Synthesis and Evaluation of Novel 2-Oxo-1,2-dihydro-3-quinolinecarboxamide Derivatives as Potent and Selective Serotonin 5-HT$_4$ Receptor Agonists

Masaji SUZUKI,* Yutaka OHUCHI, Hajime ASANUMA, Toshie KANEKO, Sadakazu YOKOMORI, Chika ITO, Yoshihiko ISOBE, and Makoto MURAMATSU

Research Center Taisho Pharmaceutical Co., Ltd., 1–403 Yoshino-Cho, Ohmiya, Saitama 330–8530, Japan.
Received June 29, 2000; accepted October 12, 2000

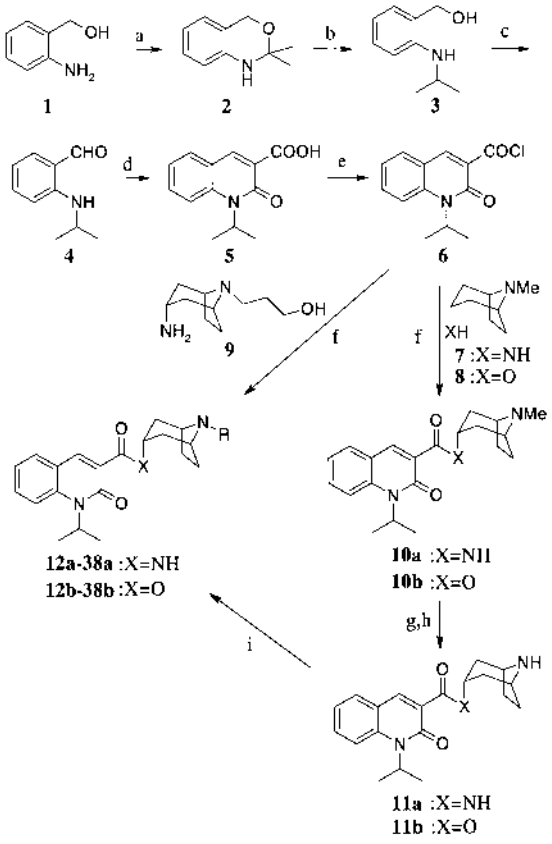
A series of 8′-substituted *N*-(*endo*-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamides were synthesized. The 5-HT$_4$ receptor agonistic activity was evaluated using the isolated guinea pig ileum preparation. Of the compounds synthesized, *N*-(*endo*-8-(3-hydroxypropyl)-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (15a, TS-951) exhibited the most potent serotonin 5-HT$_4$ receptor agonistic activity. This compound had a high affinity for the serotonin 5-HT$_4$ receptor although it had no affinities for other broad spectrum receptors. Furthermore, it remarkably enhanced gastrointestinal motility in conscious fed dogs without unfavorable effects that non-selective serotonin 5-HT$_4$ receptor agonist has. TS-951 may be useful in improving gastrointestinal dysfunction.

Key words quinolinecarboxamide; TS-951; serotonin 5-HT$_4$ receptor agonist; structure–activity relationship

Serotonin (5-HT) is a neurotransmitter which is widely distributed in the human body and has a variety of physiological effects. 5-HT receptors include seven subtypes.[1,2] The 5-HT$_4$ receptor was discovered by Dumuis *et al.* in 1988[3] and its existence in the gut was later proved. 5-HT$_4$ receptors in the gut are suggested to participate in the induction and maintenance of gastrointestinal motility. It has been reported that 5-HT$_4$ receptor agonists, cisapride[4] and renzapride,[5,6] are reported to increase gastrointestinal motility and improve gastrointestinal condition. We recently reported *N*-(*endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (**10a**) as a potent 5-HT$_4$ receptor agonist.[7] In the course of study, 1-alkyl substituents had a great influence upon 5-HT$_4$ receptor agonistic activity. Next, we took note of an influence of 8′-alkyl substituents upon 5-HT$_4$ receptor agonistic activity. In the present study, we synthesized and evaluated 8′-position substituted *N*-(*endo*-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide derivatives with the aim of finding more potent and selective 5-HT$_4$ receptor agonists.

Chemistry

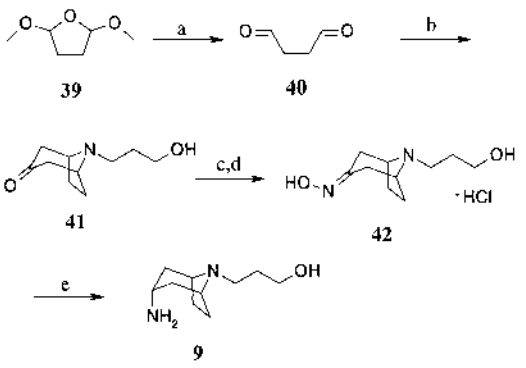
Preparation of compounds **12**—**38** was performed following the synthetic pathway depicted in Chart 1. 2-Aminobenzyl alcohol (**1**) was reacted with acetone to obtain 1,2-dihydro-2,2-dimethyl-4*H*-3,1-benzoxazine (**2**) in 93% yield, which was reduced to 2-isopropylaminobenzyl alcohol (**3**) by catalytic hydrogenation in 79% yield.[8] Compound **3** was oxidized with manganese dioxide to give benzaldehyde (**4**), which was reacted with Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) in the presence of ethylenediamine and acetic acid in MeOH. Carboxylic acid (**5**) was led to carbonyl chloride (**6**) through chlorination with thionylchloride. Carbonyl chloride (**6**) was coupled with 3-amino-8-methyl-8-azabicyclo[3.2.1]octane (**7**)[9] to give carboxamide (**10a**), or with tropine (**8**) to give carboxylate (**10b**). Demethylation of compound **10a** and **10b** with 1-chloroethyl chloroformate provided the corresponding desmethyltropane,[10] which was alkylated with various alkyl halides to give 8′-substituted tropane derivatives (**12**—**38**). In the original route, the 8′-methyl group is a protective group and required deprotection step. We examined direct synthesis of 3-amino-8-(3-hydroxy)propyl-8-azabicyclo[3.2.1]octane (**9**) in order to avoid



Reagents; a acetone, AcOH, H_2O; b H_2-Pt/C, MeOH; c MnO_2, toluene; d Meldrum's acid, ethylenediamine, AcOH, MeOH; e $SOCl_2$, toluene; f NaOH, H_2O, toluene; g ClCOOCH(Cl)Me, $ClCH_2CH_2Cl$; h MeOH; i R-Q (Q = Cl, Br, I), K_2CO_3, DMF

Chart 1

* To whom correspondence should be addressed. e-mail: s13845@ccm.taisho.co.jp



Reagents: a HCl; b 3-amino-1-propanol, acetonedicarboxylic acid, pH5; c H_2NOH, EtOH; d HCl; e H_2-PtO_2

Chart 2

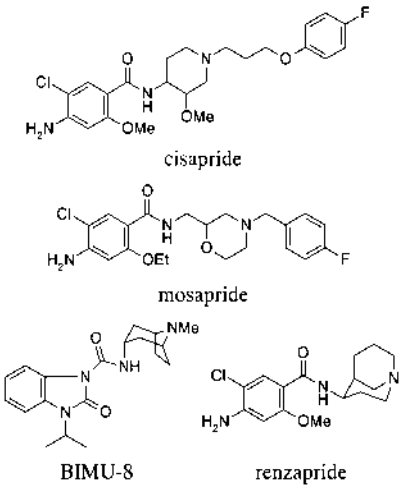


Fig. 1

deprotection step (Chart 2). 2,5-Dimethoxytetrahydrofuran (**39**) was hydrolyzed to succinaldehyde (**40**) under acidic conditions. Succinaldehyde (**40**), 3-hydroxypropylamine and acetonedicarboxylic acid were condensed in buffer solution at pH 3—4 to give tropinone (**41**), which was converted to tropinone oxime (**42**).[11] The reduction of oxime (**42**) to amine (**9**) was accomplished by catalytic reduction using Adams catalyst.[9] Compound (**9**) was reacted with **6** under general conditions. Thus, 3-hydroxypropyl group on 8′-position could be introduced beforehand and no further use for deprotection step.

Results and Discussion

The 5-HT_4 receptor agonistic activities of 8′-position substituted compounds were measured on longitudinal muscle of guinea pig ileum. The 50% effective doses (ED_{50}) of these compounds are shown in Tables 1 and 2. *N*-(*endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (**11a**) was used as a starting point to evaluate the effect of 8′-position substitution. We selected short-chain as substituents that included unsaturated bonds or heteroatoms. Our preliminary study, simple alkyl substitution of 8′-position had a slight effect on 5-HT_4 receptor agonistic activity.[12] Just as in our preliminary study, removal of the 8′-methyl group (**10a**) slightly decreased 5-HT_4 receptor agonistic activity. We first tested replacement of the methyl group by an unsaturated alkyl group (**12a**, **13a**). Introduction of a double bond (**12a**) yielded results identical to those with **11a**, but introduction of a triple bond led to decrease in activity. It appears that introduction of an unsaturated alkyl group is not effective. We next replaced a carbon with a het-

Table 1. Structures and Pharmacological Activities *in Vitro*

Compound	R	X	ED_{50} (nM)
11a	H	NH	73.6
10a	Me	NH	36.3
12a	$CH_2CH{=}CH_2$	NH	59.2
13a	$CH_2C{\equiv}CH$	NH	955
14a	$(CH_2)_2OH$	NH	45.9
15a	$(CH_2)_3OH$	NH	32.0
16a	$(CH_2)_4OH$	NH	38.5
17a	$(CH_2)_5OH$	NH	30.8
18a	$(CH_2)_6OH$	NH	62.3
19a	$(CH_2)_2OMe$	NH	15.0
20a	$(CH_2)_2OEt$	NH	18.7
21a	$(CH_2)_2O(CH_2)_2OMe$	NH	136
22a	$(CH_2)_2NEt_2$	NH	155
23a	$(CH_2)_2SMe$	NH	48.0
24a	$(CH_2)_2SO_2C_6H_5$	NH	86.6
25a	CH_2CH_2-morphorino	NH	25.5
26a	CH_2CH_2-piperidino	NH	202
27a	CH_2-(2-pyranyl)	NH	24.0
28a	$CH_2CH_2OC_6H_5$	NH	140
29a	CH_2CO_2Et	NH	84.4
30a	CH_2CO_2H	NH	66.1
31a	$(CH_2)_3CO_2Et$	NH	19.3
32a	$(CH_2)_3CO_2H$	NH	91.4
33a	COMe	NH	718
34a	CH_2COMe	NH	11.5
35a	$(CH_2)_3COMe$	NH	52.3
36a	CH_2CN	NH	184
37a	$(CH_2)_2CN$	NH	35.8
38a	CH_2CONH_2	NH	61.9
Cisapride			271

Table 2. Structure and Pharmacological Activities *in Vitro*

Compound	R	X	ED_{50} (nM)
11b	H	O	40.1
10b	Me	O	21.3
14b	$(CH_2)_2OH$	O	16.1
15b	$(CH_2)_3OH$	O	11.9
16b	$(CH_2)_4OH$	O	16.6
17b	$(CH_2)_5OH$	O	25.5
18b	$(CH_2)_6OH$	O	50.9
19b	$(CH_2)_2OMe$	O	18.4
20b	$(CH_2)_2OEt$	O	15.2
21b	$(CH_2)_2O(CH_2)_2OMe$	O	73.7
22b	$(CH_2)_2NEt_2$	O	72.6
23b	$(CH_2)_2SMe$	O	29.5
24b	$(CH_2)_2SO_2C_6H_5$	O	46.5
25b	CH_2CH_2-morphorino	O	30.8
27b	CH_2-(2-pyranyl)	O	55.9
28b	$CH_2CH_2OC_6H_5$	O	39.0
29b	CH_2CO_2Et	O	249
34b	CH_2COMe	O	24.6
35b	$(CH_2)_3COMe$	O	26.4
36b	CH_2CN	O	740
37b	$(CH_2)_2CN$	O	27.3
38b	CH_2CONH_2	O	31.4

Table 3. Affinities of TS-951 and Other 5-HT_4 Receptor Agonists in Receptor Binding Assay

Receptor	Subtype	Tissue membrane	Ligand	% of Control specific binding									(μmol/l)
				TS-951			Cisapride			Mosapride			
				0.1	1	10	0.1	1	10	0.1	1	10	
5-HT	5-HT_{1A}	Human recombinant (CHO cells)	[^{3}H]8-OH-DPAT	—	—	—	—	51	82	—	—	60	
	5-HT_{1B}	Rat cerebral cortex	[^{125}I]CYP	—	—	—	—	—	—	—	—	—	
	5-HT_{1D}	Bovine caudate	[^{3}H]5-HT	—	—	—	—	—	—	—	—	—	
	5-HT_{2A}	Human recombinant (CHO cells)	[^{3}H]Ketanserin	—	—	—	80	98	101	—	—	57	
	5-HT_{2C}	Human recombinant (CHO cells)	[^{3}H]Mesulergine	—	—	—	—	50	82	—	52	93	
	5-HT_3	Rat cerebral cortex	[^{3}H]GR65630	1555.7±587.2			183.0±23.1			1020.2±101.3			(K_i, nmol/l)
	5-HT_4	Guinea pig striatum	[^{3}H]GR113808	11.8±1.6			21.9±3.1			51.6±9.6			(K_i, nmol/l)
	5-HT_{5A}	Human recombinant (CHO cells)	[^{3}H]LSD	—	—	—	—	—	—	—	—	—	
	5-HT_6	Human recombinant (CHO cells)	[^{3}H]LSD	—	—	—	—	—	[49]	—	—	55	
	5-HT_7	Human recombinant (CHO cells)	[^{3}H]LSD	—	—	—	—	—	62	—	—	—	
Sigma	σ_1	Guinea pig cerebral cortex	[^{3}H](+)Pentazocine	—	—	—	—	65	87	—	72	98	
	σ_2	Rat cerebral cortex	[^{3}H]DTG (+300 nM (+)Pentazocine)	—	[47]	93	61	100	103	—	—	73	

—: Inhibitive potency was less than 50%.

eroatom. Hydroxy substitutions (**14a**—**18a**) were slightly more potent, with ED_{50} values of 32.0 nM (**15a**, TS-951) and 30.8 nM (**17a**). Ether substitutions (**19a**, **20a**) resulted in more potent activity, with ED_{50} values of 15.0 nM (**19a**) and 18.7 nM (**20a**). However, compound **21a** was 10 times less potent than other ether compounds. This suggests that appropriate length of alkyl chain is important in obtaining potent activity. Replacement of the oxygen of the ether with nitrogen (**22a**) or sulfur (**23a**) resulted in compounds that were less potent than **19a.** Oxygen is preferable as a heteroatom among 8′-position substituents, which is also preferable 2—3 atom distance from tropane nitrogen. About cyclic substituents, compound **25a** (ED_{50}=25.5 nM) was 6 times as potent as **26a** (ED_{50}=202 nM). The difference between **25a** and **26a** in structure was only morpholine oxygen. It appeared that an additional oxygen atom at an approximately 6-atom distance from tropane nitrogen yielded increase in activity. We next investigated carbonyl substituents. Compound **31a** had an ester introduced at the distance of three methylenes from tropane nitrogen, a position of ester oxygen that corresponded to the above additional oxygen atom. Compound **31a** exhibited potent activity, with an ED_{50} of 19.3 nM. Nevertheless, the agonistic activity of carboxylic acid (**32a**), the hydrolyzed compound of **31a**, was mild. Compound **31a** required ethyl group with ester function to exhibit potent 5-HT_4 receptor agonistic activity. Short-chain ester (**29a**), the corresponding carboxylic acid derivative (**30a**), and an amide derivative (**38a**) showed less potent activity than **31a**. Of oxoalkyl compounds, compound **34a** had the most potent 5-HT_4 receptor agonistic activity (ED_{50}=11.5 nM). Thus, hydroxyalkyl, alkoxyalkyl and oxoalkyl substituents at the 8′-position yielded potent 5-HT_4 receptor agonistic activity. All heteroatoms of substituents must exist in the appropriate positions. From among these compounds, we selected Compound **15a** (TS-951) as a candidate. Oxoalkyl substituted compound (**34a**) was unstable, and alkoxyalkyl substituted compounds (**19a**, **20a**) seems to be possessed of side effect.

To discriminate between amide and ester compounds, several ester compounds were synthesized. All ester compounds exhibited more potent activity than amide compounds with the same substituents. Nevertheless, ester compounds were easily hydrolyzed. We could not prepare caboxylic acid derivatives (**30b**, **32b**) because they readily underwent hydrolysis. It was therefore anticipated that ester compounds would be decomposed easily *in vivo.*

Receptor Selectivity of TS-951 Standard techniques were used to identify radioligand binding to each membrane tested.[13] The tissues and radiolabelled ligands used are presented in Tables 3, 4 and 5. In the displacement study, TS-951 concentration-dependently inhibited specific [^{3}H]-GR113808 binding to 5-HT_4 receptors in membranes derived from guinea pigs striatum.[14] Other 5-HT_4 receptor agonists, cisapride and mosapride,[15] also inhibited the specific binding of [^{3}H]GR113808 in a concentration-dependent manner. K_i values derived from these curves are presented in Table 3. TS-951 had no affinity for other broad spectrum receptors, although it had a weak affinity for 5-HT_3 receptors (Tables 3—5). On the other hand, cisapride and mosapride had affinities for other neurotransmitter receptors, such as 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, 5-HT_7, σ_1 and σ_2 receptors (Table 3).

Intrinsic Activity of TS-951 We investigated the functional effects of TS-951 using 5-HT_4 receptor-mediated contractions in guinea pig distal colon. 5-HT, 5-MeOT, TS-951, cisapride and BIMU8[16] caused concentration-dependent contraction of the longitudinal muscle of the guinea pig distal colon. However, mosapride was found to be inactive. The indole agonists 5-HT and 5-MeOT had full agonist activity (intrinsic activity: 1.0). On the other hand, the intrinsic activities of TS-951, cisapride and BIMU8 were 0.72, 0.49 and 0.54, respectively. The results for all compounds tested are summarized in Table 6.

Effects of TS-951 on Gastric Antral Motility TS-951 (0.003—0.3 mg/kg, *p.o.*) dose-dependently stimulated gastric antral motility in conscious fed dogs. Figure 2 shows typical effects of TS-951 (0.1 mg/kg, *p.o.*). TS-951 (0.01—0.3 mg/kg, *p.o.*) significantly increased motility index (M.I.) in the gastric antrum (Fig. 3). Cisapride (0.3—3 mg/kg, *p.o.*) also stimulated gastric antral motility in conscious fed dogs. Figure 2 shows typical effects of cisapride (1 mg/kg, *p.o.*). Cisapride (0.3—3 mg/kg, *p.o.*) significantly increased M.I. in the gastric antrum (Fig. 3).

Table 4. Affinities of TS-951 in Receptor Binding Assay

Receptor	Subtype	Tissue membrane	Ligand	% of Control TS-951 (μmol/l)		
				0.1	1	10
Adenosine	A_1	Rat cerebral cortex	[^{3}H]CPX			
	A_2	Bovine striatum	[^{3}H]CGS 21680	—	—	—
Adrenergic	α_1	Rat forebrain	[^{3}H]Prazosin	—	—	53
	α_2	Rat cerebral cortex	[^{3}H]RX 821002	—	—	—
	β	Rat cerebral cortex	[^{3}H]Dihydroalprenolol	—	—	—
Dopamine	D_1	Rat striatum	[^{3}H]SCH 23390	—	—	—
	D_2	Rat striatum	[^{3}H]Sulpiride	—	—	—
GABA	GABAA	Bovine cerebellum	[^{3}H]GABA	—	—	—
	GABAB	Rat cerebral cortex	[^{3}H]GABA	—	—	—
Histamine	H_1	Bovine cerebellum	[^{3}H]Pyrilamine	—	—	53
Muscarinic	M_1	Bovine striatum	[^{3}H]Pirenzepine	—	—	—
	M_2	Rat heart	[^{3}H]AFDX 384	—	—	55
Nicotinic	Neuronal	Rat cerebral cortex	[^{3}H]*N*-methyl-carbamyl choline iodide	—	—	—
Glutamate	NMDA	Rat forebrain	[^{3}H]CGS 19755	—	—	—
	Kainate	Rat forebrain	[^{3}H]Kainic acid	—	—	—
	Quisqualate	Rat forebrain	[^{3}H]AMPA	—	—	—
Glycine (strychnine-sensitive)		Rat spinal cord	[^{3}H]Strychnine	—	—	—
Benzodiazepine	Central	Bovine cerebral cortex	[^{3}H]Flunitrazepam	—	—	—
Glycine (strychnine-sensitive)		Rat cerebral cortex	[^{3}H]Glycine	—	—	—
Phencyclidine	PCP	Rat forebrain	[^{3}H]TCP	—	—	—
Opiate	Mu	Rat forebrain	[^{3}H]Tyr-D-Ala-Gly-NMe-Phe-Gly-ol(DAMGO)	—	—	—
	Delta	Rat forebrain	[^{3}H]Enkephalin	—	—	—
	Kappa	Guinea pig cerebellum	[^{3}H]U69593	—	—	—

—: Inhibitive potency was less than 50%.

Table 5. Affinities of TS-951 and Other 5-HT_4 Receptor Agonists in Receptor Binding Assay

Receptor	Subtype	Tissue membrane	Ligand	% of Control TS-951 (μmol/l)		
				0.1	1	10
Thyroid Releasing Hormone		Rat forebrain	[^{3}H](3MeHis2)thyroidreleasing hormone	—	—	—
Corticotropin Releasing1 Factor		Rat cerebral cortex	[^{125}I]Tyr-o-CRF	—	—	—
Neurokinin	NK_1	Rat SUBMX	[^{3}H]Substance P	—	—	—
	NK_2	Bovine duodenum	[^{125}I]Neurokinin A	—	—	—
	NK_3	Rat cerebral cortex	[^{125}I]Eledoisin	—	—	—
Ca channel	N	Rat cerebral cortex	[^{125}I]Omega-conotoxin	—	—	—
	T & L	Rat cerebral cortex	[^{3}H]Nitrendipine	—	—	—
Cl channel	TBOB	Rat cerebral cortex	[^{3}H]TBOB	—	—	—
K channel	ATP depentent	Rat cerebral cortex	[^{3}H]Glibenclamide	—	—	—
	Low conductance	Rat forebrain	[^{125}I]Apamin	—	—	—
	Voltage dependent	Rat brain	[^{125}I]Charybdotoxin	—	—	—
Leukotriene	LTB_4	Guinea pig spleen	[^{3}H]LTB4	—	—	—
	LTD_4	Guinea pig lung	[^{3}H]LTD4	—	—	—
Prostanoid	TXA_2	Human platelets	[^{3}H]SQ 29548	—	—	—
Adenylate Cyclase	Forskolin	Rat forebrain	[^{3}H]Forskolin	—	—	—
Protein Kinase C	Phorbol ester	Mouse brain	[^{3}H]Phorbol ester dibutyrate	—	—	—
Uptake Site	DA	Guinea pig striatum	[^{3}H]WIN 35428	—	—	—
	NE	Rat forebrain	[^{3}H]Desmethylimipramine	—	—	—
	5-HT	Rat forebrain	[^{3}H]Citalopram	—	—	69
	Choline	Rat cerebral cortex	[^{3}H]Choline chloride	—	—	—
Mono-Amine Oxidase	MAO-A	Rat liver	[^{14}C]5-HT	—	—	—
	MAO-B	Rat liver	[^{14}C]Phenylethylamine	—	—	—
NO Synthase			[^{3}H]Nitroarginine	—	—	—
Acetylcholinesterase				—	—	—
Choline Acetyltransferase		Rat striatum	[^{14}C]Acetyl coenzyme A	—	—	—

—: Inhibitive potency was less than 50%.

Effects of TS-951 on Colonic Motility The agonistic effect of TS-951 on colonic motility was characterized by induction of giant migrating complex (GMC)-like patterns *i.e.*, transient high-amplitude contractions with rapid-propagating velocity (Fig. 4). TS-951 also induced the defecation in some dogs without causing diarrhea and vomit (Fig. 5). TS-951

Table 6. The Contractile Potency and Efficacy of 5-HT_4 Receptor Agonists in the Guinea-Pig Ileum and Distal Colon

	Ileum[a]		Distal colon		
	EC_{50} (nmol/l)	*n*	EC_{50} (nmol/l)	i.a[b]	*n*
5-HT	8.3± 2.0	3	6.3± 0.5	1	4
5-MeOT	19.5± 4.9	3	20.8± 7.0	1.03±0.05	5
TS-951	31.9± 9.5	4	20.1± 3.4	0.72±0.01	5
Cisapride	237.1±39.3	3	155.8±33.0	0.49±0.07	5
Mosapride	163.5±35.7	4	inactive		4
BIMU8	93.4±18.3	6	156.6±65.6	0.54±0.03	5

Each value represents the mean±S.E. *a*) Electrically evoked twich response. *b*) i.a.: intrinsic activity.

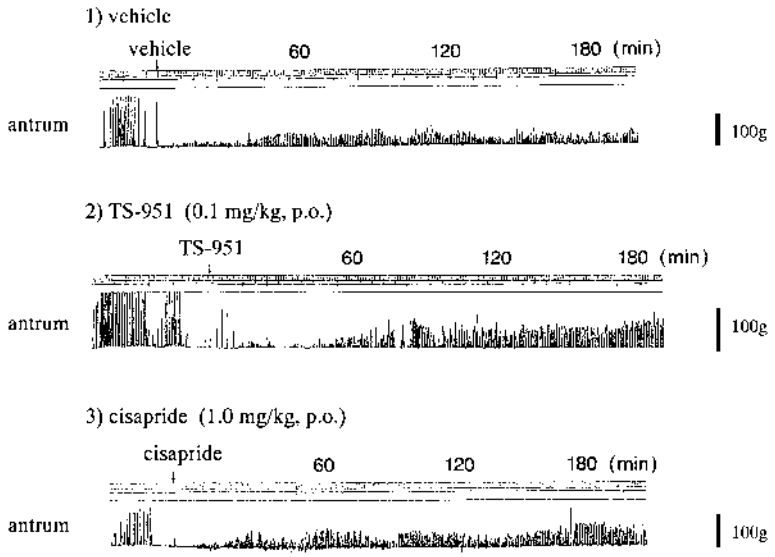


Fig. 2. Effects of TS-951 and Cisapride on Gastric Antral Motility in Conscious Fed Dogs

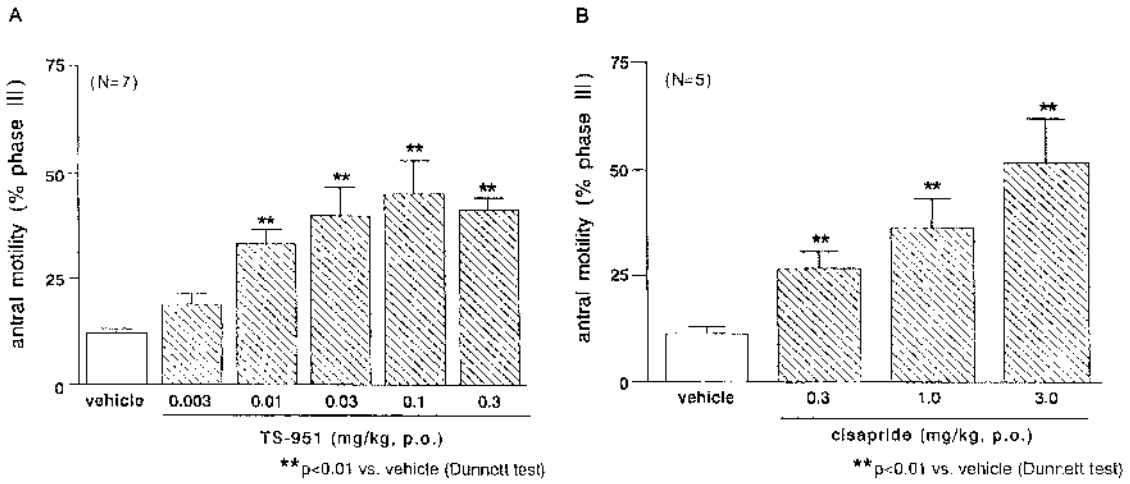


Fig. 3. Effects of TS-951 and Cisapride on Gastric Antral Motility in Conscious Fed Dogs

(0.03 mg/kg, *p.o.*) induced high-amplitude contractions and/or defecation in four tested dogs out of seven. TS-951 (0.1 and 0.3 mg/kg, *p.o.*) induced high-amplitude contractions and/or defecation in six tested dogs out of seven (Fig. 5). Cisapride (0.3, 1, 3 mg/kg, *p.o.*) induced high-amplitude contractions or defecation (Fig. 5). However, cisapride (1 mg/kg, *p.o.*) caused vomit and retrograde peristaltic contractions without inducing defecation in one tested dog out of five. Although cisapride (3 mg/kg, *p.o.*) induced defecation in three tested dogs out of five, diarrhea, vomit or retrograde peristaltic contractions were also observed in certain dogs (Fig. 5). It is suggested that TS-951 is superior to non-selective 5-HT_4 receptor agonists due to its reduced side effects. Namely, the selective 5-HT_4 receptor agonist TS-951 induced defecation without unfavorable effects that non-selective 5-HT_4 receptor agonist cisapride has.

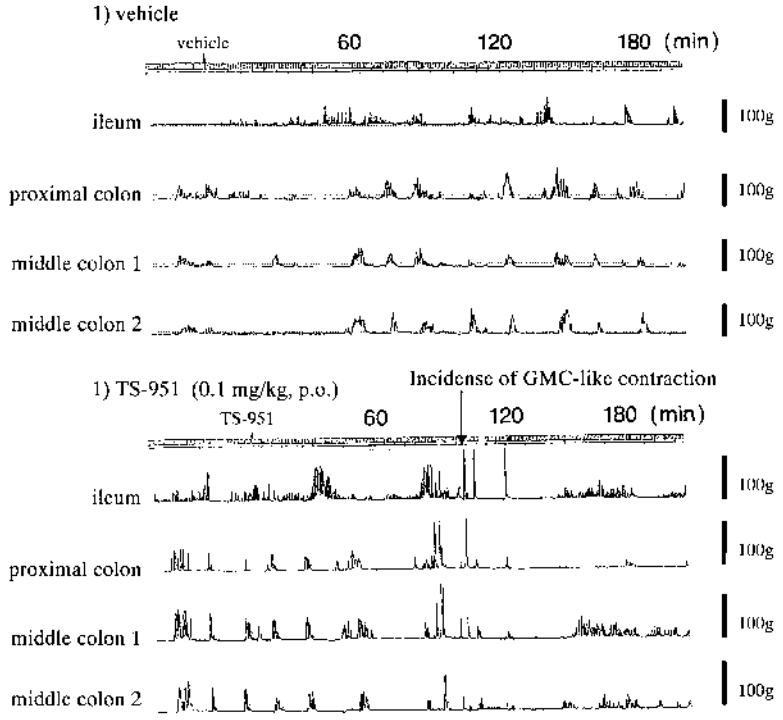


Fig. 4. Effect of TS-951 on Colonic Motility in Conscious Fed Dogs

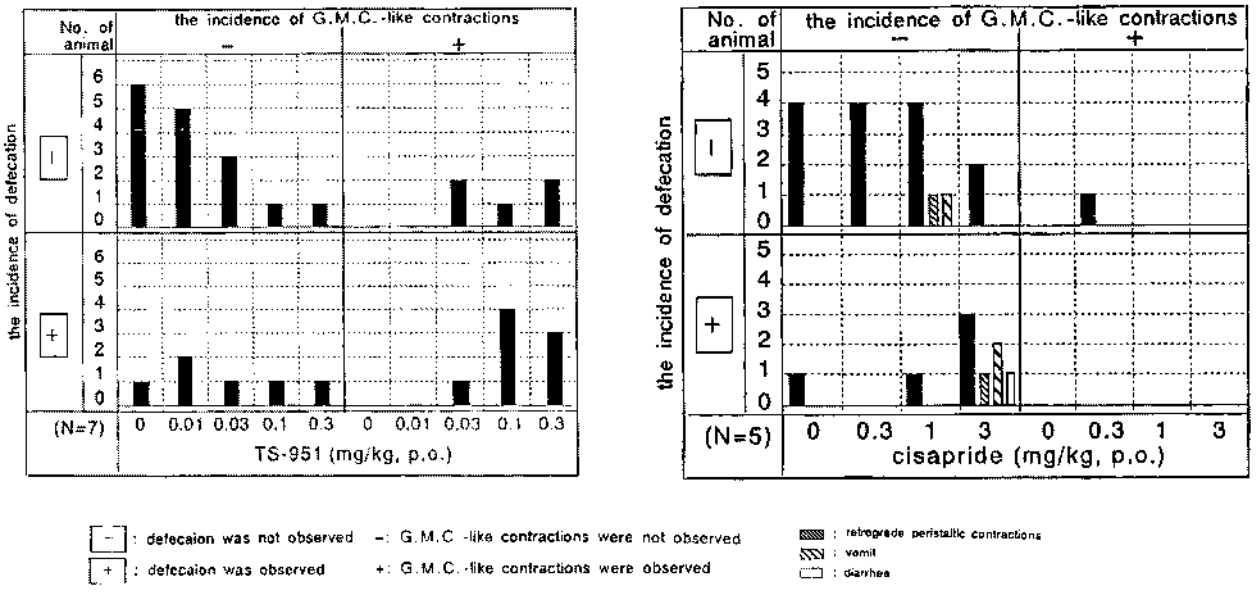


Fig. 5. Effects of TS-951 and Cisapride on Colonic Function in Conscious Fed Dogs

Conclusion

We have investigated the potencies of 2-oxo-1,2-dihydro-3-quinolinecarboxamide derivatives as 5-HT_4 receptor agonists. Of the compounds synthesized, *N*-(*endo*-8-(3-hydroxy)propyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (**15a**, TS-951) was optimal. It showed 7 times as potent 5-HT_4 receptor agonistic activity as cisapride in the regulation of electrically-evoked contraction in guinea pig muscle. TS-951 is selective for 5-HT_4 receptors as shown in receptor binding assay. This compound enhanced gastric antral and colonic motility in the fed dogs. Furthermore it induced defecation without vomit and retrograde peristeltic contractions. TS-951 is a promising compound to improve gastrointestinal dysfunction.

Experimental

Melting points were determined by a Büchi 535 melting point apparatus and are uncorrected. IR spectra (KBr) were taken on a Perkin-Elmer 1760 spectrometer. ^{1}H-NMR spectra were recorded on a Varian VXL-200 spectrometer. Chemical shifts are reported in ppm (δ) values, based on tetramethylsilane as an internal standard. MS were taken on a JEOL JMS-SX102 spectrometer. Elemental analyses were taken on a Perkin-Elmer 2400. TLC was performed on silica-gel pre-coated plates (Merck, Kieselgel 60F-254). Column chromatography was carried out over silica gel (Asahi glass, M. S. GEL. SIL.). Organic solutions during work-up were dried using anhydrous Na_2SO_4.

1,2-Dihydro-2,2-dimethyl-4*H*-3,1-benzoxadine (2) Acetone (403 g, 6.94 mol) was added to a mixture of 2-aminobenzyl alcohol (**1**) (500 g,

4.63 mol), acetic acid (8.3 g, 0.14 mol) and water (4000 g). The reaction mixture was stirred at room temperature for 1 h and was then stirred at 0 °C for 1 h. Resulting precipitates were collected by filtration, washed with water and dried, to give 700 g (93%) of **2** as a yellow solid. mp 119—121 °C (recrystallized from acetone–H_2O). ^{1}H-NMR ($CDCl_3$) δ: 1.48 (6H, s), 3.97 (1H, s), 4.83 (2H, s), 6.64 (1H, d, J=7.0 Hz), 6.79 (1H, t, J=7.0 Hz), 6.95 (1H, d, J=7.0 Hz), 7.08 (1H, t, J=7.0 Hz). IR (KBr) cm^{-1}: 3310, 1612, 1592. MS (EI) *m/z*: 163 (M^+). *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.40; H, 7.97; N, 8.64.

2-Isopropylaminobenzyl Alcohol (3) A mixture of **2** (7.0 g, 43 mmol), 5%Pt/C (0.14 g) and MeOH (70 ml) was heated at 40 °C under a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated *in vacuo.* The residue was dissolved in toluene and washed with water. The solution was evaporated *in vacuo* to give 5.6 g (79%) of **3** as a yellow oil. bp 114 °C (4 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (6H, d, J=7.2 Hz), 3.78 (1H, sept, J=7.2 Hz), 4.62 (2H, s), 6.57—6.72 (2H, m), 7.02—7.05 (1H, m), 7.15—7.27 (1H, m). IR (neat) cm^{-1}: 3391, 1608, 1587. MS (EI) *m/z*: 165 (M^+). *Anal.* Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.30; H, 9.33; N, 8.88.

2-Isopropylaminobenzaldehyde (4) A mixture of **3** (33.62 g, 0.20 mol), manganese (IV) oxide (44.12 g, 0.51 mol) and toluene (300 ml) was refluxed for 2 h. The reaction mixture was filtered, and filtrate was evaporated *in vacuo.* The residue was purified by column chromatography using hexane/AcOEt=10 : 1 to give 20.59 g (62%) of **4** as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (6H, d, J=6.4 Hz), 3.75 (1H, sept, J=6.4 Hz), 6.61—6.72 (2H, m), 7.33—7.47 (2H, m), 8.28 (1H, br), 9.80 (1H, s). IR (neat) cm^{-1}: 3317, 1652, 1610, 1579. MS (EI) *m/z*: 163 (M^+).

1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylic Acid (5) Meldrum's acid (2,2-dimethyl-1,3-dioxan-4,6-dione, 1.59 g, 11.0 mmol) was added to a mixture of ethylenediamine (0.41 ml, 6.1 mmol), acetic acid (0.70 ml, 12.2 mmol) and **4** (1.00 g, 6.13 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight and was then acidified with diluted HCl. The resulting precipitate was collected by filtration and washed with water to give 1.17 g (83%) of **5** as a colorless powder. mp 167—169 °C (recrystallized from acetone–H_2O). ^{1}H-NMR ($CDCl_3$) δ: 1.71 (6H, d, J=7.2 Hz), 5.25—5.75 (1H, br), 7.36—7.45 (1H, m), 7.69—7.85 (3H, m), 8.88 (1H, s), 14.76 (1H, s). IR (KBr) cm^{-1}: 1734, 1631. MS (EI) *m/z*: 231 (M^+). *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.42; H, 5.54; N, 6.07.

1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarbonylchloride (6) A mixture of **5** (10.0 g, 43.2 mmol) and thionyl chloride (20 ml, 274 mmol) was refluxed for 4 h. The reaction mixture was evaporated *in vacuo* to leave a residue, which was dissolved in toluene (30 ml). It was evaporated *in vacuo* again to give 10.6 g (98%) of **6** as a pale yellow solid.

***N*-(*endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (10a)** A solution of 3-Amino-8-methyl-8-azabicyclo[3.2.1]octane (**7**) (404 mg, 2.8 mmol) in toluene (3 ml) was added to a solution of **6** (540 mg, 2.2 mmol) in toluene (2 ml). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then poured into 5%NaOH and extracted with $CHCl_3$. The extract was washed with brine, dried and evaporated *in vacuo.* The residue was purified by column chromatography using $CHCl_3$, recrystallized from AcOEt to give 391 mg (51%) of **10a** as a colorless solid. mp 173—177 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.76—1.83 (2H, m), 2.00—2.40 (6H, m), 2.34 (3H, s), 3.10—3.28 (2H, m), 4.30 (1H, q, J=7.0 Hz), 5.40—5.90 (1H, br), 7.22—7.33 (1H, m), 7.55—7.70 (2H, m), 7.75 (1H, d, J=7.8 Hz), 8.83 (1H, s), 10.48 (1H, d, J=7.2 Hz). IR (KBr) cm^{-1}: 3263, 2961, 1673, 1616, 1585, 1568, 1528. MS (EI) *m/z*: 353 (M^+). *Anal.* Calcd for $C_{21}H_{27}N_3O_2$: C, 71.36; H, 7.70; N, 11.88. Found: C, 71.21; H, 7.67; N, 11.84.

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate Hydrochloride (10b)** Tropine (**8**) (5.65 g, 40.0 mmol) was added to a suspension of sodium hydride (60% mineral oil suspension, 1.60 g, 40.0 mmol) in tetrahydrofuran (THF) (100 ml), and the reaction mixture was refluxed for 2 h. After being cooled to 0 °C, **6** (8.33 g, 33.4 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water, and the mixture was acidified with diluted HCl. The aqueous layer was washed with AcOEt. The aqueous layer was made basic with K_2CO_3 and extracted with $CHCl_3$. The extract was dried and evaporated *in vacuo.* The resulting residue was crystallized from diisopropyl ether to give 2.12 g (18%) of a colorless powder, which was dissolved in EtOH (10 ml) and concentrated HCl (1 ml) was added. The mixture was evaporated *in vacuo* to afford a residue, which was recrystallized from EtOH to give 1.25 g (8.0%) of **10b** as a colorless solid. mp 252—254 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.65 (6H, d, J=7.0 Hz), 1.90—2.20 (2H, m), 2.20—2.35 (3H, m), 2.78 (3H, d), 2.80—2.92 (1H, m), 3.06—3.25 (2H, m), 5.41 (1H, t, J=4.6 Hz), 5.30—5.65 (1H, br), 7.29—7.30 (1H, m), 7.55—7.70 (3H, m), 8.32 (1H, s), 12.20—12.50 (1H, br). IR (KBr) cm^{-1}: 3538, 3424, 1709, 1656, 1619, 1565. MS (EI) *m/z*: 354 (M^+). *Anal.* Calcd for $C_{21}H_{26}N_2O_3 \cdot HCl \cdot 0.25H_2O$: C, 63.79; H, 7.01; N, 7.08. Found: C, 63.75; H, 7.40; N, 7.05.

***N*-(*endo*-8-Azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (11a)** 1-Chloroethyl chloroformate (0.41 g, 2.8 mmol) was added to a solution of **10a** (1.0 g, 2.8 mmol) in 1,2-dichloroethane (10 ml) at 0 °C. The mixture was stirred at 0 °C for 0.5 h and then refluxed for 1 h. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in MeOH (10 ml). The MeOH solution was refluxed for 1 h and the solution was evaporated *in vacuo.* The residue was purified by column chromatography using $CHCl_3$/MeOH saturated with NH_3=20 : 1, and recrystallized from AcOEt to give 530 mg (55%) of **11a** as a colorless solid. mp 202—203 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.69 (6H, d, J=7.2 Hz), 1.78—2.40 (9H, m), 3.55—3.68 (2H, m), 4.38 (1H, q, J=7.0 Hz), 5.40—5.82 (1H, br), 7.23—7.35 (1H, m), 7.56—7.70 (2H, m), 7.75 (1H, d, J=7.8 Hz), 8.83 (1H, s), 10.54 (1H, d, J=7.2 Hz). IR (KBr) cm^{-1}: 3257, 2971, 1674, 1622, 1569, 1531. MS (EI) *m/z*: 339 (M^+). *Anal.* Calcd for $C_{20}H_{25}N_3O_2$: C, 70.77; H, 7.42; N, 12.38. Found: C, 70.57; H, 7.49; N, 12.44.

***endo*-8-Azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinoline carboxylate (11b)** Demethylation of **10b** was conducted using a procedure similar to that employed in the synthesis of **11a**. 50.2%, a colorless solid. mp 137—140 °C (recrystallized from diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.67 (6H, d, J=7.2 Hz), 1.81—2.34 (8H, m), 2.45—2.62 (br, 1H), 3.53—3.67 (2H, m), 5.33 (1H, t, J=7.0 Hz), 5.30—5.75 (1H, br), 7.19—7.27 (1H, m), 7.54—7.68 (3H, m), 8.23 (1H, s). IR (KBr) cm^{-1}: 3286, 1694, 1647. MS (EI) *m/z*: 340 (M^+). *Anal.* Calcd for $C_{20}H_{24}N_2O_3 \cdot 0.25H_2O$: C, 69.58; H, 7.16; N, 8.12. Found: C, 69.54; H, 7.19; N, 7.98.

***N*-(*endo*-8-(3-Hydroxy)propyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (15a, TS-951)** A mixture of **11a** (2.00 g, 5.9 mmol), 3-bromo-1-propanol (0.53 ml, 5.9 mmol), K_2CO_3 (0.81 g, 5.9 mmol) and EtOH (50 ml) was refluxed for 10 h. The reaction mixture was evaporated *in vacuo* to give a residue, which was partitioned between water and $CHCl_3$. The organic layer was dried and evaporated *in vacuo.* The residue was purified by column chromatography using $CHCl_3$/MeOH saturated with NH_3=40 : 1, and recrystallized from AcOEt to give 510 mg (21.8%) of **15a** as a colorless solid. mp 171—172 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.62—1.78 (2H, m), 1.80—196 (2H, m), 2.00—2.38 (6H, m), 2.72 (2H, t, J=7.0 Hz), 3.32—3.52 (2H, m), 3.88 (2H, t, J=7.0 Hz), 4.30 (1H, q, J=7.0 Hz), 5.45— 5.80 (1H, br), 7.23—7.33 (1H, m), 7.56—7.70 (2H, m), 7.75 (1H, d, J=7.8 Hz), 8.83 (1H, s), 10.51 (1H, d, J=7.2 Hz). IR (KBr) cm^{-1}: 3431, 3240, 1669. MS (EI) *m/z*: 397 (M^+). *Anal.* Calcd for $C_{23}H_{31}N_3O_3$: C, 69.49; H, 7.86; N, 10.57. Found: C, 69.22; H, 7.90; N, 10.43.

***N*-(*endo*-8-(6-Hydroxy)hexyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide Hydrochloride (18a)** A mixture of **11a** (1.00 g, 2.7 mmol), 6-chloro-1-hexanol (0.30 ml, 2.7 mmol), K_2CO_3 (1.11 g, 8.0 mmol), KI (0.44 g, 2.7 mmol) and *N*,*N*-dimethylformamide (DMF) (20 ml) was heated at 100 °C for 5 h. The reaction mixture was poured into water and extracted with $CHCl_3$. The extract was dried and evaporated *in vacuo* to give a residue. The residue was purified by column chromatography using $CHCl_3$/MeOH saturated with NH_3=20 : 1, to give a yellow gum. It was dissolved in MeOH and concentrated HCl was added. The mixture was concentrated *in vacuo* and crystallized from 2-propanol (IPA). The crude product was recrystallized from IPA to give 667 mg (52.5%) of **18a** as a colorless solid. mp 251—253 °C. ^{1}H-NMR (dimethyl sulfoxide (DMSO)-d_6) δ: 1.33—1.90 (8H, m), 1.68 (6H, d, J=7.2 Hz), 2.10—2.65 (8H, m), 2.97—3.20 (2H, m), 3.58 (2H, t, J=7.0 Hz), 4.02—4.18 (2H, m), 4.32 (1H, q, J=7.0 Hz), 5.35—5.80 (1H, br), 7.34—7.43 (1H, m), 7.71—7.81 (1H, m), 7.83—7.92 (2H, m), 8.81 (1H, s). IR (KBr) cm^{-1}: 3368, 1671. MS (EI) *m/z*: 439 (M^+). *Anal.* Calcd for $C_{26}H_{37}N_3O_3 \cdot HCl \cdot 0.5H_2O$: C, 64.38; H, 7.90; N, 8.66. Found: C, 64.33; H, 8.17; N, 8.49.

***N*-(*endo*-8-Alkyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamides (12a—38a)** The alkylation of compound **11a** was conducted in a similar procedure as employed in the synthesis of **15a** and **18a**. HCl salts of alkylated compounds were made using a procedure similar to that employed in the synthesis of **11b**.

***N*-(*endo*-8-(2-Propenyl)-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (12a)** 47.7%, colorless prism. mp 126—128 °C (recrystallized from AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d,

J=7.2 Hz), 1.74—1.88 (2H, m), 2.05—2.15 (4H, m), 2.21—2.38 (2H, m), 3.08 (2H, d, J=7.0 Hz), 3.25—3.35 (2H, m), 4.33 (1H, q, J=7.0 Hz), 5.10—5.27 (2H, m), 5.40—5.80 (br, 1H), 5.95 (1H, ddd, J=7.0, 10.0, 17.0 Hz), 7.22—7.33 (1H, m), 7.56—7.70 (2H, m), 7.75 (1H, d, J=7.8 Hz), 8.83 (1H, s), 10.50 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3249, 1676. MS (EI) *m/z*: 379 (M^+). *Anal.* Calcd for $C_{23}H_{29}N_3O_2$: C, 72.79; H, 7.70; N, 11.07. Found: C, 72.51; H, 7.67; N, 11.03.

***N*-(*endo*-8-(2-Propargyl)-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (13a)** 69.9%, colorless prism. mp 201—203 °C (recrystallized from AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.69 (6H, d, J=7.2 Hz), 1.80—1.95 (2H, m), 2.07—2.24 (4H, m), 2.27 (1H, t, J=2.0 Hz), 2.29—2.47 (2H, m), 3.27 (2H, d, J=7.0 Hz), 3.43—3.53 (2H, m), 4.32 (1H, q, J=7.0 Hz), 5.35—5.87 (1H, br), 7.23—7.33 (1H, m), 7.57—7.70 (2H, m), 7.75 (1H, d, J=7.8 Hz), 8.84 (1H, s), 10.52 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3193, 2113, 1672. MS (EI) *m/z*: 377 (M^+). *Anal.* Calcd for $C_{23}H_{27}N_3O_2$: C, 73.18; H, 7.21; N, 11.13. Found: C, 72.94; H, 7.16; N, 11.12.

***N*-(*endo*-8-(2-Hydroxy)ethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (14a)** 30.1%, colorless solid. mp 160—162 °C (recrystallized from AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.78—1.92 (2H, m), 1.98—2.40 (6H, m), 2.59 (2H, t, J=7.0 Hz), 3.25—3.35 (2H, m), 3.60 (2H, t, J=7.0 Hz), 4.32 (1H, q, J=7.0 Hz), 5.48—5.80 (1H, br), 7.23—7.34 (1H, m), 7.57—7.70 (2H, m), 7.76 (1H, d, J=7.8 Hz), 8.84 (1H, s), 10.50 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3232, 1669. MS (EI) *m/z*: 383 (M^+). *Anal.* Calcd for $C_{22}H_{29}N_3O_3$: C, 68.90; H, 7.62; N, 10.96. Found: C, 68.70; H, 7.60; N, 10.79.

***N*-(*endo*-8-(4-Hydroxy)butyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (16a)** 18.4%, colorless solid. mp 162—164 °C (recrystallized from AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.60—1.92 (6H, m), 2.00—2.20 (4H, m), 2.24—2.40 (2H, m), 2.42—2.53 (2H, m), 3.29—3.38 (2H, m), 3.57—3.66 (2H, m), 4.33 (1H, q, J=7.0 Hz), 5.50—5.80 (1H, br), 7.23—7.33 (1H, m), 7.56—7.70 (2H, m), 7.75 (1H, d, J=7.8 Hz), 8.83 (1H, s), 10.51 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3411, 3260, 1667. MS (EI) *m/z*: 411 (M^+). *Anal.* Calcd for $C_{24}H_{33}N_3O_3$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.09; H, 8.12; N, 10.23.

***N*-(*endo*-8-(5-Hydroxy)pentyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (17a)** 18.4%, colorless solid. mp 148—150 °C (recrystallized from AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.40—1.92 (8H, m), 2.10—2.30 (4H, m), 2.40—2.70 (4H, m), 3.40—3.60 (2H, m), 3.67 (2H, t, J=6.8 Hz), 4.35 (1H, q, J=7.0 Hz), 5.50—5.80 (1H, br), 7.22—7.35 (1H, m), 7.59—7.70 (2H, m), 7.75 (1H, d, J=7.8 Hz), 8.83 (1H, s), 10.55 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3452, 3257, 1668. MS (EI) *m/z*: 425 (M^+). *Anal.* Calcd for $C_{25}H_{35}N_3O_3\cdot 0.3H_2O$: C, 69.67; H, 8.32; N, 9.75. Found: C, 69.51; H, 8.21; N, 9.66.

***N*-(*endo*-8-(2-Methoxy)ethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide Hydrochloride (19a)** 28.4%, colorless solid. mp 247—249 °C (recrystallized from EtOH). ^{1}H-NMR (DMSO-d_6) δ: 1.68 (6H, d, J=7.2 Hz), 2.05—2.24 (2H, m), 2.25—2.60 (4H, m), 3.10—3.20 (2H, m), 3.20—3.30 (1H, m), 3.38 (3H, s), 3.30—3.55 (1H, m), 3.95—4.18 (4H, m), 4.07 (1H, q, J=7.0 Hz), 5.30—5.80 (1H, br), 7.26—7.36 (1H, m), 7.65 (1H, s), 7.67 (1H, s), 7.77 (1H, d, J=7.6 Hz), 8.85 (1H, s), 10.68 (1H, d, J=7.5 Hz), 11.90—12.25 (1H, br). IR (KBr) cm^{-1}: 3428, 1671. MS (EI) *m/z*: 397 (M^+). *Anal.* Calcd for $C_{23}H_{31}N_3O_3\cdot HCl\cdot H_2O$: C, 61.12; H, 7.58; N, 9.29. Found: C, 61.15; H, 7.70; N, 9.03.

***N*-(*endo*-8-(2-Ethoxy)ethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (20a)** 58.7%, colorless solid. mp 99—100 °C (recrystallized from diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.2 Hz), 1.68 (6H, d, J=7.2 Hz), 1.70—1.85 (2H, m), 1.95—2.20 (4H, m), 2.20—2.44 (2H, m), 2.67 (2H, t, J=7.0 Hz), 3.31—3.39 (2H, m), 3.53 (2H, q, J=7.2 Hz), 3.61 (2H, t, J=7.0 Hz), 4.30 (1H, q, J=7.0 Hz), 5.40—5.80 (1H, br), 7.24—7.33 (1H, m), 7.56—7.70 (2H, m), 7.76 (1H, d, J=7.8 Hz), 8.84 (1H, s), 10.50 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3269, 1671. MS (EI) *m/z*: 411 (M^+). *Anal.* Calcd for $C_{24}H_{33}N_3O_3$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.93; H, 8.14; N, 10.09.

***N*-(*endo*-8-(Methoxyethoxy)ethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide Hydrochloride (21a)** 72.0%, colorless solid. mp 95—97 °C (recrystallized from EtOH–diisopropyl ether). ^{1}H-NMR (DMSO-d_6) δ: 1.68 (6H, d, J=7.2 Hz), 2.15—2.62 (8H, m), 3.29—3.38 (2H, m), 3.41 (3H, s), 3.58—3.66 (2H, m), 3.68—3.73 (2H, m), 3.85—3.90 (2H, m), 4.19 (2H, br s), 4.33 (1H, t, J=6.3 Hz), 5.40—5.80 (1H, br), 7.34—7.42 (1H, m), 7.71—7.90 (3H, m), 8.81 (1H, s). IR (KBr) cm^{-1}: 3328, 1678. MS (EI) *m/z*: 441 (M^+). *Anal.* Calcd for $C_{25}H_{35}N_3O_4\cdot HCl\cdot 0.8H_2O$: C, 60.98; H, 7.70; N, 8.53. Found: C, 60.97; H, 8.07; N, 8.52.

***N*-(*endo*-8-(2-Diethylamino)ethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide Dihydrochloride (22a)** 52.2%, colorless solid. mp 179—186 °C (recrystallized from EtOH–acetone). ^{1}H-NMR ($CDCl_3$) δ: 1.47 (6H, t, J=7.2 Hz), 1.68 (6H, d, J=7.2 Hz), 2.15—2.30 (2H, m), 2.40—2.80 (4H, m), 2.95—3.40 (6H, m), 3.65—3.90 (4H, m), 3.90—4.15 (2H, m), 4.44 (1H, q, J=6.3 Hz), 5.40—5.80 (1H, br), 7.25—7.35 (1H, m), 7.64 (1H, s), 7.65 (1H, s), 7.76 (1H, d, J=7.8 Hz), 8.81 (1H, s), 10.78 (1H. d, J=7.5 Hz), 12.10—12.40 (2H, br). IR (KBr) cm^{-1}: 3420, 1673. MS (CI) *m/z*: 439 (M+1). *Anal.* Calcd for $C_{26}H_{38}N_4O_2\cdot 2HCl\cdot 1.3H_2O$: C, 58.37; H, 8.02; N, 10.47. Found: C, 58.47; H, 8.13; N, 10.51.

***N*-(*endo*-8-(2-Methylthio)ethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (23a)** 62.7%, colorless solid. mp 168—169 °C (recrystallized from AcOEt–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.76—1.92 (2H, m), 2.17 (3H, s), 2.00—2.50 (6H, m), 2.60—2.83 (4H, m), 3.20—3.55 (2H, m), 4.32 (1H, q, J=7.0 Hz), 5.40—5.80 (1H, br), 7.24—7.35 (1H, m), 7.57—7.70 (2H, m), 7.76 (1H, d, J=7.8 Hz), 8.82 (1H, s), 10.53 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3283, 1674. MS (EI) *m/z*: 413 (M^+). *Anal.* Calcd for $C_{23}H_{31}N_3O_2S\cdot 0.5H_2O$: C, 65.37; H, 7.63; N, 9.94. Found: C, 65.45; H, 7.44; N, 9.94.

***N*-(*endo*-8-(2-Phenylsulfonyl)ethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (24a)** 63.0%, colorless solid. mp 210—211 °C (recrystallized from AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.50—2.20 (8H, m), 2.60—2.90 (2H, m), 3.00—3.55 (4H, m), 4.10—4.25 (1H, m), 5.40—5.80 (1H, br), 7.24—7.35 (1H, m), 7.52—7.80 (6H, m), 7.90—8.00 (2H, m), 8.82 (1H, s), 10.53 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3254, 1668. MS (EI) *m/z*: 507 (M^+). *Anal.* Calcd for $C_{28}H_{33}N_3O_4S\cdot 0.25H_2O$: C, 65.66; H, 6.59; N, 8.20. Found: C, 65.66; H, 6.47; N, 8.14.

***N*-(*endo*-8-(2-Morphorino)ethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (25a)** 38.3%, colorless solid. mp 177—178 °C (recrystallized from AcOEt–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.85—2.05 (4H, m), 2.05—2.40 (4H, m), 2.40—3.00 (10H, m), 3.50—3.85 (6H, m), 4.36 (1H, q, J=7.0 Hz), 5.40—5.80 (1H, br), 7.27—7.35 (1H, m), 7.61—7.70 (2H, m), 7.76 (1H, d, J=7.8 Hz), 8.84 (1H, s), 10.58 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3272, 1678. MS (EI) *m/z*: 452 (M^+). *Anal.* Calcd for $C_{26}H_{36}N_4O_3\cdot H_2O$: C, 66.36; H, 8.14; N, 11.91. Found: C, 66.60; H, 7.84; N, 11.66.

***N*-(*endo*-8-(2-Piperidino)ethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (26a)** 59.2%, colorless solid. mp 159—160 °C (recrystallized from AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.38—1.90 (8H, m), 2.05—2.15 (4H, m), 2.20—2.40 (2H, m), 2.40—2.70 (8H, m), 3.33—3.42 (2H, m), 4.30 (1H, q, J=7.0 Hz), 5.40—5.80 (1H, br), 7.23—7.33 (1H, m), 7.56—7.70 (2H, m), 7.76 (1H, d, J=7.8 Hz), 8.84 (1H, s), 10.49 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3272, 1677. MS (EI) *m/z*: 450 (M^+). *Anal.* Calcd for $C_{27}H_{38}N_4O_2$: C, 71.97; H, 8.50; N, 12.43. Found: C, 71.71; H, 8.58; N, 12.38.

***N*-(*endo*-8-(Tetrahydropyran-2-yl)ethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (27a)** 32.8%, colorless solid. mp 163—164 °C (recrystallized from AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.10—2.70 (16H, m), 3.20—3.60 (4H, m), 3.91—4.03 (1H, m), 4.30 (1H, q, J=7.0 Hz), 5.40—5.80 (1H, br), 7.23—7.35 (1H, m), 7.56—7.70 (2H, m), 7.75 (1H, d, J=7.8 Hz), 8.82 (1H, s), 10.48 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3273, 1676. MS (EI) *m/z*: 437 (M^+). *Anal.* Calcd for $C_{26}H_{35}N_3O_3$: C, 71.37; H, 8.06; N, 9.60. Found: C, 71.09; H, 8.07; N, 9.48.

***N*-(*endo*-8-(2-Phenoxy)ethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (28a)** 50.8%, colorless solid. mp 146—147 °C (recrystallized from AcOEt–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.55—1.85 (2H, m), 2.04—2.42 (6H, m), 2.88 (2H, t, J=5.5 Hz), 3.38—3.47 (2H, m), 4.15 (1H, t, J=7.0 Hz), 4.21 (1H, t, J=7.0 Hz), 5.20—5.80 (1H, br), 6.87—6.97 (3H, m), 7.20—7.40 (3H, m), 7.67—7.90 (3H, m), 8.78 (1H, s). IR (KBr) cm^{-1}: 3295, 1670. MS (EI) *m/z*: 459 (M^+). *Anal.* Calcd for $C_{28}H_{33}N_3O_3\cdot 0.25H_2O$: C, 72.46; H, 7.28; N, 9.05. Found: C, 72.24; H, 7.20; N, 9.08.

***N*-(*endo*-8-(Ethoxycarbonyl)methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (29a)** 60.7%, colorless solid. mp 106—108 °C (recrystallized from AcOEt–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.2 Hz), 1.68 (6H, d, J=7.2 Hz), 1.76—1.90 (2H, m), 2.00—2.25 (4H, m), 2.32—2.52 (2H, m), 3.30 (2H, s), 3.36—3.47 (2H, m), 4.21 (2H, q, J=7.2 Hz), 4.32 (1H, q, J=7.0 Hz), 5.40—5.80 (1H, br), 7.24—7.35 (1H, m), 7.57—7.70 (2H, m), 7.76 (1H, d, J=7.0 Hz), 8.83 (1H, s), 10.52 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3264, 1752, 1671.

MS (EI) *m/z*: 425 (M^+). *Anal.* Calcd for $C_{24}H_{31}N_3O_4 \cdot 0.25H_2O$: C, 67.03; H, 7.38; N, 9.77. Found: C, 67.04; H, 7.44; N, 9.69.

***N*-(*endo*-8-Carboxylmethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (30a)** 55.3%, colorless solid. mp 244—247 °C (recrystallized from MeOH–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 2.10—2.27 (2H, m), 2.30—2.70 (6H, m), 3.60 (2H, s), 4.03—4.15 (2H, m), 4.32 (1H, t, J=7.0 Hz), 5.30—5.70 (1H, br), 7.32—7.42 (1H, m), 7.68—7.90 (2H, m), 7.90 (1H, s), 8.80 (1H, s). IR (KBr) cm^{-1}: 3436, 1677, 1638. MS (FAB) *m/z*: 398 (M+1). *Anal.* Calcd for $C_{22}H_{27}N_3O_4 \cdot H_2O$: C, 64.15; H, 6.99; N, 10.20. Found: C, 64.08; H, 7.00; N, 10.28.

***N*-(*endo*-8-(3-Ethoxycarbonyl)propyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide Hydrochloride (31a)** 27.1%, colorless solid. mp 251—252 °C (recrystallized from EtOH). ^{1}H-NMR (DMSO-d_6) δ: 1.26 (3H, t, J=7.2 Hz), 1.68 (6H, d, J=7.2 Hz), 1.95—2.60 (10H, m), 2.91—3.07 (2H, m), 3.14—3.32 (2H, m), 3.88—3.97 (2H, m), 4.13 (2H, q, J=7.2 Hz), 4.46 (1H, q, J=7.0 Hz), 5.40—5.75 (1H, br), 7.28—7.38 (1H, m), 7.77 (2H, d, J=7.0 Hz), 8.85 (1H, s), 10.68 (1H, d, J=7.5 Hz), 12.10—12.30 (1H, br). IR (KBr) cm^{-1}: 1731, 1665. MS (EI) *m/z*: 453 (M^+). *Anal.* Calcd for $C_{26}H_{35}N_3O_4 \cdot HCl \cdot 0.25H_2O$: C, 63.15; H, 7.44; N, 8.50. Found: C, 63.36; H, 7.55; N, 8.49.

***N*-(*endo*-8-(3-Carboxyl)propyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (32a)** 75.7%, colorless solid. mp >250 °C (recrystallized from EtOH–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.60 (6H, d, J=7.2 Hz), 1.83—2.10 (4H, m), 2.10—2.65 (6H, m), 2.87—3.08 (2H, m), 3.20—3.40 (2H, m), 3.95—4.05 (2H, m), 4.08—4.25 (1H, m), 5.30—5.70 (1H, br), 7.38 (1H, t, J=7.0 Hz), 7.75 (1H, dt, J=1.0, 9.0 Hz), 7.90 (1H, d, J=9.0 Hz), 8.03 (1H, dd, J=1.0, 7.0 Hz), 8.81 (1H, s), 10.46 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3430, 1734, 1681. MS (EI) *m/z*: 425 (M^+). *Anal.* Calcd for $C_{24}H_{31}N_3O_4 \cdot 0.6H_2O$: C, 66.06; H, 7.44; N, 9.63. Found: C, 66.21; H, 7.45; N, 9.61.

***N*-(*endo*-8-Acetyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (33a)** 19.4%, colorless solid. mp 208—210 °C (recrystallized from AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.69 (6H, d, J=7.2 Hz), 2.09 (3H, s), 1.81—2.42 (8H, m), 4.13—4.22 (1H, m), 4.33—4.48 (1H, m), 4.70—4.85 (1H, m), 5.35—5.90 (1H, br), 7.26—7.37 (1H, m), 7.58—7.70 (2H, m), 7.77 (1H, d, J=7.0 Hz), 8.83 (1H, s), 10.70 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3235, 1674, 1636. MS (EI) *m/z*: 381 (M^+). *Anal.* Calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 69.25; H, 7.20; N, 11.30.

***N*-(*endo*-8-(2-Oxopropyl)-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide Hydrochloride (34a)** 7.7%, colorless solid. mp 208—211 °C (recrystallized from EtOH). ^{1}H-NMR (DMSO-d_6) δ: 1.68 (6H, d, J=7.2 Hz), 1.95—2.80 (11H, m), 3.06—3.28 (1H, m), 3.95—4.52 (4H, m), 5.35—5.75 (1H, br), 7.27—7.38 (1H, m), 7.60—7.73 (2H, m), 7.77 (1H, d, J=7.0 Hz), 8.85 (1H, s), 10.72 (1H, d, J=7.5 Hz), 11.20—11.45 (1H, br). IR (KBr) cm^{-1}: 1723, 1673. MS (FAB) *m/z*: 396 (M+1). *Anal.* Calcd for $C_{23}H_{29}N_3O_3 \cdot HCl \cdot 1.1H_2O$: C, 61.15; H, 6.96; N, 9.30. Found: C, 61.04; H, 6.99; N, 9.30.

***N*-(*endo*-8-(4-Oxopentyl)-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (35a)** 5.3%, colorless solid. mp 101—103 °C (recrystallized from diisopropyl ether–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.72—1.91 (4H, m), 1.95—2.15 (4H, m), 2.17 (3H, s), 2.20—2.60 (6H, m), 3.25—3.34 (2H, m), 4.30 (1H, q, J=7.0 Hz), 5.40—5.80 (1H, br), 7.24—7.33 (1H, m), 7.56—7.70 (2H, m), 7.75 (1H, d, J=7.0 Hz), 8.83 (1H, s), 10.49 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 1712, 1671. MS (EI) *m/z*: 423 (M^+). *Anal.* Calcd for $C_{25}H_{33}N_3O_3$: C, 70.89; H, 7.85; N, 9.92. Found: C, 70.78; H, 7.92; N, 9.67.

***N*-(*endo*-8-Cyanomethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (36a)** 53.3%, colorless solid. mp 178—181 °C (recrystallized from AcOEt–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.80—1.93 (2H, m), 2.02—2.37 (6H, m), 3.39 (2H, s), 3.34—3.46 (2H, m), 4.31 (1H, q, J=7.0 Hz), 5.40—5.80 (1H, br), 7.25—7.33 (1H, m), 7.61—7.70 (2H, m), 7.76 (1H, d, J=7.0 Hz), 8.83 (1H, s), 10.53 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 2244, 1676. MS (EI) *m/z*: 378 (M^+). *Anal.* Calcd for $C_{22}H_{26}N_4O_2 \cdot 0.25H_2O$: C, 69.00; H, 6.97; N, 14.63. Found: C, 68.90; H, 6.91; N, 14.31.

***N*-(*endo*-8-(2-Cyano)ethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (37a)** 37.4%, colorless solid. mp 177—178 °C (recrystallized from AcOEt–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.75—1.95 (2H, m), 1.95—2.82 (10H, m), 3.15—3.45 (2H, m), 4.31 (1H, q, J=7.0 Hz), 5.45—5.75 (1H, br), 7.24—7.34 (1H, m), 7.60—7.70 (2H, m), 7.75 (1H, d, J=7.0 Hz), 8.83 (1H, s), 10.51 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3266, 2246, 1677. MS *m/z*: 392 (M^+). *Anal.* Calcd for $C_{23}H_{28}N_4O_2 \cdot 0.25H_2O$: C, 69.58; H, 7.24; N, 14.11. Found: C, 69.61; H, 7.17; N, 13.95.

***N*-(*endo*-8-Carbamoylmethyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (38a)** 56.9%, colorless solid. mp >250 °C (recrystallized from EtOH). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, d, J=7.2 Hz), 1.76—2.40 (8H, m), 2.90—3.40 (4H, m), 4.33 (1H, q, J=7.0 Hz), 5.30—5.86 (1H, br), 7.23—7.34 (1H, m), 7.34—7.57 (2H, br), 7.57—7.70 (2H, m), 7.76 (1H, d, J=7.0 Hz), 8.82 (1H, s), 10.54 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3407, 1670. MS (EI) *m/z*: 396 (M^+). *Anal.* Calcd for $C_{22}H_{28}N_4O_3$: C, 66.65; H, 7.12; N, 14.13. Found: C, 66.54; H, 7.19; N, 14.03.

***endo*-8-Alkyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylates (12b—38b)** The alkylation of compound **11b** was conducted in a similar procedure as employed in the synthesis of **18a**. HCl salts of alkylated compounds were made using a procedure similar to that employed in the synthesis of **11b**.

***endo*-8-(2-Hydroxy)ethyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate Hydrochloride (14b)** 27%, colorless solid. mp 191—193 °C (recrystallized from EtOH–toluene). ^{1}H-NMR (DMSO-d_6) δ: 1.65 (6H, d, J=7.2 Hz), 2.10—2.30 (4H, m), 2.75—2.90 (2H, m), 3.03—3.18 (2H, m), 3.18—3.27 (1H, m), 3.27—3.35 (1H, m), 3.35—3.60 (1H, br), 3.95—4.20 (4H, m), 5.30—5.65 (1H, br), 5.42 (1H, t, J=4.6 Hz), 7.20—7.30 (1H, m), 7.55—7.70 (3H, m), 8.32 (1H, s), 11.25—11.50 (1H, br). IR (KBr) cm^{-1}: 3436, 1708, 1646. MS (EI) *m/z*: 384 (M^+). *Anal.* Calcd for $C_{22}H_{28}N_2O_4 \cdot HCl \cdot 0.2H_2O$: C, 62.24; H, 7.03; N, 6.59. Found: C, 62.13; H, 6.99; N, 6.60.

***endo*-8-(3-Hydroxy)propyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate (15b)** 48%, colorless solid. mp 129—131 °C (recrystallized from AcOEt–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.60—1.70 (3H, m), 1.66 (6H, d, J=7.2 Hz), 1.90—2.10 (4H, m), 2.10—2.40 (4H, m), 2.70 (2H, t, J=7.0 Hz), 3.33—3.45 (2H, m), 3.87 (2H, t, J=7.0 Hz), 5.27 (1H, t, J=7.0 Hz), 5.30—5.70 (1H, br), 7.18—7.30 (1H, m), 7.55—7.68 (3H, m), 8.22 (1H, s). IR (KBr) cm^{-1}: 3437, 3119, 1726, 1650. MS (EI) *m/z*: 398 (M^+). *Anal.* Calcd for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.58; N, 7.02. Found: C, 69.22; H, 7.65; N, 7.02.

***endo*-8-(4-Hydroxy)butyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate Hydrochloride (16b)** 10%, colorless solid. mp 209—213 °C (recrystallized from EtOH–toluene). ^{1}H-NMR (DMSO-d_6) δ: 1.65 (6H, d, J=7.2 Hz), 1.50—1.80 (2H, m), 1.95—2.30 (6H, m), 2.50—3.35 (7H, m), 3.65—3.80 (2H, m), 3.80—4.05 (2H, m), 5.30—5.60 (2H, m), 7.18—7.33 (1H, m), 7.52—7.75 (3H, m), 8.83 (1H, s). IR (KBr) cm^{-1}: 3370, 1704, 1660. MS (EI) *m/z*: 412 (M^+). *Anal.* Calcd for $C_{24}H_{32}N_2O_4 \cdot HCl$: C, 64.20; H, 7.18; N, 6.23. Found: C, 63.93; H, 7.45; N, 6.19.

***endo*-8-(5-Hydroxy)pentyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide Hydrochloride (17b)** 29%, colorless solid. mp 243—245 °C (recrystallized from EtOH–toluene). ^{1}H-NMR (DMSO-d_6) δ: 1.68 (6H, d, J=7.2 Hz), 1.40—2.60 (15H, m), 3.25—3.40 (2H, m), 3.68 (2H, t, J=7.0 Hz), 5.30 (1H, t, J=7.0 Hz), 5.30—5.70 (1H, br), 7.20—7.30 (1H, m), 7.55—7.70 (3H, m), 8.23 (1H, s). IR (KBr) cm^{-1}: 3352, 1731, 1642. MS (EI) *m/z*: 426 (M^+). *Anal.* Calcd for $C_{25}H_{34}N_2O_4 \cdot HCl$: C, 64.85; H, 7.61; N, 6.05. Found: C, 64.59; H, 7.67; N, 5.96.

***endo*-8-(6-Hydroxy)hexyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate Hydrochloride (18b)** 21%, colorless solid. mp 205—207 °C (recrystallized from EtOH–toluene). ^{1}H-NMR (DMSO-d_6) δ: 1.68 (6H, d, J=7.2 Hz), 1.20—2.75 (8H, m), 2.75—3.00 (2H, m), 3.10—3.45 (3H, m), 3.80—4.05 (3H, m), 4.39 (1H, t, J=7.0 Hz), 5.12—5.23 (1H, m), 5.23—5.50 (1H, br), 7.26—7.35 (1H, m), 7.67—7.95 (3H, m), 8.45 (1H, s), 10.02—10.25 (1H, m). IR (KBr) cm^{-1}: 3426, 1714, 1661. MS (EI) *m/z*: 440 (M^+). *Anal.* Calcd for $C_{26}H_{36}N_2O_4 \cdot HCl$: C, 65.46; H, 7.81; N, 5.87. Found: C, 65.15; H, 7.65; N, 5.76.

***endo*-8-(2-Methoxy)ethyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate Hydrochloride (19b)** 23%, colorless solid. mp 206—208 °C (recrystallized from EtOH–toluene). ^{1}H-NMR (DMSO-d_6) δ: 1.65 (6H, d, J=7.2 Hz), 2.08—2.30 (4H, m), 2.40—2.82 (3H, m), 3.08—3.30 (3H, m), 3.37 (3H, s), 3.90—4.12 (1H, m), 5.30—5.60 (1H, br), 5.41 (1H, t, J=7.0 Hz), 7.20—7.30 (1H, m), 7.55—7.70 (3H, m), 8.30 (1H, s), 12.10—12.30 (1H, br). IR (KBr) cm^{-1}: 3436, 1731, 1652. MS (EI) *m/z*: 398 (M^+). *Anal.* Calcd for $C_{23}H_{30}N_2O_4 \cdot HCl \cdot H_2O$: C, 60.98; H, 7.34; N, 6.18. Found: C, 60.89; H, 7.47; N, 5.95.

***endo*-8-(2-Ethoxy)ethyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide Hydrochloride (20b)** 34%, colorless solid. mp 185—187 °C (recrystallized from EtOH–toluene). ^{1}H-NMR

(DMSO-d_6) δ: 1.24 (3H, t, J=7.2 Hz), 1.66 (6H, d, J=7.2 Hz), 2.10—2.45 (4H, m), 2.45—2.72 (4H, m), 3.20—3.40 (2H, m), 3.59 (2H, q, J=6.8 Hz), 3.82 (2H, t, J=7.2 Hz), 4.00—4.25 (2H, m), 5.30 (1H, t, J=7.0 Hz), 5.20—5.60 (1H, br), 7.33 (1H, dt, J=1.4, 7.6 Hz), 7.68—7.87 (3H, m), 8.45 (1H, s). IR (KBr) cm^{-1}: 3435, 1704, 1654. MS (EI) m/z: 412 (M^+). *Anal.* Calcd for $C_{24}H_{32}N_2O_4 \cdot HCl$: C, 64.20; H, 7.40; N, 6.23. Found: C, 64.00; H, 7.42; N, 6.26.

***endo*-8-(Methoxyethoxy)ethyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate Hydrochloride (21b)** 71.0%, colorless solid. mp 70—75 °C (recrystallized from EtOH–diisopropyl ether). ^{1}H-NMR (DMSO-d_6) δ: 1.65 (6H, d, J=7.2 Hz), 2.11—2.20 (4H, m), 2.72—2.76 (2H, m), 3.16—3.26 (4H, m), 3.38 (3H, s), 3.52—3.66 (2H, m), 3.65—3.70 (2H, m), 4.06—4.16 (4H, m), 5.40—5.42 (2H, m), 7.21—7.29 (1H, m), 7.60—7.67 (3H, m), 8.31 (1H, s), 12.13 (1H, br). IR (KBr) cm^{-1}: 3338, 2894, 1698, 1657. MS (EI) m/z: 442 (M^+). *Anal.* Calcd for $C_{25}H_{34}N_2O_5 \cdot HCl \cdot 2H_2O$: C, 58.30; H, 7.63; N, 5.44. Found: C, 58.22; H, 7.75; N, 5.52.

***endo*-8-(2-Diethylamino)ethyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate Dihydrochloride (22b)** 45%, colorless solid. mp 240—243 °C (recrystallized from EtOH–AcOEt). ^{1}H-NMR (DMSO-d_6) δ: 1.47 (6H, t, J=7.2 Hz), 1.64 (6H, d, J=7.2 Hz), 2.15—2.30 (2H, m), 2.40—2.60 (2H, m), 2.70—2.90 (2H, m), 2.95—3.40 (6H, m), 3.60—3.93 (4H, m), 3.93—4.10 (2H, m), 5.30—5.60 (1H, m), 7.20—7.30 (1H, m), 7.51—7.70 (3H, m), 8.28 (1H, s), 12.10—12.50 (2H, br). IR (KBr) cm^{-1}: 3427, 1718, 1638. MS (FAB) m/z: 440 (M+1). *Anal.* Calcd for $C_{26}H_{37}N_3O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 59.88; H, 7.73; N, 8.05. Found: C, 59.67; H, 7.77; N, 8.00.

***endo*-8-(2-Methylthio)ethyl-8-azabicyclo[3.2.1]oct-3-yl) Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate (23b)** 12%, colorless solid. mp 130—140 °C (recrystallized from AcOEt–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.65 (6H, d, J=7.2 Hz), 1.90—2.35 (8H, m), 2.13 (3H, s), 2.60—2.89 (4H, m), 3.40—3.55 (2H, m), 5.22 (1H, t, J=7.0 Hz), 5.30—5.60 (1H, br), 7.32 (1H, dt, J=1.4, 6.8 Hz), 7.65—7.85 (3H, m), 8.39 (1H, s). IR (KBr) cm^{-1}: 3435, 1695, 1655. MS (CI) m/z: 415 (M+1). *Anal.* Calcd for $C_{23}H_{30}N_2O_3S \cdot 0.5H_2O$: C, 65.06; H, 7.60; N, 6.60. Found: C, 65.22; H, 7.48; N, 6.46.

***endo*-8-(2-Phenylsulfonyl)ethyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate (24b)** 42%, colorless solid. mp 131—133 °C (recrystallized from AcOEt–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.64 (6H, d, J=7.2 Hz), 1.70—2.15 (8H, m), 2.75 (2H, t, J=7.0 Hz), 3.00—3.20 (2H, m), 3.44 (2H, t, J=7.0 Hz), 5.04 (1H, t, J=7.0 Hz), 5.25—5.60 (1H, br), 7.27—7.37 (1H, m), 7.59—7.85 (6H, m), 7.90—8.02 (2H, m), 8.33 (1H, s). IR (KBr) cm^{-1}: 1730, 1696. MS (EI) m/z: 508 (M^+). *Anal.* Calcd for $C_{28}H_{32}N_2O_5S$: C, 66.12; H, 6.34; N, 5.50. Found: C, 65.98; H, 6.37; N, 5.50.

***endo*-8-(2-Morphorino)ethyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate Dihydrochloride (25b)** 41%, colorless solid. mp >270 °C (recrystallized from EtOH–$CHCl_3$). ^{1}H-NMR (DMSO-d_6) δ: 1.66 (6H, d, J=7.2 Hz), 2.20—2.45 (4H, m), 2.60—2.90 (4H, m), 3.10—3.50 (2H, m), 3.50—3.80 (6H, m), 3.90—4.12 (4H, m), 4.12—4.30 (2H, m), 5.32 (1H, t, J=7.0 Hz), 5.28—5.55 (1H, br), 7.33 (1H, dt, J=1.6, 6.4 Hz), 7.68—7.77 (3H, m), 8.46 (1H, s). IR (KBr) cm^{-1}: 3436, 1723, 1643. MS (CI) m/z: 454 (M+1). *Anal.* Calcd for $C_{26}H_{35}N_3O_4 \cdot 2HCl \cdot 0.25H_2O$: C, 58.81; H, 7.11; N, 7.91. Found: C, 58.68; H, 7.10; N, 7.75.

***endo*-8-(Tetrahydropyran-2-yl)ethyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate Hydrochloride (27b)** 30%, colorless solid. mp 255—257 °C (recrystallized from EtOH–toluene). ^{1}H-NMR (DMSO-d_6) δ: 1.15—1.30 (1H, m), 1.40—1.90 (5H, m), 1.65 (6H, d, J=7.2 Hz), 2.00—2.30 (4H, m), 2.60—2.95 (4H, m), 3.05—3.18 (1H, m), 3.27—3.41 (1H, m), 3.45—3.60 (1H, m), 3.65—3.75 (1H, m), 3.85—3.95 (1H, m), 4.30—4.50 (2H, m), 5.30—5.70 (2H, m), 7.20—7.30 (1H, m), 7.55—7.70 (3H, m), 8.30 (1H, s), 11.90—12.30 (1H, br). IR (KBr) cm^{-1}: 3435, 1733, 1698. MS (EI) m/z: 438 (M^+). *Anal.* Calcd for $C_{26}H_{34}N_2O_4 \cdot HCl$: C, 65.74; H, 7.42; N, 5.89. Found: C, 65.86; H, 7.49; N, 5.77.

***endo*-8-(2-Phenoxy)ethyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate Hydrochloride (28b)** 44%, colorless solid. mp 214—217 °C (recrystallized from EtOH–toluene). ^{1}H-NMR (CD_3OD) δ: 1.66 (3H, d, J=7.2 Hz), 1.68 (3H, d, J=7.2 Hz), 1.95—2.80 (8H, m), 3.40—3.80 (2H, m), 3.96—4.30 (2H, m), 4.32—4.50 (2H, m), 5.25—5.70 (2H, m), 6.94—7.07 (3H, m), 7.27—7.45 (3H, m), 7.67—7.90 (3H, m), 8.49 (1H, d, J=4.5 Hz). IR (KBr) cm^{-1}: 3440, 1724, 1638. MS (EI) m/z: 460 (M^+). *Anal.* Calcd for $C_{28}H_{32}N_2O_4 \cdot HCl \cdot 0.5H_2O$: C, 66.46; H, 6.77; N, 5.53. Found: C, 66.69; H, 6.63; N, 5.48.

***endo*-8-(Ethoxycarbonyl)methyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate Hydrochloride (29b)** 54%, colorless solid. mp 191—194 °C (recrystallized from EtOH–toluene). ^{1}H-NMR (DMSO-d_6) δ: 1.34 (3H, t, J=7.2 Hz), 1.65 (6H, d, J=7.2 Hz), 2.10—2.30 (4H, m), 2.80—2.95 (2H, m), 3.20—3.39 (2H, m), 3.71 (2H, d, J=5.6 Hz), 4.15—4.27 (2H, m), 4.34 (2H, q, J=7.2 Hz), 5.30—5.65 (1H, br), 5.44 (1H, t, J=7.0 Hz), 7.20—7.30 (1H, m), 7.55—7.72 (3H, m), 8.33 (1H, s), 12.55—12.75 (1H, br). IR (KBr) cm^{-1}: 3435, 1741, 1713, 1655. MS (EI) m/z: 426 (M^+). *Anal.* Calcd for $C_{24}H_{30}N_2O_5 \cdot HCl$: C, 62.26; H, 6.74; N, 6.05. Found: C, 62.13; H, 6.82; N, 5.94.

***endo*-8-(2-Oxopropyl)-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate Hydrochloride (34b)** 28%, colorless solid. mp 217—225 °C (recrystallized from EtOH–toluene). ^{1}H-NMR (DMSO-d_6) δ: 1.68 (6H, d, J=7.2 Hz), 2.05—2.65 (7H, m), 2.75—2.92 (2H, m), 3.15—3.33 (2H, m), 3.90—4.35 (4H, m), 5.30—5.70 (2H, br), 7.20—7.33 (1H, m), 7.55—7.73 (3H, m), 8.32 (1H, s), 11.70—12.00 (1H, br). IR (KBr) cm^{-1}: 3421, 1736, 1718, 1665. MS (CI) m/z: 397 (M+1). *Anal.* Calcd for $C_{23}H_{28}N_2O_4 \cdot HCl$: C, 63.80; H, 6.75; N, 6.47. Found: C, 63.51; H, 6.82; N, 6.28.

***endo*-8-(4-Oxopentyl)-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate Hydrochloride (35b)** 56%, colorless solid. mp 230—236 °C (recrystallized from EtOH–toluene). ^{1}H-NMR (DMSO-d_6) δ: 1.66 (6H, d, J=7.2 Hz), 1.90—2.15 (2H, m), 2.17 (3H, s), 2.15—2.45 (4H, m), 2.45—2.80 (6H, m), 2.95—3.15 (2H, m), 3.90—4.20 (2H, m), 5.31 (1H, t, J=7.0 Hz), 5.25—5.60 (1H, br), 7.36 (1H, dt, J=1.4, 6.4 Hz), 7.65—7.87 (3H, m), 8.45 (1H, s). IR (KBr) cm^{-1}: 3426, 1708, 1652. MS (EI) m/z: 424 (M^+). *Anal.* Calcd for $C_{25}H_{32}N_2O_4 \cdot HCl$: C, 65.13; H, 7.21; N, 6.07. Found: C, 65.07; H, 7.24; N, 5.99.

***endo*-8-Cyanomethyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate Hydrochloride (36b)** 50%, colorless solid. mp 209—213 °C (recrystallized from EtOH–toluene). ^{1}H-NMR (DMSO-d_6) δ: 1.65 (6H, d, J=7.2 Hz), 2.10—2.50 (4H, m), 2.70—3.00 (2H, m), 3.00—3.25 (2H, m), 4.10—4.33 (2H, m), 4.33—4.60 (2H, m), 5.30—5.60 (2H, m), 7.19—7.30 (1H, m), 7.50—7.73 (3H, m), 8.32 (1H, s), 13.30—13.50 (1H, br). IR (KBr) cm^{-1}: 3401, 1729, 1654. MS (EI) m/z: 379 (M^+). *Anal.* Calcd for $C_{22}H_{25}N_3O_3 \cdot HCl$: C, 63.53; H, 6.30; N, 10.10. Found: C, 63.28; H, 6.31; N, 9.94.

***endo*-8-(2-Cyano)ethyl-8-azabicyclo[3.2.1]oct-3-yl) 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate (37b)** 28%, colorless solid. mp 132—134 °C (recrystallized from AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.66 (6H, d, J=7.2 Hz), 1.85—2.05 (4H, m), 2.05—2.40 (4H, m), 2.40—2.80 (4H, m), 3.15—3.40 (2H, m), 5.17 (1H, t, J=7.0 Hz), 5.35—5.65 (1H, br), 7.19—7.29 (1H, m), 7.55—7.69 (3H, m), 8.21 (1H, s), 10.51 (1H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3401, 2248, 1730, 1656. MS (EI) m/z: 393 (M^+). *Anal.* Calcd for $C_{23}H_{27}N_3O_3$: C, 70.20; H, 6.91; N, 10.67. Found: C, 70.00; H, 6.92; N, 10.54.

***endo*-8-Carbamoylmethyl-8-azabicyclo[3.2.1]oct-3-yl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate (38b)** 60%, colorless solid. mp 261—264 °C (recrystallized from EtOH). ^{1}H-NMR ($CDCl_3$) δ: 1.66 (6H, d, J=7.2 Hz), 1.90—2.10 (4H, m), 2.10—2.45 (4H, m), 2.45—3.15 (2H, m), 3.15—3.45 (2H, m), 5.30 (1H, t, J=7.0 Hz), 5.30—5.80 (3H, br), 7.18—7.30 (1H, m), 7.55—7.70 (3H, m), 8.22 (1H, s). IR (KBr) cm^{-1}: 3408, 1679, 1657. MS (CI) m/z: 398 (M+1). *Anal.* Calcd for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.84; N, 10.57. Found: C, 66.32; H, 6.75; N, 10.43.

8-(3-Hydroxypropyl)-8-azabicyclo[3.2.1]octan-3-one (41) To a solution of 2,5-dimethoxytetrahydrofuran **39** (120 ml, 0.93 mol) in water (300 ml) was added HCl (45 ml) with stirring at room temperature. Twenty minutes later, the reaction solution became homogenous. Thereafter, water (450 ml), a solution of 3-amino-1-propanol (105 ml, 1.37 mol) and HCl (138 ml) in water (600 ml), a solution of 1,3-diacetonedicarboxylic acid (150 g, 1.03 mol) in water (700 ml) and a solution of Na_2HPO_4 (66 g) in water (300 ml) were successively added to the homogeneous reaction solution. The pH of the resulting solution was then adjusted to the range of 3 to 4 with 40% NaOH aqueous solution (215 ml). After bubbling was confirmed, the mixture was stirred overnight. Then HCl was added to adjust the pH of the reaction solution to 3. The reaction solution was heated to 80 °C and stirred until bubbling of carbon dioxide gas was no longer observed. After completion of the reaction, the reaction solution was cooled and NaOH aqueous solution was added thereto to render the solution alkaline. Thereafter NaCl was added, followed by extraction with $CHCl_3$. The organic layer was washed with water and dried. The organic layer was evaporated *in vacuo* to give **41** as a crude product. mp 42—43 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.57—1.68 (2H, m), 1.73—1.83 (2H, m), 2.00—2.17 (4H, m), 2.20—2.29 (2H, m), 2.66 (2H, dd, J=16.1, 4.4 Hz), 2.84 (2H, t, J=5.7 Hz), 3.62—3.66 (2H, m), 3.90 (2H, t, J=5.2 Hz), 5.12 (1H, brs). IR (KBr) cm^{-1}: 1714. MS

(EI) *m/z*: 183 (M^+). *Anal.* Calcd for $C_{10}H_{17}NO_2 \cdot 0.1H_2O$: C, 64.91; H, 9.37; N, 7.57. Found: C, 64.72; H, 9.31; N, 7.56.

8-(3-Hydroxypropyl)-8-azabicyclo[3.2.1]octan-3-one Oxime Hydrochloride (42) A crude product of **41** was dissolved in EtOH (1200 ml), and 50% hydroxylamine aqueous solution (72.9 g) was added to the solution at room temperature. After completion of the reaction, the solvent was distilled off and toluene was added. The solvent was again distilled off and the residue was dissolved in EtOH. HCl was added to the remaining solution, and the precipitated crystals were collected by filtration to give 161 g (73.9% from **39**) of **42** as a colorless solid. mp 239—242 °C (dec.). ^{1}H-NMR (MeOH-d_4) δ: 1.75—2.08 (4H, m), 2.21—2.56 (4H, m), 2.83—2.93 (1H, m), 3.19—3.45 (3H, m), 3.73 (2H, t, J=5.7 Hz), 4.14—4.20 (2H, m). IR (KBr) cm^{-1}: 1658. MS (EI) *m/z*: 198 (M^+). *Anal.* Calcd for $C_{10}H_{18}N_2O_2 \cdot HCl$: C, 51.17; H, 8.16; N, 11.93. Found: C, 51.17; H, 8.15; N, 11.93.

***endo*-3-Amino-8-(3-hydroxypropyl)-8-azabicyclo[3.2.1]octane (9)** A mixture of **42** (100 g, 0.43 mol), platinum oxide (5.0 g) and AcOH (500 ml) were stirred for 18 h under a hydrogen pressure of 5.0 kg/cm^2, with temperature maintained at 45 to 46 °C. Water was added to the reaction mixture, and the mixture was filtered. The filtrate was evaporated *in vacuo.* The residue was dissolved in water (50 ml) and MeOH (100 ml). To this solution was added a solution of oxalic acid (38.4 g) in MeOH (200 ml), followed by MeOH (200 ml). The mixture was stirred overnight at room temperature. The precipitated crystals were collected by filtration and dried to give 71.3 g (53.9%) of *endo*-3-amino-8-(3-hydroxypropyl)-8-azabicyclo[3.2.1]octane hydrochloride oxalate as a colorless solid. mp. 230—233 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 1.66—1.94 (6H, m), 1.94—2.25 (6H, m), 2.38—2.63 (2H, m), 2.71—3.10 (3H, m), 3.35—3.61 (3H, m), 3.63—4.00 (3H, m). IR cm^{-1}: 3414, 2115, 1634. MS (EI) *m/z*: 184 (M^+). *Anal.* Calcd for $C_{12}H_{23}N_2ClO_4$: C, 48.89; H, 7.86; N, 9.50. Found: C, 48.59; H, 8.10; N, 9.77. To a solution of *endo*-3-amino-8-(3-hydroxypropyl)-8-azabicyclo-[3.2.1]octane hydrochloride oxalate (30.0 g, 0.097 mol) in water (300 ml) was added $KHCO_3$ (48.3 g). The mixture was stirred at room temperature for 4 h. EtOH (300 ml) was then added. After stirring for 1 h, precipitated insoluble matter was filtered off and the filtrate was concentrated. EtOH (300 ml) was added again to the concentrate. The precipitated insoluble matter was filtered off and the filtrate was concentrated. The residue was dissolved in $CHCl_3$ (300 ml). After drying over anhydrous sodium sulfate, the solvent was distilled off to give 18.5 g (96.9%) of **9** as a colorless gum. ^{1}H-NMR ($CDCl_3$) δ: 1.43—1.50 (2H, m), 1.54—1.71 (2H, m), 1.85—2.14 (6H, m), 2.60 (2H, t, J=5.6 Hz), 3.19—3.37 (3H, m), 3.85 (2H, t, J=5.2 Hz).

***N*-(*endo*-8-(3-Hydroxy)propyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (15a, TS-951)** A mixture of **5** (0.99 g, 4.3 mmol) and toluene (10 ml) was added thionyl chloride (0.77 g, 6.5 mmol) and heated at 80 °C for 1 h. The reaction mixture was used directly to following condensation step. To a solution of NaOH (0.93 g, 23.3 mmol) and **9** (0.72 g, 3.91 mmol) in water (10 ml) was added above acid chloride solution under 10 °C. After stirred for 0.5 h, the reaction mixture was concentrated *in vacuo.* To the resulting residue were added EtOH (10 ml) and 10% aqueous NaOH solution (10 ml), and the whole was stirred at room temperature for 0.5 h. After hydrolysis was completed, additional water (20 ml) was added. The resulting precipitates was filtered to give 1.39 g (90%) of **15a** as a colorless solid.

Serotonin 5-HT$_4$ Receptor Agonist Activity Male guinea pigs of Hartley strain (Nihon SLC Inc., Shizuoka) weighing 200—400 g were housed at 20—26 °C on a 12 h light/dark cycle with free access to food and water. Animals were killed by a blow to the head and cutting of the carotid arteries. The ileum was excised 10—20 cm from the ileo-caecal junction and divided longitudinally into segments approximately 3 cm in length. The longitudinal muscle strips with the myenteric plexus attached were removed by gentle stroking with a cotton swab. The tissue was vertically suspended in an organ bath containing Krebs' solution (composition in mmol/l: NaCl, 120; KCl, 5.9; $NaHCO_3$, 15.5; NaH_2PO_4, 1.2; $CaCl_2$, 2.5; $MgCl_2$, 1.2; glucose, 11.5) gassed with a mixture of 95% O_2 and 5% CO_2 and maintained at 32 °C. Twitch responses were evoked by transmural electrical stimulation of the enteric cholinergic nerves using square-wave pulses (0.2 Hz, 1 msec pulse duration). Twitch responses were recorded isometrically with a resting tension of 0.8 g. The tissue was stimulated at supramaximal voltage to equilibration for 2—3 h. The twitch response was then decreased by voltage reduction. After obtaining a stable submaximal response, the tissue was exposed to 10 nmol/l of 5-HT. We confirmed that the tissue was sensitive to this concentration of 5-HT. This concentration of 5-HT produced a sustained increase in the twitch response. Concentration-effect curves for agonists were constructed by exposing the strips to cumulative additions of agonists. The responses to agonists were measured in terms of their ability to restore the twitch response to those obtained at supramaximal voltage. The responses were expressed as a percentage of the maximum 5-HT-evoked contraction. The ED_{50} values for agonists were determined by nonliner regression.

Intrinsic Activity Guinea pigs were killed by a blow to the head and cutting of the carotid arteries. The distal colon was excised 2—3 cm from the rectum and longitudinal muscle strips with the myenteric plexus attached were prepared. The tissue was vertically suspended in a organ bath containing Krebs' solution (composition in mmol/l: NaCl, 120; KCl, 5.9; $NaHCO_3$, 15.5; NaH_2PO_4, 1.2; $CaCl_2$, 2.5; $MgCl_2$, 1.2; glucose, 11.5) gassed with a mixture of 95% O_2 and 5% CO_2 and maintained at 37 °C. Methysergide (1 μmol/l) and ondansetron (1 μmol/l) were added to exclude any potential effects of 5-HT_1, 5-HT_2 and 5-HT_3 receptor agonism. Contractile responses were recorded using an isometric transducer. Concentration–effect curves for agonists were constructed non-cumulatively by adding increasing concentrations of agonist at 15 min time intervals. Responses were expressed as a percentage of the maximum 5-HT-evoked contraction.

Gastrointestinal Motility Beagle dogs of both sexes were housed at 20—26 °C on a 12 h light/dark cycle with free access to food and water. Dogs with strain gauge force transducers sutured to the serosa of gastric antrum, small intestine or colon were prepared to measure circular muscle contractions. The experiments started at least 14 d after surgery. The animals were deprived of food, but not water, for 18 h before each experiment. Before application of test drugs, control recordings were performed in each dog. During this recording, a previously reported motility pattern *i.e.*,[17] alternating contractile and quiescent states were confirmed at the gastric antral site in all dogs. All drugs and vehicle (5% lactic acid) were given 5—10 min after the termination of contractile state in the gastric antrum. The meal (100 kcal) was then given immediately. Gastric antral motility from the transducer was measured continuously with the measuring system and recorded and analyzed by means of a computer system (ESC-820: Star Medical). Mean gastric antral motility was quantified at 12 sequential 15-min intervals after administration. The results of motility changes observed were expressed as percent contraction of phase III, during which maximum contractions (100%) occurred. Statistical analysis of the data was performed by Dunnett multiple range test.

All experiments were performed according to the regulations of the animal ethical committee of Taisho Pharmaceutical.

References and Notes

1) Lanfumey L., Hamon M., *Actual. Chim. Ther.*, **22**, 115—126 (1996).
2) Grailhe R., Boschert U., Hen R., *Pharmacochem. Libr.*, **27**, 311—323 (1997).
3) Dumuis A., Bouhelal R., Sebben M., Cory R., Bockaert J., *Mol. Pharmacol.*, **34**, 880—887 (1988).
4) McCallum R. W., Prakash C., Campoli-Richards D. M., Goa K. L., *Drugs*, **36**, 652—681 (1988).
5) Bermudez J., Dunbar A., Sanger G. J., Turner D. H., *J. Gastrointestinal Motility*, **2**, 281—286 (1990).
6) Song C. W., Lee K. Y., Kim C. D., Chang T-M., Chey W. Y., *J. Pharmacol. Exp. Ther.*, **281**, 1312—1316 (1997).
7) Suzuki M., Kaneko T., Yokomori S., Ito C., Isobe Y., Ohtsuki H., Kawamura R., Ohuchi Y., Fukushima H., Asanuma H., Muramatsu M., The 119th Annual Meeting of the Pharmaceutical Society of Japan, Abstracts, No. 2, p. 181.
8) Schellenberg K. A., *J. Org. Chem.*, **28**, 3259—3261 (1963).
9) Archer S., Lewis T. R., Unser M. J., *J. Am. Chem. Soc.*, **79**, 4194—4198 (1957).
10) Olofson R. A., Martz J. T., *J. Org. Chem.*, **49**, 2081—2082 (1984).
11) Chou T., Cheng W., *Bull. Inst. Chem. Acad. Sin.*, **29**, 9—14, (1982).
12) 8′-Ethyl (activity=51.5±6.1), 8′-*n*-propyl (activity=61.8±7.0, ED_{50}=36.5 nM), 8′-*n*-butyl (activity=52.1±8.6), 8′-*n*-pentyl (activity=28.5±2.1). Activity (%)=compound 100 nM/5-HT 100 nM.
13) Kajita S., Ito C., Kawamura R., Yasuda S., Isobe Y., Fukushima S., *Pharmacology*, in press.
14) Tsuyuki Y., Saitoh M., Muramatsu M., *Life Sci.*, **59**, 2129—2137 (1996).
15) Kato S., Morie T., Kon T., Yoshida N., Karasawa T., Matsumoto J., *J. Med. Chem.*, **34**, 616—624 (1991).
16) Schaus J. M., Thompson D. C., Bloomquist W. E., Susemichel A. D., Calligaro D. O., Cohen M. L., *J. Med. Chem.*, **41**, 1943—1955 (1998).
17) Itoh Z., Honda R., Takeuchi S., Aizawa I., Takayanagi R., *Gastroenterol. Jpn.*, **12**, 275—283 (1977).