5-HT_3 Receptor Antagonists. 1. New Quinoline Derivatives

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A series of esters and amides of 1-alkyl-2-oxo-1,2-dihydroquinoline-4-carboxylic acid or 2-alkoxyquinoline-4-carboxylic acid containing a basic azabicycloalkyl moiety has been synthesized and evaluated for affinity for the [^{3}H]quipazine-labeled 5-HT_3 receptors. Most of the esters exhibited 10-fold more potent activity than that of ondansetron (**1**; K_i = 7.6 nM). Lipophilic substituents at the 1- or 2-position of the quinoline ring enhanced affinity for the receptors. Compounds **21** and **37** showed the highest affinity (K_i = 0.32 and 0.31 nM, respectively) among them. On the other hand, most of the amides showed 100-fold lower affinity than that of the esters. Molecular modeling studies indicated that the carbonyl moiety in **19** (ester) or **31** (amide) was not coplanar to the plane of an aromatic ring (over 20° deviation). Although some of the selected compounds exhibited potent activity in the Bezold-Jarisch (B-J) reflex test, good correlation was not observed betwen the affinity for the 5-HT_3 receptors and the activity in the B-J reflex test (in vivo). From these data, it was suggested that our quinoline derivatives might interact with the 5-HT_3 receptors in a different way from that of the reported 5-HT_3 receptor antagonists presumably due to the presence of the heterogeneity of the 5-HT_3 receptors between brain and heart.

Introduction

The heterogeneity of serotonin (5-HT) receptors has been recognized since 1957,[1] and currently four broad classes of 5-HT receptors are characterized (5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_4).[2-5] The 5-HT_3 receptor has attracted considerable attention recently, and our understanding of this receptor has increased dramatically over the past few years because of the discovery and widespread availability of its potent and selective antagonists.[6] These antagonists include ondansetron (**1**),[7] granisetron (**2**),[8] ICS 205-930 (**3**),[9] MDL 72222 (**4**),[10] and zacopride (**5**)[11] and have been shown to be effective in the control of cancer chemotherapy-induced emesis,[12,13] an event suggested to be modulated by the 5-HT_3 receptors in the area postrema.[14] In addition, evidence has been presented for the therapeutic roles of the 5-HT_3 receptor antagonists in migraine,[15] schizophrenia,[16] and anxiety.[17]

Drug Design

The selective 5-HT_3 receptor antagonists reported to date may be represented by the general structure **7**, in which an aromatic group is linked by a carbonyl-containing moiety to a basic amine. This simple model can be further refined by consideration of the three-dimensional pharmacophore. A carbonyl group is coplanar to an aromatic group, and interatomic distances in the 5-HT_3 receptor antagonist pharmacophore are in adequate ranges (O in a carbonyl group–an aromatic center, ca. 3-4 Å; O in a carbonyl group–N in a basic center, ca. 5 Å; N in a basic center–an aromatic center, ca. 7-8 Å).[18-21]

Although indole derivatives (e.g., **1-3**) or benzene derivatives (e.g., **4** and **5**) have been popular as an aromatic

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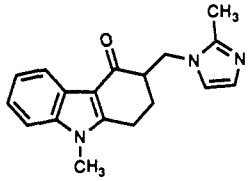
group, we focused on a quinoline ring in which a five-membered pyrrole ring in indole was replaced by a six-membered pyridine ring. A quinoline ring can be considered as a bioisostere of an indole ring, and even by this replacement a basic center can still occupy the appropriate position from an aromatic group. Furthermore, a quinoline ring can be seen also in quipazine (**6**), which is known to bind to the 5-HT_3 receptors with high affinity.[22] On the other hand, a lipophilic group such as the methyl group is located on the indole ring and indazole ring in **1** and **2**. Thus, a lipophilic substituent was introduced at the 1- or 2-position of the quinoline ring. As a basic amine, an azabicycloalkyl group was chosen as in most of the 5-HT_3 receptor antagonists (e.g., **2–5**). In this paper, we report the synthesis and the 5-HT_3 receptor antagonistic activity of a series of quinoline derivatives. Conformational properties are also discussed in relation to a pharmacophore recently proposed for the 5-HT_3 receptor antagonists.[18-21]



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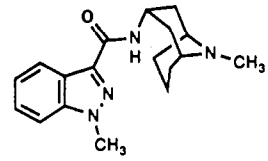

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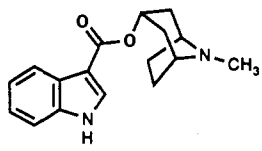

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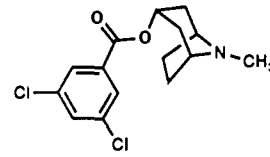

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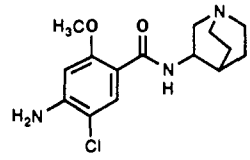

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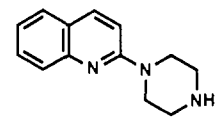

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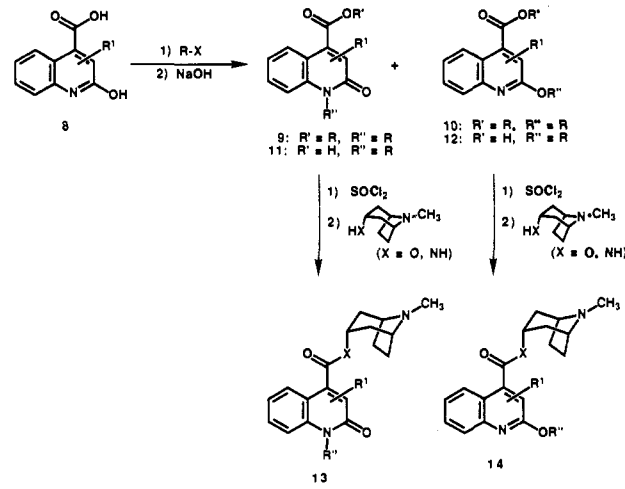
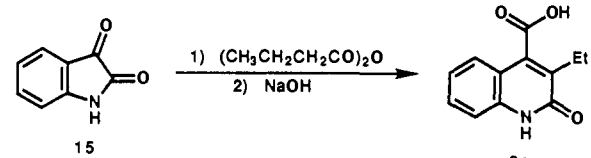
Chemistry

The general procedure for the preparation of target compounds is shown in Scheme I. Reaction of 2-hydroxy-4-quinolinecarboxylic acid (**8**) with alkyl halides afforded *N*-alkylated 2-oxo-1,2-dihydroquinolinecarboxylates **9** and *O*-alkylated quinolinecarboxylates **10**. These were hydrolyzed with an aqueous NaOH solution to afford carboxylic acids **11** and **12**, respectively. Then, **11** and **12** were treated with $SOCl_2$, followed by reaction with tropine or *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-ylamine[23] to afford target compounds **13** and **14**. When R^1 is 3-Et or 6-Me, the starting carboxylic acids **8a** and **8b** were prepared from the corresponding isatin derivatives **15** and **16** by acylation followed by treatment with an aqueous NaOH solution (Schemes II and III, respectively). 1-Phenyl-substituted compound **9b** (R = Ph, R^1 = H) was alternatively prepared according to the reported procedure.[24] 2-Oxo-1,2,3,4-tetrahydroquinolinecarboxylic acid **17** was obtained by reduction of 1-(*n*-butyl)-4-(*n*-butyloxycarbonyl)-2-oxo-1,2-dihydroquinoline (**9a**) with $LiBH_4$ followed by hydrolysis (Scheme IV). Compounds **49–51** were synthesized in a manner similar to that in Scheme I from the corresponding carboxylic acids and tropine or *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-ylamine.[23] All compounds are shown in Tables I–III.

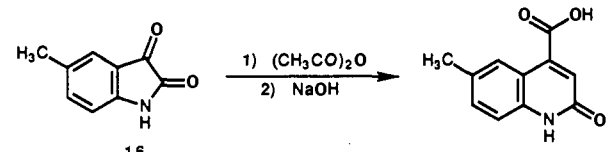
Scheme I



Scheme II



Scheme III



Scheme IV

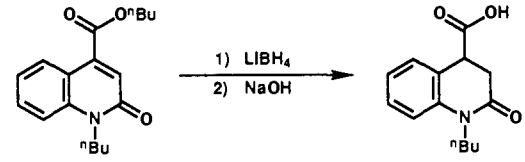


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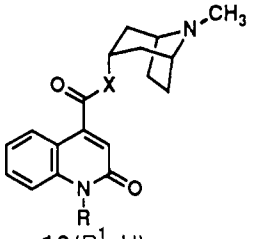
Table I. *N*-Alkyl Type

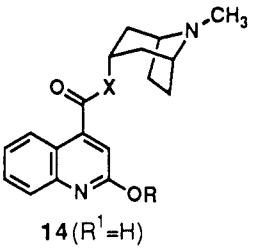


13 (R^1=H)

compd	R	X	yield, %	mp, °C	formula	anal.[a]
18	H	O	6	303.0–306.0	$C_{18}H_{20}N_2O_3$·HCl·0.6H_2O	C,H,N[c]
19	CH_3	O	18	279.0–282.0	$C_{19}H_{22}N_2O_3$·HCl·1.3H_2O	C,H,N
20	CH_3CH_2	O	14	230.0–232.0	$C_{20}H_{24}N_2O_3$·HCl·1.5H_2O	C,H,N
21	$(CH_3)_2CH$	O	37	244.0–244.5	$C_{21}H_{26}N_2O_3$·HCl·H_2O	C,H,N
22	$CH_3(CH_2)_2$	O	48	273.0–274.5	$C_{21}H_{26}N_2O_3$·HCl·0.5H_2O	C,H,N
23	$(CH_3)_2CHCH_2$	O	29	262.0–263.5	$C_{22}H_{28}N_2O_3$·HCl·0.5H_2O	C,H,N
24	$CH_3(CH_2)_3$	O	38	80–86	$C_{22}H_{28}N_2O_3$·0.5HCl·1.8H_2O	C,H,N
25	$(CH_3)_2CH(CH_2)_2$	O	28	68.5–69.0	$C_{23}H_{30}N_2O_3$·HCl·1.5H_2O	C,H,N
26	$CH_3(CH_2)_4$	O	56	72.0–75.0	$C_{23}H_{30}N_2O_3$·HCl·1.7H_2O	C,H,N
27	$CH_3(CH_2)_5$	O	42	146.5–147.5	$C_{24}H_{32}N_2O_3$·HCl·H_2O	C,H,N
28	$C_6H_5CH_2$	O	14	115.5–117.0	$C_{25}H_{26}N_2O_3$·HCl·4H_2O	C,H,N
29	C_6H_5	O	27	128.5–129.5	$C_{24}H_{24}N_2O_3$·HCl·2H_2O	C,H,N
30	H	NH	23	231.8–235.2	$C_{18}H_{21}N_3O_2$·$C_4H_4O_4$[b]·H_2O	C,H,N
31	CH_3	NH	23	254.5–255.5	$C_{19}H_{23}N_3O_2$·$C_4H_4O_4$[b]	C,H,N[d]
32	$CH_3(CH_2)_2$	NH	22	239.7–242.2	$C_{21}H_{27}N_3O_2$·$C_4H_4O_4$[b]·0.3H_2O	C,H,N
33	$CH_3(CH_2)_3$	NH	36	217.8–219.0	$C_{22}H_{29}N_3O_2$·$C_4H_4O_4$[b]	C,H,N
34	C_6H_5	NH	51	251.2–256.2	$C_{24}H_{25}N_3O_2$·$C_4H_4O_4$[b]	C,H,N[e]

[a] Analyses for the elements indicated were within ±0.4% of the theoretical values. [b] $C_4H_4O_4$, fumaric acid. [c] N: calcd, 7.79; found, 8.33. [d] C: calcd, 62.57; found, 61.14. N: calcd, 9.52; found, 10.53. [e] C: calcd, 66.79; found, 65.96. H: calcd, 5.80; found, 6.42.

Table II. *O*-Alkyl Type



14 (R^1=H)

compd	R	X	yield, %	mp, °C	formula	anal.[a]
35	CH_3	O	35	198.0–200.5	$C_{19}H_{22}N_2O_3$·0.5$C_4H_4O_4$[b]·H_2O	C,H,N
36	CH_3CH_2	O	16	103.0–103.5	$C_{20}H_{24}N_2O_3$·$C_4H_4O_4$[b]·0.5H_2O	C,H,N
37	$(CH_3)_2CH$	O	30	160.5–161.0	$C_{21}H_{26}N_2O_3$·$C_4H_4O_4$[b]·0.3H_2O	C,H,N
38	$CH_3(CH_2)_2$	O	15	154.0–162.0	$C_{21}H_{26}N_2O_3$·$C_4H_4O_4$[b]·0.5H_2O	C,H,N
39	$(CH_3)_2CHCH_2$	O	13	162.0–165.5	$C_{22}H_{28}N_2O_3$·1.5$C_4H_4O_4$[b]·0.5H_2O	C,H,N
40	$CH_3(CH_2)_3$	O	22	124.0	$C_{22}H_{28}N_2O_3$·$C_4H_4O_4$[b]·H_2O	C,H,N
41	$CH_3(CH_2)_4$	O	8	156.0–160.0	$C_{23}H_{30}N_2O_3$·1.5$C_4H_4O_4$[b]·0.5H_2O	C,H,N
42	$CH_3(CH_2)_5$	O	7	168.5–169.0	$C_{24}H_{32}N_2O_3$·$C_4H_4O_4$[b]·0.5H_2O	C,H,N
43	$(CH_3)_2CH$	NH	13	122.7–127.5	$C_{21}H_{27}N_3O_2$·$C_4H_4O_4$[b]·1.5H_2O	C,H,N
44	$CH_3(CH_2)_2$	NH	30	189.8–191.3	$C_{21}H_{27}N_3O_2$·$C_4H_4O_4$[b]	C,H,N[c]
45	$CH_3(CH_2)_3$	NH	20	196.8–198.1	$C_{22}H_{29}N_3O_2$·$C_4H_4O_4$[b]	C,H,N

[a,b] See footnotes *a* and *b* in Table I. [c] C: calcd, 63.95; found, 63.43. N: calcd, 8.95; found, 9.53.

Results and Discussion

The neuroblastoma–glioma NG 108-15 cells are known to express the 5-HT$_3$ receptors characterized by [^{3}H]ICS 205-930 binding assay.[25] The 5-HT$_3$ receptors labeled by [^{3}H]quipazine in the above cells were reported to be similar to those labeled by the selective 5-HT$_3$ receptor antagonist, [^{3}H]GR 65630.[26] Thus, compounds 18–51 were evaluated for 5-HT$_3$ receptor binding affinity versus [^{3}H]quipazine in NG 108-15 cells[25,27] (Tables IV and V).

Most of the esters containing a tropine moiety, (**18–29, 35–42**), inhibited potently [^{3}H]quipazine binding (K_i; 10^{-9} to 10^{-10} M order). Among them, **21–24, 26, 29** (*N*-alkyl type at the 1-position; R = *i*-Pr, *n*-Pr, *i*-Bu, *n*-Bu, *n*-Pen, and Ph, respectively), and **35–41** (*O*-alkyl type at the 2-position; R = Me, Et, *i*-Pr, *n*-Pr, *i*-Bu, *n*-Bu, and *n*-Pen, respectively) showed about 3- to 20-fold higher affinity for the 5-HT$_3$ receptors (K_i; 10^{-10} M order) than that of ondansetron (**1**; K_i = 7.6 nM) or granisetron (**2**; K_i = 2.1 nM). Either in the *N*-alkyl type or the *O*-alkyl type, the

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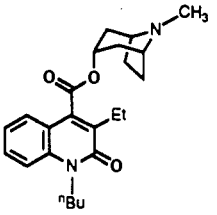
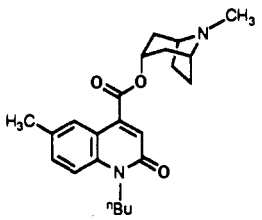
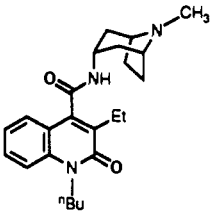
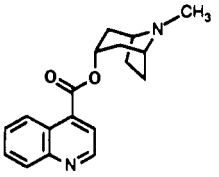
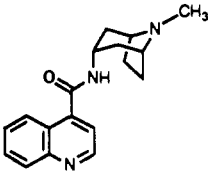
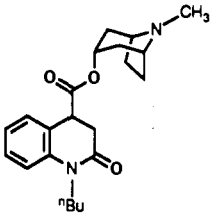
Table III. Other Compounds

compd	structure	yield, %	mp, °C	formula	anal.[a]
46		45	128.0–129.0	$C_{24}H_{32}N_2O_3 \cdot HCl \cdot 1.8H_2O$	C,H,N
47		12	121.5–122.0	$C_{23}H_{30}N_2O_3 \cdot HCl \cdot 2H_2O$	C,H,N
48		46	155.9–158.8	$C_{24}H_{33}N_3O_2 \cdot C_4H_4O_4{}^b \cdot 1.5H_2O$	C,H,N
49		40	178.5–180.0	$C_{18}H_{20}N_2O_2 \cdot 2HCl \cdot H_2O$	C,H,N[c]
50		44	261–262	$C_{18}H_{21}N_3O \cdot C_4H_4O_4{}^b \cdot 0.5H_2O$	C,H,N
51		9	hygroscopic	$C_{22}H_{30}N_2O_3 \cdot HCl \cdot 2.2H_2O$	C,H,N

[a,b] See foonotes *a* and *b* in Table I. [c] N: calcd, 7.23; found, 8.03.

highest affinity was observed when R was *i*-Pr (**21**; K_i = 0.32 nM and **37**; K_i = 0.31 nM) and affinity reduced when the length of an alkyl chain became shorter or longer.

In indolizine derivatives,[28] indole derivatives,[29] or indoline derivatives,[30] introduction of a methyl group or an ethyl group into the 1-position was appropriate for the potent activity. A quinoline derivative **49**, unsubstituted at the 1- and 2-position, showed lower affinity for the 5-HT_3 receptors than that of the corresponding 2-oxo-1,2-dihydroquinoline derivative **18**. Introduction of an ethyl group at the 3-position of **24** reduced affinity (compare **46** with **24**). 6-Methyl substitution also led to the reduction of affinity (**47**). Similar results have been previously reported for indazole derivatives[28] or imidazolone derivatives,[30] in which introduction of any substituents on the benzene ring, except for fluorine (a small substituent), resulted in the reduction of activity.

A 1,2,3,4-tetrahydroquinoline derivative **51**, where the planarity of the area consisting of an aromatic ring and a carbonyl moiety was impaired by sp^3-carbons at the 3- and 4-position of the ring, exhibited relatively low affinity for the 5-HT_3 receptors (K_i = 8.7 nM).

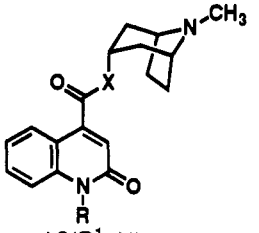
From these structure–activity relationships, the quinoline derivatives seem to interact with the 5-HT_3 receptors in a manner similar to that of the indole or indazole derivatives such as **2** or **3**. However, the amides, either an *N*-alkyl type (**30–34**) or an *O*-alkyl type (**43–45, 48**), showed

(28) Bermudez, J.; Fake, C. S.; Joiner, G. F.; Joiner, K. A.; King, F. D.; Miner, W. D.; Sanger, G. J. 5-Hydroxytryptamine (5-HT_3) Receptor Antagonists. 1. Indazole and Indolizine-3-carboxylic Acid Derivatives. *J. Med. Chem.* **1990**, *33*, 1924–1929.

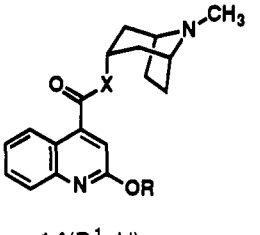
(29) Bermudez, J.; Dabbs, S.; Joiner, K. A.; King, F. D. 5-Hydroxytryptamine (5-HT_3) Receptor Antagonists. 2. 1-Indolinecarboxamides. *J. Med. Chem.* **1990**, *33*, 1929–1932.

(30) Turconi, M.; Nicola, M.; Quintero, M. G.; Maiocchi, L.; Micheletti, R.; Giraldo, E.; Donetti, A. Synthesis of a New Class of 2,3-Dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic Acid Derivatives as Highly Potent 5-HT_3 Receptor Antagonists. *J. Med. Chem.* **1990**, *33*, 2101–2108.

Table IV. 5-HT$_3$ Receptor Binding Affinity and Antagonism of Benzold–Jarisch Reflex (1)



13(R^1=H)



14(R^1=H)

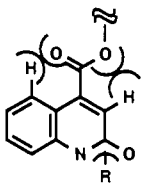
compd	R(13)	R(14)	X	5-HT$_3$ receptor binding affinity:[a] K_i,[b] nM	inhibition of B-J reflex: ED_{50}[c] (mg/kg, iv) at 5 min
18	H		O	4.4 ± 0.09	0.017
19	CH_3		O	2.6 ± 0.20	0.18
20	CH_3CH_2		O	1.1 ± 0.07	0.022
21	$(CH_3)_2CH$		O	0.32 ± 0.045	0.081
22	$CH_3(CH_2)_2$		O	0.45 ± 0.009	0.33
23	$(CH_3)_2CHCH_2$		O	0.47 ± 0.021	0.069
24	$CH_3(CH_2)_3$		O	0.68 ± 0.036	0.041
25	$(CH_3)_2CH(CH_2)_2$		O	1.5 ± 0.0	0.059
26	$CH_3(CH_2)_4$		O	0.96 ± 0.09	0.059
27	$CH_3(CH_2)_5$		O	1.1 ± 0.07	NT[d]
28	$C_6H_5CH_2$		O	1.3 ± 0.05	NT
29	C_6H_5		O	0.51 ± 0.012	0.044
30	H		NH	>100	NT
31	CH_3		NH	>100	NT
32	$CH_3(CH_2)_2$		NH	67 ± 16	NT
33	$CH_3(CH_2)_3$		NH	60 ± 4.9	NT
34	C_6H_4		NH	63 ± 9	NT
35		CH_3	O	0.58 ± 0.015	5.64
36		CH_3CH_2	O	0.88 ± 0.025	0.070
37		$(CH_3)_2CH$	O	0.31 ± 0.021	1.62
38		$CH_3(CH_2)_2$	O	0.32 ± 0.006	6.78
39		$(CH_3)_2CHCH_2$	O	0.44 ± 0.064	0.24
40		$CH_3(CH_2)_3$	O	0.39 ± 0.020	0.20
41		$CH_3(CH_2)_4$	O	0.86 ± 0.10	1.13
42		$CH_3(CH_2)_5$	O	3.2 ± 0.26	7.68
43		$(CH_3)_2CH$	NH	53 ± 19	NT
44		$CH_3(CH_2)_2$	NH	42 ± 11	NT
45		$CH_3(CH_2)_3$	NH	19 ± 2.5	NT
1 (ondansetron)				7.6 ± 0.59	0.021
2 (granisetron)				2.1 ± 0.26	0.019

[a] [^{3}H]Quipazine-labeled 5-HT$_3$ receptor sites in NG108-15. [b] K_i value was determined as described in the Experimental Section. Results are expressed as mean values ± SEM after individual measurement (no. of determinations is three). [c] ED_{50}, i.e. the dose of antagonists causing 50% reduction of serotonin effect was calculated by linear-regression analysis (no. of rats is four). [d] Not tested.

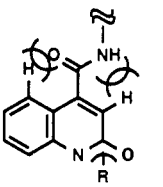
100-fold lower affinity for the 5-HT$_3$ receptors than the esters (**18–29, 35–42, 46**). This result is greatly contrasting to that of indazole derivatives where the esters are equipotent to or slightly less potent than the amides.[28]

It seems, therefore, that the amides might not be coplanar to the quinoline ring more than the esters, since a NH group in the amide group is expected to be bulkier than oxygen in the ester group (compare **52** with **53**). In quinoline derivatives such as **52** and **53**, there are some strong steric interactions between the ester or amide group and the proton at the 3- or 5-position compared with those in indole and indazole derivatives. Consequently, affinity of the amides for the 5-HT$_3$ receptors might be reduced. Recently, many papers[18–21] described the important factors for high affinity for the 5-HT$_3$ receptors, one of which is the coplanarity between an aromatic ring and a carbonyl moiety.

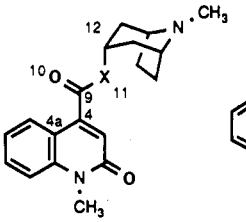
Thus, studies on such structural properties for 5-HT$_3$ receptor antagonists **19**, **31**, **54**, and **55**, the latter two compounds of which are known to be potent 5-HT$_3$ receptor antagonists, were performed on an IRIS 4D/310 GTXB workstation with QUANTA 3.2/CHARMm 21.3.[31] A



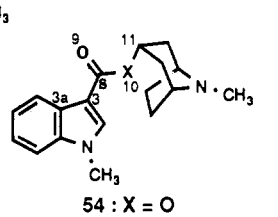
52



53



19 : X = O
31 : X = NH



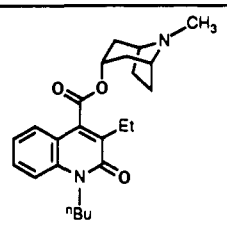
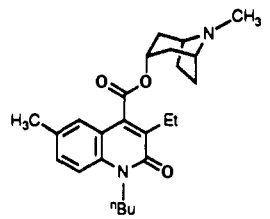
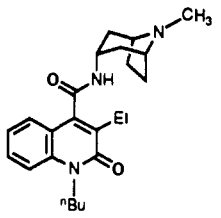
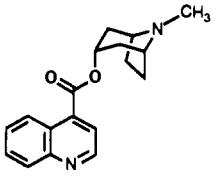
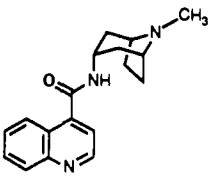
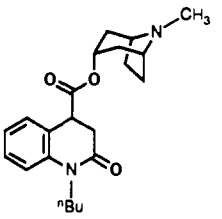
54 : X = O
55 : X = NH

crystal structure of granisetron (**2**)[32] was retrieved from the Cambridge Structural Database[33] and modified with

(31) QUANTA/CHARMm, Polygen Corp., 200 Fifth Ave., Waltham, MA 02254. (1986, 1987, 1988, 1991).

(32) Fludzinski, P.; Evrard, D. A.; Bloomquist, W. E.; Lacefield, W. B.; Pfeifer, W.; Jones, N. D.; Deeter, J. B.; Cohen, M. L. Indazoles as Indole Bioisosteres: Synthesis and Evaluation of the Tropanyl Ester and Amide of Indazole-3-carboxylate as Antagonists at the Serotonin 5HT$_3$ Receptor. *J. Med. Chem.* **1987**, *30*, 1535–1537.

Table V. 5-HT_3 Receptor Binding Affinity and Antagonism of Bezold–Jarisch Reflex (2)

compd	structure	5-HT_3 receptor binding affinity:[a] K_i,[b] nM	inhibition of B-J reflex: Ed_{50}[c] (mg/kg, iv) at 5 min
46		160 ± 19	NT[d]
47		44 ± 3.8	NT
48		>100	NT
49		7.1 ± 1.1	NT
50		>100	NT
51		8.7 ± 1.9	NT
1 (ondansetron)		7.6 ± 0.59	0.021
2 (granisetron)		2.1 ± 0.26	0.019

[a–d] See footnotes *a–d* in Table IV.

standard bond angles and lengths for our compounds. Global energy minima were determined by performing a conformational search about rotatable bonds at increments of 30° [C(8)–O(10) or C(8)–N(10), and O(10)–C(11) or N(10)–C(11)] and 20° [C(3)–C(8)] for indoles and 30° [C(9)–O(11) or C(9)–N(11), and O(11)–C(12) or N(11)–C(12)] and 20° [C(4)–C(9)] for quinolines. The lowest-energy conformation was then minimized using Adopted-basis Newton–Paphson technique[34,35] (nonbonded parameter cutoff = 15 Å).

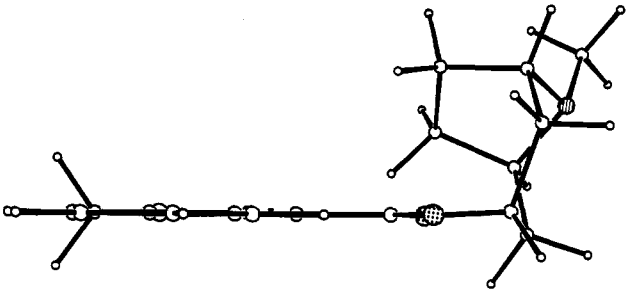


Figure 1. The energetic minimum of **54** viewed along the aromatic plane.

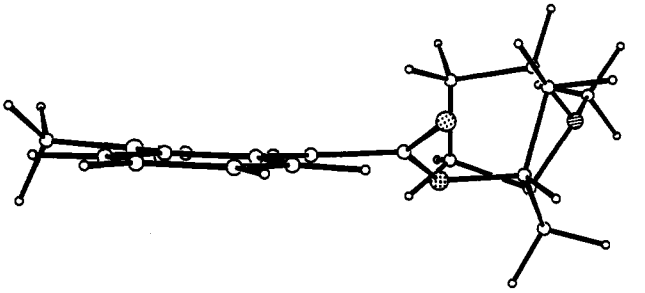


Figure 2. The energetic minimum of **19** viewed along the aromatic plane.

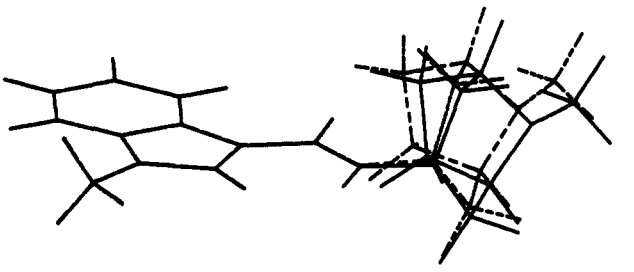


Figure 3. Superimposition of **54** (dotted line) and **55** (solid line) in the minimum-energy conformation.

The dihedral angle of C(3a)–C(3)–C(8)–O(10) in the minimum-energy conformer of **54** was calculated to be 178.8° (Figure 1) and the corresponding angle of **55** to be 178.3°. Since both of these dihedral angles were not so much deviated from 180°, the coplanarity between the aromatic ring and the carbonyl moiety was confirmed to be important for 5-HT_3 receptor binding affinity as described before.[18–21] On the other hand, the dihedral angle of C(4a)–C(4)–C(9)–O(11) in the minimum-energy conformer of **19** (ester) has been calculated to be 156.0° (Figure 2) and the corresponding angle of **31** (amide) to be 149.2°. This result is greatly surprising because the carbonyl moiety was estimated to be over 20° deviated from the plane of an aromatic ring. Superimposition of **54** and **55**, or **19** and **31** in the minimum-energy conformation is shown in Figures 3 and 4, and superimposition of **19** and **54** with the tropine moieties fitted together is shown in Figure 5. However, the energy difference between the coplanar conformation, which is not a stable one, and the minimum-energy conformation of **19** was calculated to be ca. 0.5 kcal. Thus, the molecules might easily

(33) Allen, F. H.; Bellard, S.; Brice, M. D.; Cartwright, B. A.; Doubleday, A.; Higgs, H.; Hummelink, T.; Hummelink-Peters, B. G.; Kennard, O.; Motherwell, W. D.; Rodgers, R. J.; Watson, G. D. The Cambridge Crystallographic Data Centre: Computer-based Search, Retrieval, Analysis and Display of Information. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1979**, *B35*, 2331–2339.

(34) Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M. CHARMM: A Program for Macromolecular Energy, Minimization, and Dynamics Calculations. *J. Comput. Chem.* **1983**, *4*, 187–217.

(35) Karplus, M.; McCammon, J. A. Dynamics of Proteins: Elements and Function. *Annu. Rev. Biochem.* **1983**, *52*, 263–300.

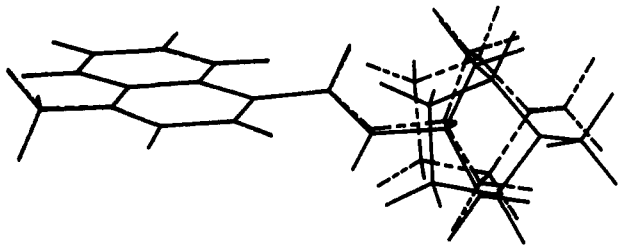


Figure 4. Superimposition of 19 (dotted line) and 31 (solid line) in the minimum-energy conformation.

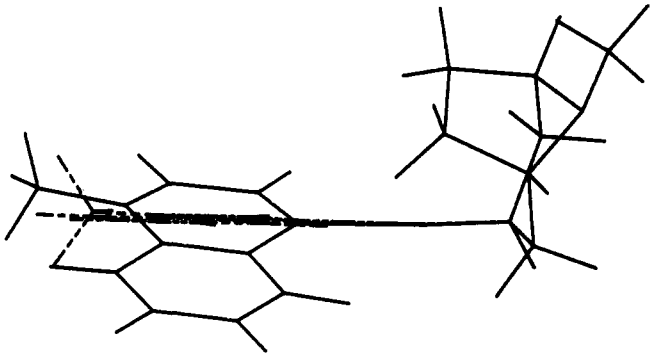


Figure 5. Superimposition of 19 (dotted line) and 54 (solid line) with the tropine moieties fitted together in the minimum-energy conformation.

populate the planar conformation during their interactions with the 5-HT$_3$ receptors. The interatomic distances (O in a carbonyl group–an aromatic center; O in a carbonyl group–N in a basic center; N in a basic center–an aromatic center) in these compounds were similar to the reported values (data not shown). Therefore, the big difference between receptor affinities of 19 (ester) and 31 (amide) might not be explained by their small difference in dihedral angles and suggests that the bioactive conformation of these quinoline derivatives might be different from that of the reported 5-HT$_3$ receptor antagonists.

With respect to the selected compounds, 5-HT$_3$ receptor antagonistic activity in vivo was examined by their ability to inhibit the 5-HT induced bradycardia [Bezold–Jarisch (B-J) reflex test[36]] in rats (Table IV). This effect (B-J reflex) is known to be mediated by reflex stimulation of the vagus nerve following activation of the sensory nerve located in the wall of the right ventricle.[37] In this test, generally, an *N*-alkyl type of compounds exhibited potent activity, and activity of compounds **18**, **22**, **24**, and **29** were comparable to that of ondansetron or granisetron. On the contrary, an *O*-alkyl type of compounds showed less potent activity except for compound **36** (compare **35**, **37**, **38**, **39**, **40**, and **41** with **19**, **21**, **22**, **23**, **24**, and **26**, respectively). Since these compounds were stable at pH 7 (buffer) for several hours, this result associated with an *O*-alkyl type of compounds was surprising. Compounds **21**, **37**, and **38**, which showed the highest affinity for the 5-HT$_3$ receptors, were less potent than ondansetron or granisetron in the B-J reflex test. On the other hand, compound **18** showed 10-fold lower affinity for the 5-HT$_3$ receptors than those of **21**, **37**, and **38**, but exhibited the equipotent activity with those of ondansetron or granisetron in the B-J reflex test.

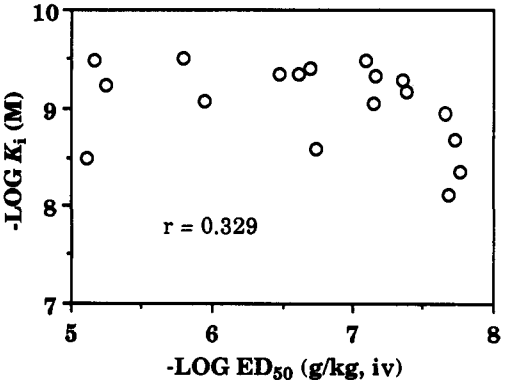


Figure 6. Correlation between the binding affinities (–log K_i) and the activities in the Bezoled–Jarisch reflex test (–log ED_{50}).

These data indicate that activity in the B-J reflex test did not have good correlation with the K_i values in the 5-HT$_3$ receptor binding test (Figure 6). Unlike the 5-HT$_3$ antagonists of Nagel et al.,[38] intravenous injection of our compounds did not have the property of inducing a transient bradycardia when examined in the B-J reflex test before injection of serotonin. Thus, they are not partial agonists at the 5-HT$_3$ receptors. These results also suggest that our compounds interact with the 5-HT$_3$ receptors in a different way from that of the reported 5-HT$_3$ antagonists and that the heterogeneity of the 5-HT$_3$ receptors between brain and heart might be present.[39] Pharmacokinetic, mechanistic, and detailed molecular modeling studies about these compounds are in progress.

In conclusion, we have described a series of 5-HT$_3$ receptor antagonists, quinolinecarboxylic acid esters and amides containing an azabicycloalkyl moiety. Molecular modeling studies and pharmacological studies suggest that our quinoline derivatives might interact with the 5-HT$_3$ receptors in a different way from that of the reported 5-HT$_3$ antagonists presumably due to the presence of the heterogeneity of the 5-HT$_3$ receptors between brain and heart.

Experimental Section

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a JEOL JNM GX-270 FT NMR or a Hitachi R-90H FT NMR spectrometer with Me_4Si as an internal standard and mass spectra on a JMS-SX102 instrument. Melting points were determined with a Büchi-510 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a JASCO IR-810 spectrometer. Elemental analyses were performed by the analytical department of our laboratories. Most of the compounds were very hygroscopic and some were analyzed by high resolution mass spectra (JMS-SX 102).

Chemistry. The following procedures are representatives of the general methods that are described in the text.

1-(*n*-Butyl)-2-oxo-1,2-dihydro-4-quinolinecarboxylic Acid (11a) and 2-(*n*-Butyloxy)-4-quinolinecarboxylic Acid (12a). To a suspension of NaH (1.39 g, 57.9 mmol) in DMF (120 mL) was added portionwise 2-hydroxy-4-quinolinecarboxylic acid (**8c**; 5.00 g, 26.4 mmol) with stirring. Then, a solution of *n*-butyl iodide (10.7 g, 58.0 mmol) in DMF (70 mL) was dropwise added

(36) Dunbar, A. W.; McClelland, C. M.; Sanger, G. J. BRL 24924: A Stimulant of Gut Motility Which is Also a Potent Antagonist of the Bezold-Jarisch Reflex in Anesthetised Rats. *Br. J. Pharmacol.* **1986**, *88*, 319P.
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with stirring under ice cooling. The mixture was stirred at room temperature for 1 day further. After the reaction was completed, an aqueous saturated $NaHCO_3$ solution was added to the mixture followed by extraction with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography with hexane–EtOAc (7:1) as eluent to give 2-(*n*-butyloxy)-4-(*n*-butyloxycarbonyl)-1,2-dihydroquinoline (**10a**; 2.68 g, 34%) from the first fraction and 1-(*n*-butyl)-4-(*n*-butyloxycarbonyl)-2-oxo-1,2-dihydroquinoline (**9a**; 2.05 g, 26%) from the second fraction. Compound **10a**: ^1H NMR ($CDCl_3$) δ 8.60 (d, 1 H, J = 8.1 Hz), 7.88 (d, 1 H, J = 8.1 Hz), 7.1–7.8 (m, 3 H), 4.2–4.8 (m, 4 H), 0.4–2.2 (m, 14 H) and compound **9a**: ^1H NMR ($CDCl_3$) δ 8.35 (d, 1 H, J = 8.1 Hz), 6.9–7.8 (m, 4 H), 3.9–4.7 (m, 4 H), 0.5–2.1 (m, 14 H). A mixture of compound **9a** (2.04 g, 6.77 mmol), NaOH (0.54 g, 13.50 mmol), H_2O (40 mL), and dioxane (40 mL) was stirred at room temperature for 30 min. After usual workup, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography with $CHCl_3$–MeOH (5:1) as eluent to give compound **11a** (1.44 g, 87%): ^1H NMR (DMSO-d_6) δ 8.31 (d, 1 H, J = 8.1 Hz), 7.30–7.75 (m, 2 H), 6.95–7.30 (m, 1 H), 6.61 (s, 1 H), 4.23 (t, 2 H, J = 7.0 Hz), 1.05–1.90 (m, 4 H), 0.93 (t, 3 H, J = 6.4 Hz). Similarly, compound **12a** was obtained (90%): ^1H NMR (DMSO-d_6) δ 8.67 (d, 1 H, J = 8.1 Hz), 6.95–7.85 (m, 4 H), 4.40 (t, 2 H, J = 6.1 Hz), 1.10–1.95 (m, 4 H), 0.94 (t, 3 H, J = 6.5 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 1-(*n*-Butyl)-2-oxo-1,2-dihydro-4-quinolinecarboxylate Hemihydrochloride (24).** A mixture of compound **11a** (5.00 g, 20.4 mmol) and $SOCl_2$ (40 mL) was refluxed for 30 min. Excess $SOCl_2$ was removed under reduced pressure, and anhydrous THF (80 mL) was added (solution A). 15% *n*-BuLi–hexane solution was added to the mixture of tropine (3.11 g, 22.0 mmol) and anhydrous THF (15 mL) at 0 °C followed by stirring for 15 min further. After concentration of the mixture under reduced pressure, anhydrous THF (20 mL) and solution A were dropwise added under an argon atmosphere. The mixture was stirred at 0 °C for 1 h. Then the solvent was evaporated under reduced pressure, and to the residue was added a small quantity of MeOH and H_2O followed by extraction with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography with $CHCl_3$–MeOH (10:1) as eluent. The product was dissolved in $CHCl_3$, and to this solution was added EtOAc saturated with HCl. The mixture was poured into cold Et_2O with stirring, and the precipitated crystals were collected by filtration and dried to give compound **24** as the hydrochloride (3.12 g, 38%): IR (KBr) 1727, 1650, 1584, 1447, 1228, 1025, 762 cm^{-1}; HRMS m/z 368.2127 (M^+), $C_{22}H_{28}N_2O_3$ requires 368.2100; ^1H NMR (DMSO-d_6) δ 8.21 (d, 1 H, J = 8.1 Hz), 7.60–7.81 (m, 2 H), 7.34 (m, 1 H), 7.05 (s, 1 H), 5.28 (m, 1 H), 4.28 (t, 2 H, J = 7.6 Hz), 3.88 (m, 2 H), 2.0–2.9 (m, 11 H), 1.62 (m, 2 H), 1.41 (m, 2 H), 0.94 (t, 3 H, J = 7.3 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2-oxo-1,2-dihydro-4-quinolinecarboxylate hydrochloride (18)**: IR (KBr) 1734, 1666, 1548, 1434, 1217, 1027, 788, 762 cm^{-1}; HRMS m/z 312.1477 (M^+), $C_{18}H_{20}N_2O_3$ requires 312.1474; ^1H NMR (DMSO-d_6) δ 12.16 (brs, 1 H), 10.88 (brs, 1 H), 8.16 (d, 1 H, J = 7.3 Hz), 7.58 (m, 1 H), 7.42 (d, 1 H, J = 7.6 Hz), 7.25 (m, 1 H), 6.96 (s, 1 H), 5.26 (m, 1 H), 3.89 (m, 2 H), 2.67 (s, 3 H), 1.95–2.90 (m, 8 H).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 1-methyl-2-oxo-1,2-dihydro-4-quinolinecarboxylate hydrochloride (19)**: IR (KBr) 1722, 1651, 1588, 1450, 1250, 1027, 780, 748 cm^{-1}; HRMS m/z 326.1627 (M^+), $C_{19}H_{22}N_2O_3$ requires 326.1630; ^1H NMR (DMSO-d_6) δ 10.93 (brs, 1 H), 8.21 (d, 1 H, J = 8.4 Hz), 7.72 (m, 1 H), 7.64 (d, 1 H, J = 8.7 Hz), 7.35 (m, 1 H), 7.06 (s, 1 H), 5.28 (m, 1 H), 3.89 (m, 2 H), 3.67 (s, 3 H), 2.67 (s, 3 H), 1.95–2.95 (m, 8 H).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 1-ethyl-2-oxo-1,2-dihydro-4-quinolinecarboxylate hydrochloride (20)**: IR (KBr) 1725, 1651, 1644, 1587, 1445, 1219, 1027, 789, 748 cm^{-1}; MS m/z 340 (M^+); ^1H NMR (DMSO-d_6) δ 10.97 (brs, 1 H), 8.21 (d, 1 H, J = 7.8 Hz), 7.60–7.80 (m, 2 H), 7.35 (m, 1 H), 7.05 (s, 1 H), 5.27 (m, 1 H), 4.33 (q, 2 H, J = 7.1 Hz), 3.89 (m, 2 H), 2.67 (d, 3 H, J = 5.1 Hz), 1.95–2.80 (m, 8 H), 1.24 (t, 3 H, J = 7.1 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 1-isopropyl-2-oxo-1,2-dihydro-4-quinolinecarboxylate hydrochloride (21)**: IR (KBr) 1727, 1651, 1590, 1445, 1218, 1026, 794, 762 cm^{-1}; MS m/z 354 (M^+); ^1H NMR (DMSO-d_6) δ 10.88 (brs, 1 H), 8.18 (d, 1 H, J = 8.2 Hz), 7.84 (d, 1 H, J = 8.8 Hz), 7.67 (m, 1 H), 7.32 (m, 1 H), 6.97 (s, 1 H), 5.36 (m, 1 H), 5.27 (m, 1 H), 3.89 (m, 2 H), 2.67 (s, 3 H), 1.95–2.90 (m, 8 H), 1.57 (d, 6 H, J = 6.8 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2-oxo-1-(*n*-propyl)-1,2-dihydro-4-quinolinecarboxylate hydrochloride (22)**: IR (KBr) 1720, 1657, 1590, 1451, 1241, 1288, 1021, 783, 747 cm^{-1}; MS m/z 354 (M^+); ^1H NMR (DMSO-d) δ 10.91 (brs, 1 H), 8.21 (d, 1 H, J = 8.3 Hz), 7.53–7.82 (m, 2 H), 7.34 (m, 1 H), 7.05 (s, 1 H), 5.28 (m, 1 H), 4.25 (t, 2 H, J = 7.7 Hz), 3.89 (m, 2 H), 2.67 (m, 3 H), 1.9–2.9 (m, 8 H), 1.67 (m, 2 H), 0.97 (t, 3 H, J = 7.4 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 1-isobutyl-2-oxo-1,2-dihydro-4-quinolinecarboxylate hydrochloride (23)**: IR (KBr) 1721, 1658, 1652, 1590, 1450, 1240, 1025, 787, 753 cm^{-1}; MS m/z 368 (M^+); ^1H NMR (DMSO-d_6) δ 10.85 (brs, 1 H), 8.21 (d, 1 H, J = 7.8 Hz), 7.60–7.80 (m, 2 H), 7.34 (m, 1 H), 7.06 (s, 1 H), 5.28 (m, 1 H), 4.19 (d, 2 H, J = 7.6 Hz), 3.89 (m, 2 H), 2.67 (d, 3 H, J = 4.6 Hz), 1.90–2.80 (m, 9 H), 0.92 (d, 6 H, J = 6.5 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 1-isopentyl-2-oxo-1,2-dihydro-4-quinolinecarboxylate hydrochloride (25)**: IR (KBr) 1724, 1658, 1651, 1592, 1453, 1251, 1078, 1023, 783, 746 cm^{-1}; MS m/z 382 (M^+); ^1H NMR (DMSO-d_6) δ 10.89 (brs, 1 H), 8.21 (d, 1 H, J = 8.1 Hz), 7.72 (m, 1 H), 7.60 (d, 1 H, J = 8.5 Hz), 7.34 (m, 1 H), 7.04 (s, 1 H), 5.28 (m, 1 H), 4.30 (t, 2 H, J = 7.8 Hz), 3.87 (m, 2 H), 2.68 (s, 3 H), 2.00–2.85 (m, 8 H), 1.74 (m, 1 H), 1.51 (m, 2 H), 0.98 (d, 6 H, J = 6.6 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2-oxo-1-(*n*-pentyl)-1,2-dihydro-4-quinolinecarboxylate hydrochloride (26)**: IR (KBr) 1723, 1658, 1651, 1592, 1452, 1246, 1225, 1023, 782, 745 cm^{-1}; HRMS m/z 382.2249 (M^+), $C_{23}H_{30}N_2O_3$ requires 382.2256; ^1H NMR (DMSO-d_6) δ 10.82 (brs, 1 H), 8.21 (d, 1 H, J = 8.2 Hz), 7.60–7.80 (m, 2 H), 7.34 (m, 1 H), 7.05 (s, 1 H), 5.28 (m, 1 H), 4.27 (t, 2 H, J = 7.6 Hz), 3.89 (m, 2 H), 2.67 (d, 3 H, J = 5.1 Hz), 2.00–2.80 (m, 8 H), 1.64 (m, 2 H), 1.20–1.50 (m, 4 H), 0.88 (t, 3 H, J = 7.0 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 1-(*n*-hexyl)-2-oxo-1,2-dihydro-4-quinolinecarboxylate hydrochloride (27)**: IR (KBr) 1722, 1658, 1649, 1589, 1454, 1239, 1227, 1023, 784 cm^{-1}; MS m/z 396 (M^+); ^1H NMR (DMSO-d_6) δ 10.90 (brs, 1 H), 8.21 (d, 1 H, J = 8.1 Hz), 7.55–7.80 (m, 2 H), 7.34 (m, 1 H), 7.05 (s, 1 H), 5.27 (m, 1 H), 4.27 (t, 2 H, J = 7.7 Hz), 3.89 (m, 2 H), 2.67 (d, 3 H, J = 4.9 Hz), 1.95–2.80 (m, 8 H), 1.63 (m, 2 H), 1.10–1.50 (m, 6 H), 0.87 (t, 3 H, J = 7.1 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 1-benzyl-2-oxo-1,2-dihydro-4-quinolinecarboxylate hydrochloride (28)**: IR (KBr) 1728, 1658, 1594, 1454, 1261, 1212, 1022, 761, 727 cm^{-1}; HRMS m/z 402.1918 (M^+), $C_{25}H_{26}N_2O_3$ requires 402.1943; ^1H NMR (DMSO-d_6) δ 10.86 (brs, 1 H), 8.23 (d, 1 H, J = 8.3 Hz), 7.60 (m, 1 H), 7.49 (d, 1 H, J = 8.3 Hz), 7.10–7.45 (m, 6 H), 7.18 (s, 1 H), 5.57 (s, 2 H), 5.30 (m, 1 H), 3.90 (m, 2 H), 2.68 (d, 3 H, J = 5.1 Hz), 2.00–2.80 (m, 8 H).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2-oxo-1-phenyl-1,2-dihydro-4-quinolinecarboxylate hydrochloride (29)**: IR (KBr) 1726, 1658, 1589, 1448, 1243, 1224, 1131, 1022, 767, 707 cm^{-1}; MS m/z 388 (M^+); ^1H NMR (DMSO-d) δ 11.03 (brs, 1 H), 8.23 (d, 1 H, J = 6.8 Hz), 7.40–7.80 (m, 4 H), 7.25–7.45 (m, 3 H), 7.14 (s, 1 H), 6.60 (d, 1 H)J = 8.5 Hz), 5.32 (m, 1 H), 3.91 (m, 2 H), 2.68 (d, 3 H), 2.0–3.0 (m, 8 H).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2-methoxy-4-quinolinecarboxylate hemifumarate (35)**: IR (KBr) 3440 (br), 1725, 1609, 1571, 1380, 1332, 1222, 1025, 794, 763 cm^{-1}; HRMS m/z 326.1634 (M^+), $C_{19}H_{22}N_2O_3$ requires 326.1630; ^1H NMR (DMSO-d_6) δ 8.52 (d, 1 H, J = 8.4 Hz), 7.89 (d, 1 H, J = 8.3 Hz), 7.76 (m, 1 H), 7.55 (m, 1 H), 7.41 (s, 1 H), 6.54 (s, 1 H), 5.29 (m, 1 H), 4.05 (s, 3 H), 3.51 (m, 2 H), 2.48 (s, 3 H), 1.85–2.55 (m, 8 H).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2-ethoxy-4-quinolinecarboxylate fumarate (36)**: IR (KBr) 3420 (br), 1721, 1594, 1569, 1379, 1322, 1214, 1026, 790, 768 cm^{-1}; MS m/z 340 (M^+); ^1H NMR (DMSO-d_6) δ 8.50 (d, 1 H, J = 8.4 Hz), 7.86 (d, 1 H, J = 8.3 Hz), 7.75 (m, 1 H), 7.54 (m, 1 H), 7.39 (s, 1 H), 6.55

(s, 2 H), 5.28 (m, 1 H), 4.52 (q, 2 H, J = 7.0 Hz), 3.54 (m, 2 H), 2.49 (s, 3 H), 2.30–2.60 (m, 2 H), 1.90–2.25 (m, 6 H), 1.41 (t, 3 H, J = 7.0 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2-(isopropyloxy)-4-quinolinecarboxylate fumarate (37)**: IR (KBr) 3440 (br), 1728, 1600, 1567, 1394, 1314, 1216, 1026, 795, 773 cm^{-1}; HRMS m/z 354.1975 (M$^+$), $C_{21}H_{26}N_2O_3$ requires 354.1943; ^{1}H NMR (DMSO-d) δ 8.49 (d, 1 H, J = 8.4 Hz), 7.84 (d, 1 H, J = 8.4 Hz), 7.73 (m, 1 H), 7.52 (m, 1 H), 7.33 (s, 1 H), 6.55 (s, 2 H), 5.52 (m, 1 H), 5.28 (m, 1 H), 3.54 (m, 2 H), 2.50 (s, 3 H), 1.85–2.55 (m, 8 H), 1.40 (d, 6 H, J = 6.1 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2-(*n*-propyloxy)-4-quinolinecarboxylate fumarate (38)**: IR (KBr) 3430 (br), 1721, 1601, 1569, 1217, 1025, 792 cm^{-1}; MS m/z 354 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 8.49 (d, 1 H, J = 8.4 Hz), 7.86 (d, 1 H, J = 8.3 Hz), 7.74 (m, 1 H), 7.53 (m, 1 H), 7.39 (s, 1 H), 6.55 (s, 2 H), 5.29 (m, 1 H), 4.42 (t, 2 H, J = 6.8 Hz), 3.54 (m, 2 H), 2.49 (s, 3 H), 1.90–2.55 (m, 8 H), 1.83 (m, 2 H), 1.02 (t, 3 H, J = 7.4 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2-(isobutyloxy)-4-quinolinecarboxylate sesquifumarate (39)**: IR (KBr) 3430 (br), 1726, 1601, 1568, 1383, 1326, 1219, 1026, 792, 769 cm^{-1}; MS m/z 368 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 8.49 (d, 1 H, J = 8.4 Hz), 7.86 (d, 1 H, J = 8.4 Hz), 7.75 (m, 1 H), 7.54 (m, 1 H), 7.41 (s, 1 H), 6.56 (s, 3 H), 5.30 (m, 1 H), 4.25 (d, 2 H, J = 6.6 Hz), 3.64 (m, 2 H), 2.56 (s, 3 H), 2.35–2.70 (m, 2 H), 1.90–2.30 (m, 7 H), 1.03 (d, 6 H, J = 6.8 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2-(*n*-butyloxy)-4-quinolinecarboxylate fumarate (40)**: IR (KBr) 3400 (br), 1723, 1603, 1216, 1026, 794 cm^{-1}; MS m/z 368 (M$^+$); ^{1}H NMR (DMSO-d) δ 8.49 (d, 1 H, J = 8.4 Hz), 7.86 (d, 1 H, J = 8.3 Hz), 7.74 (m, 1 H), 7.53 (m, 1 H), 7.39 (s, 1 H), 6.56 (s, 2 H), 5.29 (m, 1 H), 4.47 (t, 2 H, J = 6.7 Hz), 3.60 (m, 2 H), 2.53 (s, 3 H), 1.9–2.5 (m, 8 H), 1.79 (m, 2 H), 1.48 (m, 2 H), 0.97 (t, 3 H, J = 7.3 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2-(*n*-pentyloxy)-4-quinolinecarboxylate sesquifumarate (41)**: IR (KBr) 3420 (br), 1723, 1602, 1569, 1215, 1026, 973, 794, 770 cm^{-1}; MS m/z 382.2283 (M$^+$), $C_{23}H_{30}N_2O_3$ requires 382.2256; ^{1}H NMR (DMSO-d_6) δ 8.49 (d, 1 H, J = 8.4 Hz), 7.85 (d, 1 H, J = 8.3 Hz), 7.74 (m, 1 H), 7.53 (m, 1 H), 7.40 (s, 1 H), 6.56 (s, 3 H), 5.29 (m, 1 H), 4.46 (t, 2 H, J = 6.7 Hz), 3.63 (m, 2 H), 2.55 (s, 3 H), 2.35–2.65 (m, 2 H), 1.95–2.30 (m, 6 H), 1.81 (m, 2 H), 1.25–1.55 (m, 4 H), 0.91 (t, 3 H, J = 7.1 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2-(*n*-hexyloxy)-4-quinolinecarboxylate fumarate (42)**: IR (KBr) 3430 (br), 1727, 1600, 1570, 1377, 1325, 1215, 1026, 795, 769 cm^{-1}; MS m/z 396 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 8.49 (d, 1 H, J = 8.5 Hz), 7.85 (d, 1 H, J = 8.4 Hz), 7.74 (m, 1 H), 7.53 (m, 1 H), 7.39 (s, 1 H), 6.55 (s, 2 H), 5.28 (m, 1 H), 4.46 (t, 2 H, J = 6.7 Hz), 3.53 (m, 2 H), 2.48 (s, 3 H), 2.30–2.65 (m, 2 H), 1.90–2.25 (m, 6 H), 1.80 (m, 2 H), 1.15–1.60 (m, 6 H), 0.88 (t, 3 H, J = 6.9 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 4-quinolinecarboxylate dihydrochloride (49)**: IR (KBr) 1728, 1595, 1253, 1156, 1027, 854, 799, 768 cm^{-1}; HRMS m/z 296.1518 (M$^+$), $C_{18}H_{20}N_2O_2{\cdot}2HCl{\cdot}H_2O$ requires 296.1525; ^{1}H NMR (DMSO-d) δ 11.11 (brs, 1 H), 9.19 (d, 1 H, J = 4.6 Hz), 8.75 (d, 1 H, J = 8.6 Hz), 8.24 (d, 1 H, J = 8.3 Hz), 8.06 (d, 1 H, J = 4.6 Hz), 7.94 (m, 1 H), 7.82 (m, 1 H), 5.35 (m, 1 H), 3.91 (m, 2 H), 2.68 (d, 3 H, J = 5.1 Hz), 1.95–2.90 (m, 8 H).

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-(*n*-butyl)-2-oxo-1,2-dihydro-4-quinolinecarboxamide Fumarate (33)**. A mixture of compound **12a** (1.23 g, 5.01 mmol) and $SOCl_2$ (10 mL) was refluxed for 30 min and then concentrated under reduced pressure (the acid chloride A). A suspension of NaH (12.0 mg, 5.00 mmol) in anhydrous THF (40 mL) was stirred at room temperature under an argon atmosphere. A solution of *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-ylamine[23] (0.70 g, 4.99 mmol) in anhydrous THF (20 mL) was added to the mixture followed by stirring at room temperature for 1 h further. The acid chloride A was portionwise added to this solution and the mixture was stirred at room temperature for 2 h. Then 1 N HCl was added to acidify the mixture which was washed twice with $CHCl_3$. Then an aqueous saturated $NaHCO_3$ solution was added to basify the mixture followed by extraction twice with $CHCl_3$. The organic layer was collected and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and to the residue was added H_2O (35 mL). The precipitated crystals were collected by filtration and dried. To this product, *i*-PrOH (40 mL) and fumaric acid (0.26 g, 2.24 mmol) were added, and the mixture was stirred at room temperature. Hexane (15 mL) was added to this solution at room temperature with stirring and the precipitated crystals were collected by filtration and dried to give compound **33** as the fumarate (0.87 g, 36%): IR (KBr) 3420, 1708, 1642, 1583, 1451, 1297, 981, 755 cm^{-1}; MS m/z 367 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 8.67 (d, 1 H, J = 4.2 Hz), 7.55–7.85 (m, 3 H), 7.29 (m, 1 H), 6.57 (s, 1 H), 6.53 (s, 2 H), 4.27 (t, 2 H, J = 7.5 Hz), 4.03 (m, 1 H), 3.64 (m, 2 H), 2.57 (s, 3 H), 1.9–2.5 (m, 8 H), 1.60 (m, 2 H), 1.41 (m, 2 H), 0.94 (t, 3 H, J = 7.2 Hz).

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1,2-dihydro-4-quinolinecarboxamide fumarate (30)**: IR (KBr) 3240 (br), 3015, 1668, 1635, 1538, 1431, 1091, 973, 754, 637 cm^{-1}; MS m/z 311 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 11.89 (brs, 1 H), 8.59 (d, 1 H, J = 4.1 Hz), 7.68 (d, 1 H, J = 8.1 Hz), 7.53 (m, 1 H), 7.36 (d, 1 H, J = 7.6 Hz), 7.19 (m, 1 H), 6.51 (s, 2 H), 6.46 (s, 1 H), 4.01 (m, 1 H), 3.54 (m, 2 H), 2.50 (s, 3 H), 1.97–2.56 (m, 8 H).

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-methyl-2-oxo-1,2-dihydro-4-quinolinecarboxamide fumarate (31)**: IR (KBr) 1656, 1636, 1586, 1539, 1456, 1374, 1198, 986, 751 cm^{-1}; HRMS m/z 325.1785 (M$^+$), $C_{18}H_{23}N_3O_2{\cdot}C_4H_4O_4$ requires 325.1790; ^{1}H NMR (DMSO-d_6) δ 8.62 (d, 1 H, J = 4.4 Hz), 7.58–7.76 (m, 3 H), 7.30 (m, 1 H), 6.59 (s, 1 H), 6.51 (s, 2 H), 4.02 (m, 1 H), 3.65 (s, 3 H), 3.56 (m, 2 H), 2.51 (s, 3 H), 1.98–2.50 (m, 8 H).

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1-(*n*-propyl)-1,2-dihydro-4-quinolinecarboxamide fumarate (32)**: IR (KBr) 3430 (br), 1690, 1640, 1584, 1530, 1451, 1368, 1296, 1257, 1201, 1093, 987, 760 cm^{-1}; HRMS m/z 353.2098 (M$^+$), $C_{21}H_{27}N_3O_2$ requires 353.2103; ^{1}H NMR (DMSO-d_6) δ 8.62 (d, 1 H, J = 4.4 Hz), 7.50–7.85 (m, 3 H), 7.28 (m, 1 H), 6.56 (s, 1 H), 6.51 (s, 2 H), 4.22 (t, 2 H, J = 7.7 Hz), 4.02 (m, 1 H), 3.53 (m, 2 H), 2.50 (m, 3 H), 1.9–2.5 (m, 8 H), 1.65 (m, 2 H), 0.98 (t, 3 H, J = 7.4 Hz). H_2O content 0.74% (method of Fischer, K.), $C_{21}H_{27}N_3O_2{\cdot}C_4H_4O_4{\cdot}0.3H_2O$ requires 1.14%.

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1-phenyl-1,2-dihydro-4-quinolinecarboxamide fumarate (34)**: IR (KBr) 3300 (br), 1640, 1587, 1451, 1292, 1088, 748 cm^{-1}; HRMS m/z 387.1959 (M$^+$), $C_{24}H_{25}N_3O_2{\cdot}C_4H_4O_4$ requires 387.1947; ^{1}H NMR (DMSO-d_6) δ 8.69 (d, 1 H, J = 4.4 Hz), 7.77 (d, 1 H, J = 8.0 Hz), 7.55–7.68 (m, 3 H), 7.46 (m, 1 H), 7.25–7.31 (m, 3 H), 6.64 (s, 2 H), 6.57 (d, 1 H, J = 8.3 Hz), 6.49 (s, 1 H), 4.05 (m, 1 H), 3.45 (m, 2 H), (s, 3 H), 1.90–2.51 (m, 8 H).

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-(isopropyloxy)-4-quinolinecarboxamide fumarate (43)**: IR (KBr) 3400 (br), 1710, 1641, 1600, 1567, 1399, 1315, 1179, 1106, 982, 767 cm^{-1}; MS m/z 353 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 8.62 (d, 1 H, J = 4.4 Hz), 7.95 (d, 1 H, J = 7.5 Hz), 7.79 (d, 1 H, J = 8.4 Hz), 7.68 (m, 1 H), 7.44 (m, 1 H), 6.89 (s, 1 H), 6.52 (s, 2 H), 5.52 (m, 1 H), 4.06 (m, 1 H), 3.58 (m, 2 H), 2.53 (s, 3 H), 1.7–2.6 (m, 8 H), 1.38 (d, 6 H, J = 6.2 Hz).

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-(*n*-propyloxy)-4-quinolinecarboxamide fumarate (44)**: IR (KBr) 3440 (br), 1702, 1658, 1587, 1536, 1406, 1327, 1181, 982, 762 cm^{-1}; HRMS m/z 353.2114 (M$^+$), $C_{22}H_{27}N_3O_2{\cdot}C_4H_4O_4$ requires 353.2104; ^{1}H NMR (DMSO-d_6) δ 8.61 (d, 1 H, J = 4.0 Hz), 7.95 (d, 1 H, J = 8.3 Hz), 7.80 (d, 1 H, J = 7.5 Hz), 7.69 (m, 1 H), 7.45 (m, 1 H), 6.96 (s, 1 H), 6.51 (s, 2 H), 4.41 (t, 2 H, J = 6.6 Hz), 4.06 (m, 1 H), 3.55 (m, 2 H), 2.51 (s, 3 H), 1.8–2.5 (m, 8 H), 1.81 (m, 2 H), 1.02 (t, 3 H, J = 7.4 Hz).

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-(*n*-butyloxy)-4-quinolinecarboxamide fumarate (45)**: IR (KBr) 3430 (br), 1700, 1658, 1601, 1572, 1407, 1328, 1238, 1195, 799, 761 cm^{-1}; MS m/z 367 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 8.60 (d, 1 H, J = 4.2 Hz), 7.95 (d, 1 H, J = 7.2 Hz), 7.80 (d, 1 H, J = 7.7 Hz), 7.69 (m, 1 H), 7.45 (m, 1 H), 6.95 (s, 1 H), 6.51 (s, 2 H), 4.45 (t, 2 H, J = 6.6 Hz), 4.05 (m, 1 H), 3.54 (m, 2 H), 2.50 (s, 3 H), 1.9–2.5 (m, 8 H), 1.78 (m, 2 H), 1.48 (m, 2 H), 0.96 (t, 3 H, J = 7.3 Hz).

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-quinolinecarboxamide fumarate (50)**: IR (KBr) 1666, 1578, 1548, 1415, 1288, 983, 797 cm^{-1}; MS m/z 295 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 8.99 (d, 1 H, J = 4.3 Hz), 8.68 (d, 1 H, J = 4.3 Hz), 8.05–8.15 (m, 2 H), 7.81 (m, 1 H), 7.66 (m, 1 H), 7.51 (d, 1 H, J = 4.3 Hz), 6.52 (s, 2 H), 4.09 (m, 1 H), 3.62 (m, 2 H), 2.51 (s, 3 H), 2.04–2.50 (m, 8 H).

3-Ethyl-2-oxo-1,2-dihydro-4-quinolinecarboxylic Acid (8a). A mixture of isatin (15; 10.4 g, 70.7 mmol), butyric anhydride (60 mL), and pyridine (2 mL) was stirred with heating at 140 °C for 30 min. After cooling, the solution was poured into H_2O, and with further cooling, dilute NaOH was added to basify the mixture. The solution was refluxed for 30 min, and after cooling, dilute HCl was added to acidify the solution. The precipitated crystals were collected by filtration, washed with H_2O, and dried to give compound **8a** (3.96 g, 26%): ^{1}H NMR ($CDCl_3$) δ 7.05–7.70 (m, 4 H), 2.53 (q, 2 H, J = 7.3 Hz), 1.20 (t, 3 H, J = 7.3 Hz).

***endo*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-(*n*-butyl)-3-ethyl-2-oxo-1,2-dihydro-4-quinolinecarboxylate hydrochloride (46):** IR (KBr) 1741, 1651, 1643, 1601, 1453, 1309, 1219, 1080, 1025, 749 cm^{-1}; HRMS m/z 396.2437 (M^+), $C_{24}H_{32}N_2O_3$ requires 396.2413; ^{1}H NMR (DMSO-d_6) δ 10.89 (brs, 1 H), 7.56–7.73 (m, 2 H), 7.50 (d, 1 H, J = 8.1 Hz), 7.31 (m, 1 H), 5.44 (m, 1 H), 4.29 (t, 2 H, J = 7.7 Hz), 3.87 (m, 2 H), 2.66 (m, 3 H), 2.53 (q, 2 H, J = 7.3 Hz), 1.8–2.9 (m, 8 H), 1.63 (m, 2 H), 1.42 (m, 2 H), 1.13 (t, 3 H, J = 7.3 Hz), 0.95 (t, 3 H, J = 7.3 Hz). H_2O content 6.81% (method of K. Fischer), $C_{24}H_{32}N_2O_3 \cdot HCl \cdot 1.8H_2O$ requires 6.97%.

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-(*n*-butyl)-3-ethyl-2-oxo-1,2-dihydro-4-quinolinecarboxamide fumarate (48):** IR (KBr) 2960, 1629, 1589, 1457, 982, 754 cm^{-1}; MS m/z 395 (M^+); ^{1}H NMR (DMSO-d_6) δ 8.71 (d, 1 H, J = 4.4 Hz), 7.54–7.63 (m, 2 H), 7.59 (d, 1 H, J = 7.6 Hz), 7.27 (d, 1 H, J = 7.6 Hz), 6.53 (s, 2 H), 4.23–4.33 (m, 2 H), 4.13 (m, 1 H), 3.61 (M, 2 H), 2.55 (s, 3 H), 1.91–2.58 (m, 10 H), 1.61 (m, 2 H), 1.42 (m, 2 H), 1.12 (t, 3 H, J = 7.2 Hz), 0.96 (t, 3 H, J = 7.2 Hz).

6-Methyl-2-oxo-1,2-dihydro-4-quinolinecarboxylic Acid (8b). To a suspension of NaH (2.00 g, 50.0 mmol) in toluene (80 mL) was added portionwise 5-methylisatin (16; 8.06 g, 50.0 mmol) with stirring at 0 °C. Under ice cooling, Ac_2O (4.7 mL, 50.0 mmol) was added dropwise followed by heating at 80 °C for 1 h further with stirring. Then, an aqueous saturated $NaHCO_3$ solution was added to the mixture. The precipitated crystals were collected by filtration, washed with H_2O, and dried to give 1-acetyl-5-methylisatin (4.84 g, 47%): ^{1}H NMR ($CDCl_3$) δ 8.29 (d, 1 H, J = 8.5 Hz), 7.57 (s, 1 H), 7.52 (d, 1 H, J = 8.5 Hz), 2.72 (s, 3 H), 2.40 (s, 3 H). A mixture of the compound described above (4.84 g, 23.7 mmol) and 2 N NaOH (100 mL) were refluxed for 30 min. Then dilute HCl was added to acidify the mixture. The precipitated crystals were collected by filtration, washed with H_2O, and dried to give compound **8b** (3.61 g, 75%) as a crude product.

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 1-(*n*-butyl)-6-methyl-2-oxo-1,2-dihydro-4-quinolinecarboxylate hydrochloride (47):** IR (KBr) 1722, 1645, 1585, 1249, 1164, 1077, 1028 cm^{-1}; MS m/z 382 (M^+); ^{1}H NMR (DMSO-d_6) δ 11.01 (brs, 1 H), 8.00 (s, 1 H), 7.55 (s, 2 H), 7.02 (s, 1 H), 5.27 (m, 1 H), 4.26 (t, 2 H, J = 7.6 Hz), 3.89 (m, 2 H), 2.67 (s, 3 H), 2.39 (s, 3 H), 1.95–2.90 (m, 8 H), 1.61 (m, 2 H), 1.40 (m, 2 H), 0.93 (t, 3 H, J = 7.3 Hz).

1-(*n*-Butyl)-2-oxo-1,2,3,4-tetrahydro-4-quinolinecarboxylic Acid (17). To a suspension of $LiBH_4$ (1.10 g, 50.6 mmol) in THF (25 mL) was added portionwise a solution of compound **9a** (13.26 g, 44.0 mmol) in THF (75 mL). After stirring for 3 h at room temperature, a small quantity of H_2O was added to the solution and the mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography with $CHCl_3$–MeOH (100:1) as eluent to give 1-(*n*-butyl)-4-(*n*-butyloxycarbonyl)-2-oxo-1,2,3,4-tetrahydroquinoline (1.88 g, 14%): ^{1}H NMR ($CDCl_3$) δ 7.05–7.35 (m, 2 H), 6.80–7.10 (m, 2 H), 3.6–4.2 (m, 5 H), 2.55–3.20 (m, 2 H), 1.05–2.00 (m, 8 H), 0.70–1.10 (m, 6 H). A mixture of the compound described above (2.53 g, 8.36 mmol), NaOH (1.67 g, 41.75 mmol), H_2O (40 mL), and dioxane (40 mL) were stirred at room temperature for 15 min. Then, dilute HCl was added to neutralize the mixture. The solvent was evaporated under reduced pressure, and the residue was purifid by silica gel column chromatography with $CHCl_3$–MeOH (10:1) as eluent to give compound **17** (1.73 g, 84%): ^{1}H NMR (DMSO-d_6) δ 6.85–7.50 (m, 4 H), 3.6–4.1 (m, 3 H), 2.55–2.9 (m, 2 H), 1.0–1.8 (m, 4 H), 0.88 (t, 3 H, J = 6 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 1-(*n*-butyl)-2-oxo-1,2,3,4-tetrahydro-4-quinolinecarboxylate hydrochloride (51):** IR (KBr) 1727, 1652, 1590, 1457, 1376, 1027, 759 cm^{-1}; HRMS m/z 370.2276 (M^+), $C_{22}H_{30}N_2O_3$ requires 370.2256; ^{1}H NMR (DMSO-d_6) δ 7.25–7.45 (m, 2 H), 7.17 (d, 1 H, J = 7.9 Hz), 7.06 (m, 1 H), 4.85 (m, 1 H), 1.5–4.2 (m, 15 H), 2.57 (d, 3 H, J = 4.5 Hz), 1.43 (m, 2 H), 1.23 (m, 2 H), 0.86 (t, 3 H, J = 7.2 Hz).

Biology. 5-HT$_3$ Receptor Binding Test. Using a membrane fraction of rat neuroblastoma–glioma NG 108-15 cells, the binding activities of the test compounds at the 5-HT$_3$ receptors were examined. A membrane fraction of NG 108-15 cells was prepared according to the method of Neijt et al.[25] The receptor binding experiment was performed using [^{3}H]quipazine,[26] a high affinity ligand for the 5-HT$_3$ receptors. A membrane fraction obtained from 3 × 10^5 cells of NG 108-15 cells was suspended in 20 mM Tris-HCl (1 mL, pH 7.5), hereafter referred to as buffer) containing NaCl (154 mM). Then, 2 nM [^{3}H]quipazine (2519.7 GBq/mmol; Du Pont Co., Ltd.) and various concentrations of the test compound were added to the suspension followed by incubation at 37 °C for 60 min. Ice-cold buffer (4 mL) was added to terminate the reaction, and then the mixture was filtered through a Whatman GF/C glass fiber filter. The filter was washed five times with ice-cold buffer (2 mL), and put in a scintillation vial containing EX-H (8 mL; Wako Pure Chemicals, Inc.). Radioactivity on the filter was counted in a liquid scintillation counter (Tri-Carb 2200CA; Packard Co., Ltd.). The specific binding was determined by subtracting the nonspecific binding (in the presence of 10 μM MDL 72222[10]) from the total binding. The K_i values were derived from the IC_{50} (concentration of 50% inhibition) values according to the method of Cheng and Prusoff.[40] The K_d value of [^{3}H]quipazine in NG 108-15 was 6.8 ± 0.37 nM (mean ± SEM).

Pharmacology. Bezold–Jarisch Reflex Test. The Bezold–Jarisch reflex assay was carried out according to the reported procedure.[36] Male Wistar rats (230–330 g, SLC) were anesthesized with urethane 1.25 g/kg ip and the trachea cannulated. Blood pressure was recorded from the left carotid artery, via a saline/heparin-filled pressure transducer from which the heart rate was also continuously monitored. Compounds were injected intravenously into the exterior jugular vein. The B-J reflex was evoked by rapid, bolus iv injection of 5-HT 30 μg/kg, and consistent responses were established every 12 min before each challenge with 5-HT. An ED_{50} was calculated at the dose which reduced the 5-HT-induced bradycardia by 50%.

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