1.4	2.1	1.5
23a	0.035	0.53	15.1
23b	3.5	7.9	2.3
23c	0.47	1.8	3.8
23d	0.11	3.1	28.2
23e	2.0	2.2	1.1
23f	0.036	1.0	27.8
24	0.96	3.4	3.5
26	0.047	0.99	21.1
SK-946	0.12	1.1	9.2
(−)YM796	1.8	4.3	2.4
SR46559	0.12	0.85	7.1

a) See footnote a) in Table 3.

naphthalene derivatives (Table 4). These derivatives had similar activities to the quinoline derivatives, however, introduction of alkyl groups to the nitrogen atom of the linking moiety had significant influence on activity. Compound **21b** had high affinity for the muscarinic receptor, about 4 times stronger than that of **21a**. However, replacement of the *N*-methyl group by an *N*-ethyl group decreased the activity (**21d** *versus* **21e** in Table 4).

To examine the effect of the methylene chain of the linking group, **21f** with a two-methylene chain was prepared and found to be more active than **21c** with a one-methylene chain. However, compound **23b** with an *N*-methyl group and a two-methylene chain was less active than compound **23a** with an *N*-methyl and a one-methylene chain.

The effect of substituents on the naphthalene ring was next examined. Introduction of an electron-withdrawing group to the 4-position (**21d**, **23f**, and **26**) had little influence on affinity for muscarinic receptors. However, an electron-donating group in the 4-position lowered activity (**23a** *versus* **23d**). Introduction of an amino moiety to the 2-position, of a nitro group to the 1-position had little influence on affinities (**21a** *versus* **21g**).

From these results, certain naphthalene derivatives had higher affinity and selectivity for the muscarinic M1 receptor than the corresponding quinoline derivatives. Naphthalene derivatives with an *N*-methyl group and one-methylene linker at the 2-position and an electron-donating group at the 4-position (**21d**, **23a**, **23f**, and **26**) had more potent activities than (−)-YM796 and SR46559, with regards to affinity and selectivity to the M1 receptor. Therefore, these derivatives were chosen for further study as M1 muscarinic receptor agonists. Among them, *N*-methyl-4-nitronaphthalene derivative **21d** showed very high affinity for the M1 muscarinic receptor (K_i = 48 nM) and high M1 selectivity (M2/M1 index = 22.9),

Table 5. Effect of Compounds on Scopolamine-Induced Failure of Step-through Passive Avoidance Response in ddY Mice

Compd.	Dose (μg/kg)		*n*	R.T.[a] (sec)	Criteria[b] (%)
Normal			20	283.5±9.34***	85^{+++}
Scopolamine control			30	86.5±17.41	10
17a	100	(i.p.)	20	100.4±20.9	10
	1000	(i.p.)	20	164.0±23.3	30
	10000	(i.p.)	20	184.9±24.1*	25
21d	0.1	(*p.o.*)	20	118.9±23.4	15
	1.0	(*p.o.*)	20	185.8±24.9*	40^{++}
	10	(*p.o.*)	20	198.8±24.1**	40^{++}
	100	(*p.o.*)	20	180.0±24.8*	40^{++}
(±)YM796	1.0	(*p.o.*)	20	125.4±21.6	15
	10	(*p.o.*)	20	118.5±22.3	10
	100	(*p.o.*)	20	184.4±24.4*	30^{+}

a) R.T.: the latency in retention trial. b) Criteria (%) = achievement number of the avoidance task/total number of the test. $*p<0.05$, $**p<0.01$, $***p<0.001$ *vs.* control (Student's *t*-test). $^{+}p<0.05$, $^{++}p<0.01$, $^{+++}p<0.001$ *vs.* control (Fisher's exact probability test).

and also ameliorated scopolamine induced impairment in passive avoidance tasks at 1.0 μg/kg (*p.o.*) (Table 5). These tests confirmed that compound **21d** had high activity as a M1 muscarinic receptor agonist and was progressed to further study.

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded at 60 MHz with a JEOL JNM-60 spectrometer, or at 270 MHz with a JEOL JNM-GSX270 spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard and the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = double doublet and dt = double triplet. Mass spectra (MS) were recorded on a JEOL JMS-DX300, or on a JEOL JMS-SX102. Infrared (IR) spectra were taken with a JASCO IR-810, or Perkin–Elmer 1600.

(1-Azabicyclo[3.3.0]octan-5-yl)carbonitrile (3a)[9] A solution of 1,7-dichloroheptan-4-one (**1**) (38.0 g, 208 mmol) and 2-amino-2-cyanopropane (52.0 g, 618 mmol) in MeOH (200 ml) was stirred at 20—25 °C under ammonia gas atmosphere for 1 d. The reaction mixture was then concentrated *in vacuo*. To the resulting mixture was added water (150 ml) and CH_2Cl_2 (300 ml), followed by NaOH (29.0 g) under ice cooling. The CH_2Cl_2 phase was separated and the aqueous mixture extracted with CH_2Cl_2 (150 ml × 3). The combined CH_2Cl_2 solution was dried and concentrated *in vacuo*. The residue was distilled under reduced pressure (74 °C/0.7 mmHg) to give 24.7 g (87.2%) of **3a** as a colorless oil. MS *m/z*: 136 (M^+), 108 (base peak). IR (neat) cm^{-1}: 2950, 2230. ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.38 (8H, m, 2,3-CH_2 of pyrrolidine), 2.59 (2H, dt, J = 10, 6 Hz, N–CH_2), 3.21 (2H, dt, J = 10, 6 Hz, N–CH_2).

(1-Azabicyclo[3.3.0]octan-5-yl)acetonitrile (3b)[10] NH_3 gas (13.6 g) was introduced to a stirred suspension of **1** (16.4 g, 89.6 mmol) and cyanoacetic acid (38.1 g, 448 mmol) in 28% ammonia water (52.6 ml) at 15 °C. After *n*-hexane (16.0 ml) was added to the suspension, it was stirred for 40 h at the same temperature. The water phase was then concentrated at 70 °C under moderate reduced pressure. To the residue was added 20% NaOH solution (120 ml) and the mixture extracted with EtOAc (100 ml × 3). The extract was dried, evaporated, and distilled under reduced pressure (92 °C/3 mmHg) to give 7.38 g (54.9%) of **3b** as a colorless oil. MS *m/z*: 150 (M^+), 110 (base peak). IR (neat) cm^{-1}: 2959, 2870, 2245. ^{1}H-NMR ($CDCl_3$) δ: 1.67—2.01 (8H, m, 2,3-CH_2 of pyrrolidine), 2.40 (2H, s, CH_2–CN), 2.62 (2H, dt, J = 11, 6 Hz, N–CH_2), 3.13 (2H, dt, J = 11, 6 Hz, N–CH_2).

[2-(1-Azabicyclo[3.3.0]octan-5-yl)ethyl]amine (9b)[11] Raney-Ni (3.33 g) was added to a suspension of NaOH (4.41 g, 110 mmol) and **3b** (8.27 g, 55.1 mmol) in MeOH (46 ml). The suspension was stirred at 20—25 °C under H_2 atmosphere for 1 d. MeOH (60 ml) was then added to the resulting mixture, and insoluble materials removed by filtration. The evaporated filtrate was treated with water and extracted with AcOEt,

dried, and concentrated *in vacuo*. The residual oil was distilled under reduced pressure (67—68 °C/1 mmHg) to give 5.35 g (63.0%) of **9b** as a colorless oil. CIMS *m/z*: 155 [$(M+1)^+$, base peak]. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (2H, br s, NH_2), 1.45—1.83 (10H, m, 2,3-CH_2 of pyrrolidine and $-C\underline{H}_2-CH_2-NH_2$), 2.57 (2H, dt, $J=11$, 6 Hz, N–CH_2), 2.69—2.78 (2H, m, $CH_2-C\underline{H}_2-NH_2$), 2.98 (2H, dt, $J=11$, 6 Hz, N–CH_2).

Procedure A. 4-Amino-3-(1-azabicyclo[3.3.0]octan-5-yl)carbonylaminoquinoline (15a) To a stirred solution of 3,4-diaminoquinoline (5.52 g, 34.7 mmol) in pyridine (330 ml) was slowly added **6a** (7.70 g, 36.5 mmol) at −15 to −20 °C. After stirring at room temperature for 16 h, the reaction mixture was concentrated *in vacuo*, and saturated aqueous $NaHCO_3$ was added to the residue. The mixture was extracted with $CHCl_3$, washed with brine, dried, and concentrated *in vacuo*. The residue was chromatographed on alumina eluting with $CHCl_3$–MeOH (100/0→50/1) to give an oily product. The resulting oil was crystallized from EtOH–ether to give 3.05 g (29.7%) of **15a** as pale yellow crystals. MS *m/z*: 296 (M^+), 110 (base peak). IR (KBr) cm^{-1}: 3350, 3200, 2960, 1640. ^{1}H-NMR (DMSO-d_6) δ: 1.75—2.39 (8H, m, 3,4-CH_2 of pyrrolidine), 2.67—2.78 (2H, m, $-CH_2-$N), 3.20—3.27 (2H, m, $-CH_2-$N), 6.26 (2H, s, NH_2), 7.52 (1H, t, $J=7$ Hz, 6- or 7-H of quinoline), 7.68 (1H, t, $J=7$ Hz, 6- or 7-H of quinoline), 7.88 (1H, d, $J=7$ Hz, 8-H of quinoline), 8.32 (1H, d, $J=7$ Hz, 5-H of quinoline), 8.40 (1H, s, 2-H of quinoline), 9.83 (1H, s, NHCO).

4-Amino-3-[(1-azabicyclo[3.3.0]octan-5-yl)acetylamino]quinoline (15b) In a similar manner, 3,4-diaminoquinoline (1.26 g, 7.91 mmol) and **6b** (1.71 g, 8.31 mmol) gave 1.10 g (44.8%) of **15b** as pale yellow crystals. MS *m/z*: 310 (M^+), 110 (base peak). IR (KBr) cm^{-1}: 3350, 3150, 2960, 1700. ^{1}H-NMR (DMSO-d_6) δ: 1.57—2.08 (8H, m, 3,4-CH_2 of pyrrolidine), 2.41 (2H, s, $-CH_2-$CO), 2.56—2.68 (2H, m, 2-CH_2 of pyrrolidine), 2.92—3.09 (2H, m, 2-CH_2 of pyrrolidine), 6.78 (2H, s, NH_2), 7.42 (1H, t, $J=8$ Hz, 6- or 7-H of quinoline), 7.59 (1H, t, $J=8$ Hz, 6- or 7-H of quinoline), 7.77 (1H, d, $J=8$ Hz, 8-H of quinoline), 8.18 (1H, d, $J=8$ Hz, 5-H of quinoline), 8.24 (1H, s, 2-H of quinoline), 9.35 (1H, s, CONH).

Procedure B. 3-(1-Azabicyclo[3.3.0]octan-5-yl)methylamino-4-nitroquinoline 1-Oxide (16a) A solution of 3-bromo-4-nitroquinoline *N*-oxide (1.25 g, 4.65 mmol) and **9a** (1.31 g, 9.34 mmol) in MeOH (50.0 ml) was stirred at reflux temperature for 2 h. The reaction mixture was then concentrated *in vacuo*, and the residue chromatographed on alumina, eluting with $CHCl_3$–MeOH (100/1) to give an oily product. The resulting oil was crystallized from $CHCl_3$–ether to give 1.35 g (88.4%) of **16a** as a red powder. CIMS *m/z*: 329 [$(M+1)^+$], 110 (base peak). IR (KBr) cm^{-1}: 3258, 2961, 1551. ^{1}H-NMR ($CDCl_3$) δ: 1.63—1.95 (8H, m, 3,4-CH_2 of pyrrolidine), 2.64—2.77 (2H, m, 2-CH_2 of pyrrolidine), 3.10—3.22 (2H, m, 2-CH_2 of pyrrolidine), 3.48 (2H, d, $J=4$ Hz, $-C\underline{H}_2-$NH), 5.91 (1H, br s, NH), 7.57 (1H, t, $J=8$ Hz, 6- or 7-H of quinoline), 7.75 (1H, t, $J=8$ Hz, 6- or 7-H of quinoline), 8.12 (1H, d, $J=8$ Hz, 5-H of quinoline), 8.56 (1H, s, 2-H of quinoline), 8.73 (1H, d, $J=8$ Hz, 8-H of quinoline).

3-[2-(1-Azabicyclo[3.3.0]octan-5-yl)ethyl]amino-4-nitroquinoline 1-Oxide (16b) Similarly, reaction of 3-bromo-4-nitroquinoline *N*-oxide (640 mg, 2.38 mmol) with **9b** (730 mg, 4.73 mmol) gave an oily product, that was crystallized from $CHCl_3$–ether to give 720 mg (87.9%) of **16b** as a red powder. CIMS *m/z*: 343 [$(M+1)^+$], 110 (base peak). IR (KBr) cm^{-1}: 3252, 2954, 1549. ^{1}H-NMR ($CDCl_3$) δ: 1.58—1.88 (10H, m, 3,4-CH_2 of pyrrolidine and $-C\underline{H}_2-CH_2-$NH), 2.60—2.71 (2H, m, 2-CH_2 of pyrrolidine), 3.06—3.18 (2H, m, 2-CH_2 of pyrrolidine), 3.90 (2H, dd, $J=11$, 7 Hz, $-CH_2-C\underline{H}_2-$NH), 7.53 (1H, t, $J=8$ Hz, 6- or 7-H of quinoline), 7.72 (1H, t, $J=8$ Hz, 6- or 7-H of quinoline), 8.10 (1H, d, $J=8$ Hz, 5-H of quinoline), 8.50 (1H, s, NH), 8.53 (1H, s, 2-H of quinoline), 8.73 (1H, d, $J=8$ Hz, 5-H of quinoline).

4-(1-Azabicyclo[3.3.0]octan-5-yl)methylamino-3-nitroquinoline (18) Similarly, reaction of 4-chloro-3-nitroquinoline (7.90 g, 36.8 mmol) with **9a** (5.66 g, 40.5 mmol) in DMF gave 10.6 g (92.2%) of **18** as a yellow powder. CIMS *m/z*: 313 [$(M+1)^+$, base peak]. IR (KBr) cm^{-1}: 3252, 2954, 1549. ^{1}H-NMR ($CDCl_3$) δ: 1.54—1.88 (8H, m, 3,4-CH_2 of pyrrolidine), 2.58—2.73 (2H, m, 2-CH_2 of pyrrolidine), 2.99—3.15 (2H, m, 2-CH_2 of pyrrolidine), 3.81 (2H, s, $-C\underline{H}_2-$NH), 7.55 (1H, t, $J=7$ Hz, 6- or 7-H of quinoline), 7.81—7.91 (2H, m, 8- and 6- or 7-H of quinoline), 8.47 (1H, d, $J=7$ Hz, 5-H of quinoline), 9.15 (1H, s, 2-H of quinoline), 10.00 (1H, br s, NH).

1-(1-Azabicyclo[3.3.0]octan-5-yl)methylamino-2-nitronaphthalene (21a) Similarly, a solution of 1-chloro-2-nitronaphthalene (3.10 g, 14.9 mmol) and **9a** (4.19 g, 29.9 mmol) in EtOH (44.0 ml) was stirred at 115—120 °C in a sealed tube for 10 h to give 3.90 g (84.1%) of **21a** as yellow crystals. MS *m/z*: 311 (M^+), 110 (base peak). IR (KBr) cm^{-1}: 3190, 2950, 1565, 1520. ^{1}H-NMR ($CDCl_3$) δ: 1.59—1.92 (8H, m, 3,4-CH_2 of pyrrolidine), 2.66—2.73 (2H, m, 2-CH_2 of pyrrolidine), 3.13—3.22 (2H, m, 2-CH_2 of pyrrolidine), 3.69 (2H, d, $J=5$ Hz, $-C\underline{H}_2-$NH), 7.05 (1H, d, $J=9$ Hz, 4-H of naphthalene), 7.43 (1H, t, $J=8$ Hz, 7-H of naphthalene), 7.59 (1H, t, $J=8$ Hz, 6-H of naphthalene), 7.73 (1H, d, $J=8$ Hz, 5-H of naphthalene), 8.08 (1H, d, $J=9$ Hz, 3-H of naphthalene), 8.31 (1H, d, $J=8$ Hz, 8-H of naphthalene), 9.49 (1H, br s, NH).

1-[*N*-(1-Azabicyclo[3.3.0]octan-5-yl)methyl-*N*-methylamino]-2-nitronaphthalene (21b) Similarly, a solution of 1-chloro-2-nitronaphthalene (2.12 g, 10.2 mmol) and **11a** (3.16 g, 20.5 mmol) in pyridine (22.0 ml) was stirred at 110—115 °C for 6 h to give 2.85 g (85.9%) of **21b** as a yellow oil. CIMS *m/z*: 326 [$(M+1)^+$], 110 (base peak). IR (neat) cm^{-1}: 2953, 1522. ^{1}H-NMR ($CDCl_3$) δ: 1.44—1.81 (8H, m, 3,4-CH_2 of pyrrolidine), 2.50—2.58 (2H, m, 2-CH_2 of pyrrolidine), 2.93—3.01 (2H, m, 2-CH_2 of pyrrolidine), 2.97 (2H, s, N–CH_2–C), 3.23 (3H, s, N–CH_3), 7.59—7.63 (2H, m, 5,8-H of naphthalene), 7.62 (1H, d, $J=9$ Hz, 3- or 4-H of naphthalene), 7.69 (1H, d, $J=9$ Hz, 3- or 4-H of naphthalene), 7.85—7.88 (1H, m, 6- or 7-H of naphthalene), 8.36—8.40 (1H, m, 6- or 7-H of naphthalene).

1-(1-Azabicyclo[3.3.0]octan-5-yl)methylamino-4-nitronaphthalene (21c) Similarly, a solution of 1-chloro-4-nitronaphthalene (4.20 g, 20.2 mmol) and **9a** (5.67 g, 40.4 mmol) in EtOH (15.0 ml) was stirred at 115—120 °C in a sealed tube for 8 h to give 3.20 g (50.9%) of **21c** as yellow crystals. MS *m/z*: 311 (M^+), 110 (base peak). IR (KBr) cm^{-1}: 3276, 2942, 1580, 1493. ^{1}H-NMR ($CDCl_3$) δ: 1.69—1.92 (8H, m, 3,4-CH_2 of pyrrolidine), 2.70—2.81 (2H, m, 2-CH_2 of pyrrolidine), 3.08—3.21 (2H, m, 2-CH_2 of pyrrolidine), 3.19 (2H, d, $J=4$ Hz, NH–$C\underline{H}_2-$), 6.45 (1H, d, $J=9$ Hz, 2-H of naphthalene), 6.50 (1H, br s, NH), 7.53 (1H, t, $J=8$ Hz, 7-H of naphthalene), 7.70 (1H, t, $J=8$ Hz, 6-H of naphthalene), 7.88 (1H, d, $J=8$ Hz, 8-H of naphthalene), 8.49 (1H, d, $J=9$ Hz, 3-H of naphthalene), 9.07 (1H, d, $J=8$ Hz, 5-H of naphthalene).

1-[*N*-(1-Azabicyclo[3.3.0]octan-5-yl)methyl-*N*-methylamino]-4-nitronaphthalene (21d) Similarly, a solution of 1-chloro-4-nitronaphthalene (3.96 g, 19.1 mmol), **11a** (5.88 g, 38.1 mmol) and NaI (400 mg) in pyridine (42.0 ml) was stirred in a sealed tube at 120—125 °C for 12 h to give 4.86 g (78.2%) of **21d** as a yellow oil. CIMS *m/z*: 326 [$(M+1)^+$], 110 (base peak). IR (neat) cm^{-1}: 2950, 1570. ^{1}H-NMR ($CDCl_3$) δ: 1.51—1.96 (8H, m, 3,4-CH_2 of pyrrolidine), 2.58 (2H, dt, $J=10$, 6 Hz, 2-CH_2 of pyrrolidine), 3.00 (2H, dt, $J=10$, 6 Hz, 2-CH_2 of pyrrolidine), 3.12 (3H, s, CH_3), 3.37 (2H, s, N–CH_2–C), 7.11 (1H, d, $J=9$ Hz, 2-H of naphthalene), 7.55 (1H, t, $J=8$ Hz, 6- or 7-H of naphthalene), 7.68 (1H, t, $J=8$ Hz, 6- or 7-H of naphthalene), 8.26 (1H, d, $J=8$ Hz, 8-H of naphthalene), 8.31 (1H, d, $J=9$ Hz, 3-H of naphthalene), 8.78 (1H, d, $J=8$ Hz, 5-H of naphthalene).

1-[*N*-(1-Azabicyclo[3.3.0]octan-5-yl)methyl-*N*-ethylamino]-4-nitronaphthalene (21e) Similarly, a solution of 1-chloro-4-nitronaphthalene (2.00 g, 9.63 mmol), **13** (3.24 g, 19.3 mmol) and NaI (580 mg) in pyridine (20.0 ml) was stirred in a sealed tube at 190 °C for 20 h to give 1.00 g (30.6%) of **21e** as a yellow oil. MS *m/z*: 339 (M^+), 310, 110 (base peak). IR (neat) cm^{-1}: 2959, 2867, 1566. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, t, $J=7$ Hz, $C\underline{H}_3-CH_2-$), 1.40—1.89 (8H, m, 3,4-CH_2 of pyrrolidine), 2.53 (2H, dt, $J=11$, 6 Hz, 2-CH_2 of pyrrolidine), 2.99 (2H, dt, $J=11$, 6 Hz, 2-CH_2 of pyrrolidine), 3.33 (2H, s, N–CH_2–C), 3.44 (2H, q, $J=7$ Hz, $CH_3-C\underline{H}_2-$), 7.26 (1H, d, $J=9$ Hz, 2-H of naphthalene), 7.57 (1H, ddd, $J=8$, 7, 2 Hz, 6- or 7-H of naphthalene), 7.69 (1H, ddd, $J=8$, 7, 2 Hz, 6- or 7-H of naphthalene), 8.30 (1H, d, $J=9$ Hz, 3-H of naphthalene), 8.34 (1H, d, $J=8$ Hz, 8-H of naphthalene), 8.74 (1H, d, $J=8$ Hz, 5-H of naphthalene).

1-[2-(1-Azabicyclo[3.3.0]octan-5-yl)ethylamino]-4-nitronaphthalene (21f) Similarly, a solution of 1-chloro-4-nitronaphthalene (980 mg, 4.72 mmol) and **9b** (1.44 g, 9.34 mmol) in EtOH (20.0 ml) was stirred in a sealed tube at 120—125 °C for 6 h to give 590 mg (38.4%) of **21f** as yellow crystals. MS *m/z*: 325 (M^+), 110 (base peak). IR (KBr) cm^{-1}: 3150, 2950, 1580. ^{1}H-NMR ($CDCl_3$) δ: 1.57—1.88 (8H, m, 3,4-CH_2 of pyrrolidine), 1.94 (2H, t, $J=6$ Hz, $-C\underline{H}_2-CH_2-$NH), 2.69—2.75 (2H, m, 2-CH_2 of pyrrolidine), 3.07—3.13 (2H, m, 2-CH_2 of pyrrolidine), 3.48 (2H, t, $J=6$ Hz, $-CH_2-C\underline{H}_2-$NH), 6.34 (1H, d, $J=9$ Hz, 2-H of naphthalene), 7.49 (1H, t, $J=8$ Hz, 6- or 7-H of naphthalene), 7.68 (1H, t, $J=8$ Hz, 6- or 7-H of naphthalene), 7.84 (1H, d, $J=8$ Hz, 8-H of naphthalene), 8.54 (1H, d, $J=9$ Hz, 3-H of naphthalene), 9.11 (1H, d, $J=8$ Hz, 5-H of naphthalene), 9.80 (1H, br s, NH).

2-(1-Azabicyclo[3.3.0]octan-5-yl)methylamino-1-nitronaphthalene

(21g) Similarly, a solution of 2-ethoxy-1-nitronaphthalene (6.00 g, 27.6 mmol) and **9a** (4.07 g, 29.0 mmol) in EtOH (40.0 ml) was stirred in a sealed tube at 155—165 °C for 6 h to give 3.36 g (39.1%) of **21g** as yellow crystals. MS *m/z*: 311 (M^+), 110 (base peak). IR (KBr) cm^{-1}: 3290, 2955, 1635, 1555. ^{1}H-NMR ($CDCl_3$) δ: 1.68—1.95 (8H, m, 3,4-CH_2 of pyrrolidine), 2.65—2.78 (2H, m, 2-CH_2 of pyrrolidine), 3.13—3.21 (2H, m, 2-CH_2 of pyrrolidine), 3.30 (2H, d, J=5 Hz, -C<u>H</u>$_2$-NH), 7.06 (1H, d, J=9 Hz, 3-H of naphthalene), 7.31 (1H, t, J=8 Hz, 6- or 7-H of naphthalene), 7.58 (1H, t, J=8 Hz, 6- or 7-H of naphthalene), 7.65 (1H, d, J=8 Hz, 5-H of naphthalene), 7.76 (1H, d, J=9 Hz, 4-H of naphthalene), 8.77 (1H, d, J=8 Hz, 8-H of naphthalene), 9.18 (1H, br s, NH).

Procedure C. 3-(1-Azabicyclo[3.3.0]octan-5-yl)methylamino-4-nitroquinoline (17a) To a solution of **16a** (900 mg, 2.74 mmol) in $CHCl_3$ (60.0 ml) was added dropwise PCl_3 (4.76 ml, 47.4 mmol) at −10 °C. After stirring at 0 °C for 16 h, the resulting mixture was poured into ice-water (500 ml), and basified with $NaHCO_3$. The mixture was extracted with $CHCl_3$, dried, and concentrated *in vacuo*. The residue was chromatographed on alumina eluting with $CHCl_3$–CCl_4 to give an oily product, that was crystallized from $CHCl_3$–hexane to give 560 mg (65.4%) of **17a** as pale yellow crystals. CIMS *m/z*: 313 [$(M+1)^+$], 110 (base peak). IR (KBr) cm^{-1}: 3242, 2947, 1568. ^{1}H-NMR ($CDCl_3$) δ: 1.61—1.92 (8H, m, 3,4-CH_2 of pyrrolidine), 2.68—2.76 (2H, m, 2-CH_2 of pyrrolidine), 3.15—3.22 (2H, m, 2-CH_2 of pyrrolidine), 3.60 (2H, d, J=4 Hz, NH-C<u>H</u>$_2$-), 6.01 (1H, br s, NH), 7.40 (1H, t, J=8 Hz, 6- or 7-H of quinoline), 7.61 (1H, t, J=8 Hz, 6- or 7-H of quinoline), 7.95 (1H, d, J=8 Hz, 8-H of quinoline), 8.09 (1H, d, J=8 Hz, 5-H of quinoline), 8.63 (1H, s, 2-H of quinoline).

3-[2-(1-Azabicyclo[3.3.0]octan-5-yl)ethyl]amino-4-nitroquinoline (17b) Similarly, **16b** (190 mg, 0.555 mmol) was treated with PCl_3 (3.00 ml, 29.9 mmol) gave a yellow solid. The solid was recrystallized from $CHCl_3$–ether to give 120 mg (66.3%) of **17b** as pale yellow crystals. CIMS *m/z*: 327 [$(M+1)^+$], 110 (base peak). IR (KBr) cm^{-1}: 3246, 2950, 1564. ^{1}H-NMR ($CDCl_3$) δ: 1.58—1.91 (10H, m, 3,4-CH_2 of pyrrolidine and NH-CH_2-C<u>H</u>$_2$-), 2.63—2.76 (2H, m, 2-CH_2 of pyrrolidine), 3.11—3.23 (2H, m, 2-CH_2 of pyrrolidine), 3.96 (2H, dd, J=10, 6 Hz, NH-C<u>H</u>$_2$-CH_2-), 7.38 (1H, t, J=8 Hz, 6- or 7-H of quinoline), 7.59 (1H, t, J=8 Hz, 6- or 7-H of quinoline), 7.92 (1H, d, J=8 Hz, 8-H of quinoline), 8.07 (1H, d, J=8 Hz, 5-H of quinoline), 8.17 (1H, br s, NH), 8.58 (1H, s, 2-H of quinoline).

Procedure D. 3-Amino-4-(1-azabicyclo[3.3.0]octan-5-yl)methylamino-quinoline Dihydrochloride (19) A suspension of **18** (6.00 g, 19.2 mmol) and 10%Pd–C (2.00 g) in ethanol (1200 ml) was stirred under a hydrogen stream at room temperature for 2 h. The reaction mixture was filtered and concentrated *in vacuo* to obtain 5.40 g of a red oil. The resulting oil was chromatographed on alumina eluting with $CHCl_3$–hexane and dissolved in 200 ml of ethanol, treated with HCl gas, and concentrated *in vacuo*. The solid was recrystallized from EtOH–ether to give 4.80 g (70.5%) of **19** as pale red crystals. MS *m/z*: 282 (M^+), 110 (base peak). IR (KBr) cm^{-1}: 3200, 2980, 1620. ^{1}H-NMR (DMSO-d_6) δ: 1.78—2.16 (8H, m, 3,4-CH_2 of pyrrolidine), 3.15—3.26 (2H, m, 2-CH_2 of pyrrolidine), 3.45—3.53 (2H, m, 2-CH_2 of pyrrolidine), 4.47 (2H, s, NH-C<u>H</u>$_2$-), 7.75 (1H, t, J=7 Hz, 6- or 7-H of quinoline), 7.88 (1H, t, J=7 Hz, 6- or 7-H of quinoline), 8.10 (1H, d, J=7 Hz, 8-H of quinoline), 8.50 (1H, br s, NH), 8.57 (1H, s, 2-H of quinoline), 8.86 (1H, d, J=8 Hz, 5-H of quinoline), 11.90 (2H, br s, NH_2).

Procedure E. 9-[(1-Azabicyclo[3.3.0]octan-5-yl)methylamino]-1,2,3,4-tetrahydroacridine Dihydrochloride (20) To a solution of 9-amino-1,2,3,4-tetrahydroacridine HCl·3/2H_2O (4.56 g, 17.4 mmol) in DMF (124 ml) was added 60% NaH (5.22 g, 131 mmol) at 20 °C, and the mixture was stirred at 40 °C for 10 min. The chloride **8a** (3.41 g, 17.4 mmol) was then added to the mixture at −20 °C. After stirring at 15 to 20 °C for 16 h, the reaction mixture was poured into ice-water (200 ml) and extracted with benzene. The extract was washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed on alumina to give an oily product, that was treated with HCl–EtOH and crystallized from EtOH–ether to give 6.17 g (82.9%) of **20** as a white powder. MS *m/z*: 321 (M^+), 110 (base peak). IR (KBr) cm^{-1}: 3350, 2950, 1580. ^{1}H-NMR (DMSO-d_6) δ: 1.85—2.18 (12H, m, 2,3-CH_2-acridine and 3,4-CH_2-pyrrolidine), 2.85—3.58 (8H, m, 1,4-CH_2-acridine and 2-CH_2-pyrrolidine), 4.43 (2H, d, J=6 Hz, NH-C<u>H</u>$_2$-), 7.71 (1H, t, J=7 Hz, 6- or 7-H of acridine), 7.98 (1H, t, J=7 Hz, 6- or 7-H of acridine), 8.17 (1H, d, J=7 Hz, 8-H of acridine), 8.30 (1H, br s, NH), 8.73 (1H, d, J=8 Hz, 5-H of acridine), 12.03 (1H, br s, N^+H).

Procedure F. 1-[*N*-(1-Azabicyclo[3.3.0]octan-5-yl)methyl-*N*-methylamino]naphthalene (23a) To a solution of *N*-formyl-1-naphthylamine (1.83 g, 10.7 mmol) in DMF (50.0 ml) was added 60% NaH (1.68 g, 42.0 mmol) at −40 °C, and the mixture was stirred at 10—15 °C for 30 min. **8a** (2.30 g, 11.7 mmol) was then added to the mixture at −40 °C. After stirring at 10—15 °C overnight, the reaction mixture was poured into ice-water (200 ml) and extracted with $CHCl_3$ (300 ml). The extract was washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed on silica gel to give 3.02 g (95.9%) of 1-[*N*-(1-azabicyclo[3.3.0]octan-5-yl)methyl-*N*-formylamino]naphthalene (**22a**) as a pale yellow oil. MS *m/z*: 294 (M^+), 110 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 1.23—1.77 (8H, m, 3,4-CH_2-pyrrolidine), 2.43—2.56 (2H, m, 2-CH_2-pyrrolidine), 2.89—3.05 (2H, m, 2-CH_2-pyrrolidine), 3.62—4.14 (2H, m, C-CH_2-N-), 7.39—7.60 (4H, m, aromatic H), 7.84—7.95 (3H, m, aromatic H), 8.31 (1H, s, CHO).

A solution of **22a** (2.89 g, 9.82 mmol) in THF (50.0 ml) was added dropwise to BH_3–THF (1 M) (40.0 ml, 40.0 mmol), stirred at room temperature for 3 d and refluxed for 1 h. To the reaction mixture was added 6 N HCl (5.80 ml) in an ice-bath. The organic solvent was removed by distillation under atmospheric pressure. The resulting mixture was alkalized with NaOH pellets in an ice-bath, extracted with Et_2O (80 ml × 4), dried, and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with AcOEt–triethylamine to give 2.49 g (90.4%) of **23a** as a pale yellow oil. MS *m/z*: 280 (M^+), 110 (base peak). IR (neat) cm^{-1}: 2952, 1576, 1393. ^{1}H-NMR ($CDCl_3$) δ: 1.46—2.06 (8H, m, 3,4-CH_2-pyrrolidine), 2.57 (2H, dt, J=10, 6 Hz, 2-CH_2-pyrrolidine), 2.90 (3H, s, N-CH_3), 3.02 (2H, dt, J=10, 6 Hz, 2-CH_2-pyrrolidine), 3.18 (2H, s, C<u>H</u>$_2$-N-CH_3), 7.25 (1H, d, J=8 Hz, 2-H of naphthalene), 7.39 (1H, t, J=8 Hz, 3-H of naphthalene), 7.40—7.53 (2H, m, 6,7-H of naphthalene), 7.54 (1H, d, J=8 Hz, 4-H of naphthalene), 7.79—7.83 (1H, m, 5-H of naphthalene), 8.31—8.34 (1H, m, 8-H of naphthalene).

1-[*N*-[2-(1-Azabicyclo[3.3.0]octan-5-yl)ethyl]-*N*-methylamino]naphthalene (23b), 1-[2-(1-Azabicyclo[3.3.0]octan-5-yl)ethyl]aminonaphthalene (23c) A similar reaction of *N*-formyl-1-naphthylamine (1.90 g, 11.1 mmol) with 60% NaH (1.68 g, 42.0 mmol) and **8b** (2.57 g, 12.2 mmol) as described for **22a** gave 1.80 g (52.6%) of 1-[*N*-[2-(1-azabicyclo-[3.3.0]octan-5-yl)ethyl]-*N*-formylamino]naphthalene (**22b**) as a colorless oil and 1.05 g (33.8%) of **23c** as a colorless oil. **22b**: MS *m/z*: 308 (M^+), 110 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 1.51—1.88 (10H, m, 3,4-CH_2-pyrrolidine and OHC-N-CH_2-C<u>H</u>$_2$-), 2.52 (2H, dt, J=11, 6 Hz, 2-CH_2-pyrrolidine), 2.91 (2H, dt, J=11, 6 Hz, 2-CH_2-pyrrolidine), 3.45—4.25 (2H, m, OHC-N-C<u>H</u>$_2$-CH_2-), 7.33 (1H, dd, J=7, 1 Hz, 2-H of naphthalene), 7.46—7.69 (3H, m, 4,6,7-H of naphthalene), 7.82—7.94 (3H, m, 3,5,8-H of naphthalene), 8.21 (1H, s, CHO).

23c: MS *m/z*: 280 (M^+), 110 (base peak). IR (neat) cm^{-1}: 3239, 2955, 1583, 1538. ^{1}H-NMR ($CDCl_3$) δ: 1.62—1.87 (8H, m, 3,4-CH_2-pyrrolidine), 1.94 (2H, t, J=6 Hz, NH-CH_2-C<u>H</u>$_2$-), 2.66 (2H, dt, J=10, 6 Hz, 2-CH_2-pyrrolidine), 3.10 (2H, dt, J=10, 6 Hz, 2-CH_2-pyrrolidine), 3.35 (2H, t, J=6 Hz, NH-C<u>H</u>$_2$-CH_2), 6.48 (1H, d, J=8 Hz, 2-H of naphthalene), 7.14 (1H, d, J=8 Hz, 4-H of naphthalene), 7.33 (1H, t, J=8 Hz, 3-H of naphthalene), 7.37—7.44 (2H, m, 6,7-H of naphthalene), 7.74—7.77 (1H, m, 5- or 8-H of naphthalene), 7.82—7.86 (1H, m, 5- or 8-H of naphthalene).

In a similar manner to the synthesis of **23a**, **22b** (1.70 g, 5.51 mmol) was treated with BH_3–THF (1 M) (22.0 ml, 22.0 mmol) to give 1.51 g (93.1%) of **23b** as a colorless oil. MS *m/z*: 294 (M^+), 110 (base peak). IR (neat) cm^{-1}: 2953, 1576. ^{1}H-NMR ($CDCl_3$) δ: 1.45—1.83 (10H, m, 3,4-CH_2-pyrrolidine and CH_3-N-CH_2-C<u>H</u>$_2$-), 2.56 (2H, dt, J=10, 6 Hz, 2-CH_2-pyrrolidine), 2.86 (3H, s, CH_3), 2.99 (2H, dt, J=10, 6 Hz, 2-CH_2-pyrrolidine), 3.08—3.15 (2H, m, CH_3-N-C<u>H</u>$_2$-CH_2-), 7.10 (1H, d, J=8 Hz, 2-H of naphthalene), 7.38 (1H, t, J=8 Hz, 3-H of naphthalene), 7.43—7.48 (2H, m, 6,7-H of naphthalene), 7.51 (1H, d, J=8 Hz, 4-H of naphthalene), 7.79—7.82 (1H, m, 5- or 8-H of naphthalene), 8.20—8.24 (1H, m, 5- or 8-H of naphthalene).

1-[*N*-(1-Azabicyclo[3.3.0]octan-5-yl)methyl-*N*-methylamino]-4-methoxynaphthalene (23d) A similar reaction of *N*-formyl-4-methoxy-1-naphthylamine (4.50 g, 22.4 mmol) with 60% NaH (4.48 g, 112 mmol) and **8a** (5.29 g, 26.9 mmol), as described for **22a**, gave 6.60 g (91.0%) of 1-[*N*-(1-azabicyclo[3.3.0]octan-5-yl)methyl-*N*-formylamino]-4-methoxynaphthalene (**22d**) as a yellow oil. CIMS *m/z*: 325 [$(M+1)^+$, base peak]. ^{1}H-NMR ($CDCl_3$) δ: 1.23—1.80 (8H, m, 3,4-H of pyrrolidine), 2.43—2.57 (2H, m, 2-H of pyrrolidine), 2.89—3.07 (2H, m, 2-H of pyrrolidine), 3.57—4.14 (2H, m, OHC-N-C<u>H</u>$_2$-), 4.04 (3H, s, OCH_3),

6.80 (1H, d, $J=8$ Hz, 3-H of naphthalene), 7.31 (1H, d, $J=8$ Hz, 2-H of naphthalene), 7.51—7.65 (2H, m, 6,7-H of naphthalene), 7.76 (1H, dd, $J=7$, 2 Hz, 5-H of naphthalene), 8.27 (1H, s, CHO), 8.32 (1H, dd, $J=7$, 2 Hz, 8-H of naphthalene).

In a similar manner to the synthesis of **23a**, **22d** (2.90 g, 8.95 mmol) was treated with BH_3–THF (1 M) (40.0 ml, 40.0 mmol) to give 2.66 g (96.0%) of **23d** as a colorless oil. CIMS m/z: 311 $[(M+1)^+]$, 110 (base peak). IR (neat) cm^{-1}: 2950, 1580. ^{1}H-NMR ($CDCl_3$) δ: 1.42—2.04 (8H, m, 3,4-H of pyrrolidine), 2.56 (2H, dt, $J=11$, 7 Hz, 2-H of pyrrolidine), 2.82 (3H, s, CH_3), 3.01 (2H, dt, $J=11$, 7 Hz, 2-H of pyrrolidine), 3.11 (2H, s, CH_3–N–C$\underline{H}_2$–), 3.97 (3H, s, OCH_3), 6.75 (1H, d, $J=8$ Hz, 3-H of naphthalene), 7.19 (1H, d, $J=8$ Hz, 2-H of naphthalene), 7.43—7.57 (2H, m, 6,7-H of naphthalene), 8.23 (1H, dd, $J=7$, 2 Hz, 5- or 8-H of naphthalene), 8.34 (1H, dd, $J=7$, 2 Hz, 5- or 8-H of naphthalene).

1-(1-Azabicyclo[3.3.0]octan-5-yl)methylamino-4-methoxynaphthalene (23e) To a stirred suspension of $LiAlH_4$ (1.76 g, 46.3 mmol) in THF (23.0 ml) was added dropwise a solution of **22d** (3.00 g, 9.26 mmol) in THF (20.0 ml) at room temperature, and the mixture was stirred at reflux temperature for 1 h. After the reaction mixture was cooled to 0 °C, the remaining $LiAlH_4$ was decomposed by cautious addition of H_2O. The resulting mixture was filtered, and the precipitate washed with THF. The combined filtrate was dried and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with AcOEt–triethylamine, to give 1.80 g (62.7%) of **23e** as a colorless oil. CIMS m/z: 297 $(M+1)^+$, 110 (base peak). IR (neat) cm^{-1}: 3200, 2950, 1590. ^{1}H-NMR ($CDCl_3$) δ: 1.65—2.02 (8H, m, 3,4-H of pyrrolidine), 2.71 (2H, dt, $J=11$, 6 Hz, 2-H of pyrrolidine), 3.03 (2H, s, NH–C$\underline{H}_2$–), 3.12 (2H, dt, $J=11$, 6 Hz, 2-H of pyrrolidine), 3.94 (3H, s, OCH_3), 4.71 (1H, br s, NH), 6.50 (1H, d, $J=8$ Hz, 3-H of naphthalene), 6.73 (1H, d, $J=8$ Hz, 2-H of naphthalene), 7.46—7.49 (2H, m, 6,7-H of naphthalene), 7.86—7.90 (1H, m, 5- or 8-H of naphthalene), 8.21—8.25 (1H, m, 5- or 8-H of naphthalene).

1-[*N*-(1-Azabicyclo[3.3.0]octan-5-yl)methyl-*N*-methylamino]-4-fluoronaphthalene (23f) In a similar manner to the synthesis of **22a**, reaction of *N*-formyl-4-fluoro-1-naphthylamine (1.90 g, 10.0 mmol) with 60% NaH (1.61 g, 40.3 mmol) and **8a** (2.17 g, 11.1 mmol) gave 2.90 g (92.8%) of 1-[*N*-(1-azabicyclo[3.3.0]octan-5-yl)methyl-*N*-formylamino]-4-fluoronaphthalene (**22f**) as a pale yellow oil. MS m/z: 312 (M^+), 110 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 1.26—1.78 (8H, m, 3,4-H of pyrrolidine), 2.44—2.58 (2H, m, 2-H of pyrrolidine), 2.89—3.04 (2H, m, 2-H of pyrrolidine), 3.58—4.19 (2H, m, OHC–N–C$\underline{H}_2$–), 7.20 (1H, dd, $J=10$, 8 Hz, 3-H of naphthalene), 7.36 (1H, dd, $J=8$, 5 Hz, 2-H of naphthalene), 7.57—7.67 (2H, m, 6,7-H of naphthalene), 7.81—7.85 (1H, m, 8-H of naphthalene), 8.15—8.20 (1H, m, 5-H of naphthalene), 8.28 (1H, s, CHO).

As described for **23a**, **22f** (2.78 g, 8.90 mmol) was treated with BH_3–THF (1 M) (35.6 ml, 35.6 mmol) to give 2.55 g (96.0%) of **23f** as a pale yellow oil. MS m/z: 298 (M^+), 110 (base peak). IR (neat) cm^{-1}: 2953, 2863, 1464. ^{1}H-NMR ($CDCl_3$) δ: 1.45—2.05 (8H, m, 3,4-H of pyrrolidine), 2.57 (2H, dt, $J=10$, 6 Hz, 2-H of pyrrolidine), 2.85 (3H, s, CH_3), 3.01 (2H, dt, $J=10$, 6 Hz, 2-H of pyrrolidine), 3.12 (2H, s, CH_3–N–C$\underline{H}_2$–), 7.05 (1H, dd, $J=10$, 8 Hz, 3-H of naphthalene), 7.17 (1H, dd, $J=8$, 5 Hz, 2-H of naphthalene), 7.49—7.56 (2H, m, 6,7-H of naphthalene), 8.05—8.08 (1H, m, 8-H of naphthalene), 8.32—8.36 (1H, m, 5-H of naphthalene).

Procedure G. 1-(1-Azabicyclo[3.3.0]octan-5-yl)methylamino-5-nitronaphthalene (24) A suspension of 5-nitro-1-naphthylamine (800 mg, 4.25 mmol), **8a** (1.68 g, 8.57 mmol) and K_2CO_3 (1.73 g, 12.5 mmol) in nitrobenzene (50.0 ml) was stirred at 150—155 °C for 8 h. After concentration *in vacuo*, brine (80 ml) was added to the residue, which was then extracted with $CHCl_3$ (300 ml). The extract was dried, evaporated, and chromatographed on silica gel eluting with AcOEt–triethylamine to give an oily product, that was crystallized from *n*-hexane to give 480 mg (36.3%) of **24** as red crystals. CIMS m/z: 312 $[(M+1)^+$, base peak]. IR (KBr) cm^{-1}: 3320, 2950, 1580. ^{1}H-NMR ($CDCl_3$) δ: 1.68—1.97 (8H, m, 3,4-CH_2 of pyrrolidine), 2.70—2.78 (2H, m, 2-CH_2 of pyrrolidine), 3.06 (2H, d, $J=5$ Hz, NH–C$\underline{H}_2$–), 3.08—3.16 (2H, m, 2-CH_2 of pyrrolidine), 5.39 (1H, br s, NH), 6.67 (1H, d, $J=8$ Hz, 2-H of naphthalene), 7.45 (1H, t, $J=8$ Hz, 3-H of naphthalene), 7.52 (1H, t, $J=8$ Hz, 7-H of naphthalene), 7.76 (1H, d, $J=8$ Hz, 8-H of naphthalene), 8.11 (1H, d, $J=8$ Hz, 4-H of naphthalene), 8.16 (1H, d, $J=8$ Hz, 6-H of naphthalene).

Procedure H. 1-[*N*-(1-Azabicyclo[3.3.0]octan-5-yl)methyl-*N*-methylamino]-4-chloronaphthalene (26) A mixture of **21d** (7.00 g, 21.5 mmol), 10% Pd–C (2.50 g), and EtOH (200 ml) was hydrogenated at 10—15 °C under atmospheric pressure for 1.5 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give 6.37 g (quant.) of *N*-(1-azabicyclo[3.3.0]octan-5-yl)methyl-*N*-methyl-1,4-naphthalenediamine (**25**) as a pale red oil. CIMS m/z: 295 $[(M+1)^+$, base peak]. ^{1}H-NMR ($CDCl_3$) δ: 1.42—2.05 (8H, m, 3,4-CH_2 of pyrrolidine), 2.56 (2H, dt, $J=10$, 6 Hz, 2-CH_2 of pyrrolidine), 2.81 (3H, s, CH_3), 3.02 (2H, dt, $J=10$, 6 Hz, 2-CH_2 of pyrrolidine), 3.10 (2H, s, CH_3–N–C$\underline{H}_2$–), 4.02 (2H, br s, NH_2), 6.75 (1H, d, $J=8$ Hz, 3-H of naphthalene), 7.15 (1H, d, $J=8$ Hz, 2-H of naphthalene), 7.45—7.50 (2H, m, 6,7-H of naphthalene), 7.81 (1H, dd, $J=7$, 2 Hz, 5-H of naphthalene), 8.40 (1H, dd, $J=7$, 2 Hz, 8-H of naphthalene).

To a stirred solution of **25** (6.31 g, 21.4 mmol) and conc. HCl (55.0 ml, 652 mmol) in H_2O (27.5 ml) was added dropwise a solution of $NaNO_2$ (1.40 g, 20.3 mmol) in H_2O (8 ml) at −5 °C. After stirring at the same temperature for 15 min, it was added to a stirred suspension of CuCl (8.50 g, 85.9 mmol) in conc. HCl (18.0 ml) at 83—85 °C, and the whole was stirred at the same temperature for 5 min. Ice was then added to the reaction mixture, and the whole alkalized with 10% NaOH, and extracted with $CHCl_3$ (150 ml × 5). The extract was dried and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with AcOEt–triethylamine to give 950 mg (14.1%) of **26** as a pale yellow oil. MS m/z: 314 (M^+), 110 (base peak). IR (neat) cm^{-1}: 2953, 2863, 1584. ^{1}H-NMR ($CDCl_3$) δ: 1.45—2.02 (8H, m, 3,4-CH_2 of pyrrolidine), 2.57 (2H, dt, $J=10$, 6 Hz, 2-CH_2 of pyrrolidine), 2.89 (3H, s, CH_3), 3.02 (2H, dt, $J=10$, 6 Hz, 2-CH_2 of pyrrolidine), 3.16 (2H, s, CH_3–N–C$\underline{H}_2$–), 7.16 (1H, d, $J=8$ Hz, 2-H of naphthalene), 7.48 (1H, d, $J=8$ Hz, 3-H of naphthalene), 7.50—7.61 (2H, m, 6,7-H of naphthalene), 8.23 (1H, dd, $J=7$, 2 Hz, 8-H of naphthalene), 8.36 (1H, dd, $J=7$, 2 Hz, 5-H of naphthalene).

AcChE Inhibitory Assay Acetylcholine esterase activity was determined by the method of Ellman *et al.*[12] with acetylthiocholine iodide as the substrate. Each compound was dissolved in dimethyl sulfoxide (DMSO). A mixture of 0.75 ml of 0.1 M Na-phosphate buffer (pH 7), 0.10 ml of 10 mM acetylthiocholine iodide and 2.0 mM 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB), 0.05 ml of each compound solution, and 0.10 ml of 0.05 U/ml human erythrocyte AcChE was incubated at 37 °C and the absorbance at 412 nm was recorded with a spectrometer. The activity was calculated by applying the molecular extinction coefficient of 2-nitro-5-mercaptobenzoic acid.

Preparation of Rat Brain Homogenate A rat brain homogenate was prepared according to the method of Yamamura and Snyder.[14] An Sprague–Dawley male rat was sacrificed by decapitation, and the brain was excised. After the cerebellum was removed from the whole brain, the remaining sample was homogenized in 10 volumes of buffer (0.32 M sucrose) in a Potter–Elvehjem glass homogenizer. The resulting homogenate was centrifuged at $1000 \times g$ for 10 min at 4 °C, and the precipitate removed. The supernatant was recentrifuged at $40000 \times g$ for 15 min at 4 °C. The pellet thus obtained was washed with 20 mM HEPES buffer (pH 7.4) by resuspension and recentrifugation. The membrane preparation was stored at −70 °C until required.

[^{3}H]Pirenzepine Binding Inhibition Assay for M1 receptors was performed according to the method of Flynn and Mash.[13] A mixture consisting of 0.035 ml of the membrane preparation (protein content : 0.6 mg), 1 ml of an assay buffer (50 mM phosphoric acid, pH 7.4) containing 2.0 nM [^{3}H]pirenzepine, and 1 ml of a test compound solution was allowed to react at room temperature for 60 min. To the reaction mixture was added 3.0 ml of the chilled assay buffer, and the mixture was filtered through Whatman GF/B filter paper, previously impregnated with a 0.1% polyethyleneimine solution for 60 min. The filter cake was washed twice with 3.0 ml of the assay buffer. An emulsion scintillator was added to the removed filter paper, and scintillation was measured using a liquid scintillation counter to obtain the competition binding data. These data were analyzed to calculate the 50% inhibitory concentration (IC_{50}) value of the test compound on [^{3}H]pirenzepine binding to M1 receptor homogenate.

[^{3}H]QNB Binding Inhibition Assay for M2 receptors was performed according to the method of Flynn and Mash.[13] A mixture consisting of 0.035 ml of the membrane preparation (protein content: 0.6 mg), 1 ml of an assay buffer (20 mM HEPES, pH 7.4) containing 2.0 nM [^{3}H]QNB and 6 mM pirenzepine, and 1 ml of a test compound solution was allowed to react at room temperature for 60 min. The estimation of filter-bound radioactivity and data analysis to obtain the IC_{50} of the test compound on [^{3}H]QNB binding to M2 receptors were similar to those in the case of [^{3}H]pirenzepine binding.

Passive Avoidance Performance in Scopolamine-Treated Mice A pas-

sive avoidance learning test using ddY mice was conducted to examine whether scopolamine-induced inhibition of memory retention could be improved by the compounds prepared in the present work.

A training box composed of a light room and a dark room having the same structure was used. The dark room was designed so that a foot shock was given to a test animal *via* grids in the floor. An opening was provided on the partitioning wall of the two rooms to let animals in and out freely.

The animal was put in the light room. Immediately after the animal moved into the dark room, a foot shock was applied until the animal returned to the light room (engram acquirement test). After 24 h of training, the animal was again put in the light room, and the time required for the animal to move to the dark room was measured up to 300 s (remembrance test).

Scopolamine hydrobromide dissolved in physiological saline was administered i.p. to a mouse at a dose of 0.25 mg/kg 15 min before the engram acquirement test (preparation of retention defect model). Five min after scopolamine administration, a test compound was administered *p.o.* (or i.p.) to the mouse.

Data from the remembrance test were analyzed to obtain a percent prolongation of memory retention time of the test group relative to that of the saline-treated control group.

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