

5-HT₃ 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 [³H]quipazine-labeled 5-HT₃ 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 between the affinity for the 5-HT₃ 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-HT₃ receptors in a different way from that of the reported 5-HT₃ receptor antagonists presumably due to the presence of the heterogeneity of the 5-HT₃ 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-HT₁, 5-HT₂, 5-HT₃, and 5-HT₄).²⁻⁵ The 5-HT₃ 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-HT₃ receptors in the area postrema.¹⁴ In addition, evidence has been presented for the therapeutic roles of the 5-HT₃ receptor antagonists in migraine,¹⁵ schizophrenia,¹⁶ and anxiety.¹⁷

Drug Design

The selective 5-HT₃ 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-HT₃ 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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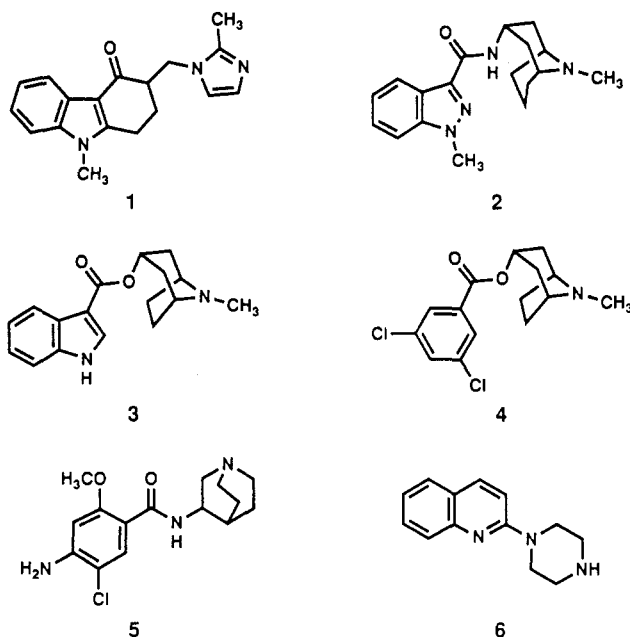
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group, we focused on a quinoline ring in which a five-membered pyrrole ring in indole was replaced by a six-membered pyridine ring. A quinoline ring can be con-



Ar ---- (carbonyl) ---- N

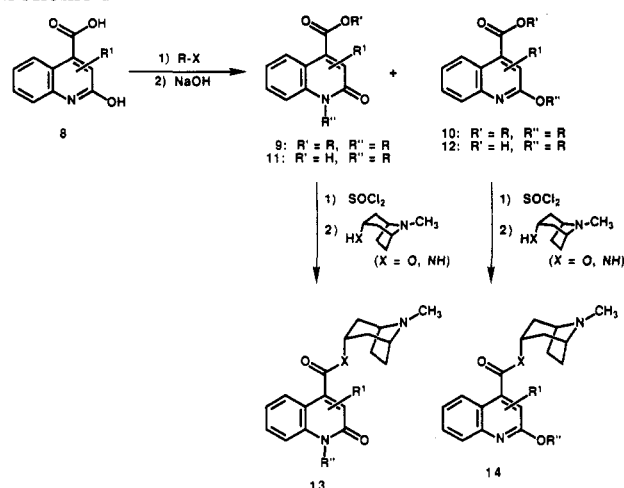
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sidered as a bioisostere of an indole ring, and even by this replacement a basic center can still occupy the appropriate position from an aromatic group. Furthermore, a quinoline ring can be seen also in quipazine (6), which is known to bind to the 5-HT₃ 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-HT₃ receptor antagonists (e.g., 2–5). In this paper, we report the synthesis and the 5-HT₃ receptor antagonistic activity of a series of quinoline derivatives. Conformational properties are also discussed in relation to a pharmacophore recently proposed for the 5-HT₃ receptor antagonists.^{18–21}

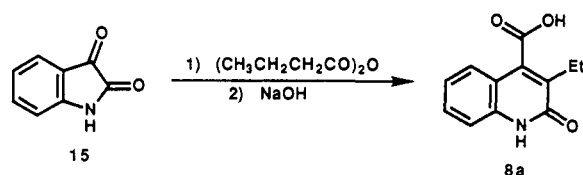
Chemistry

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

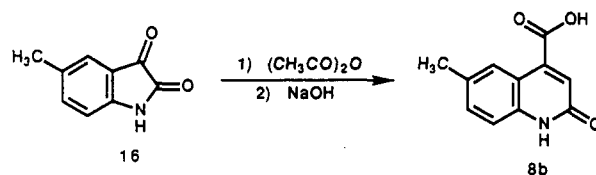
Scheme I



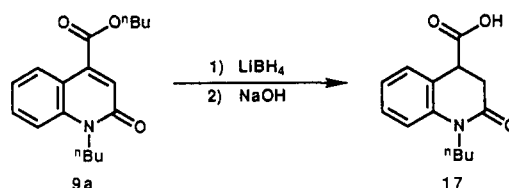
Scheme II



Scheme III



Scheme IV



carboxylic acids 11 and 12, respectively. Then, 11 and 12 were treated with SOCl₂, followed by reaction with tropine or *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-ylamine²³ to afford target compounds 13 and 14. When R¹ 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, R¹ = 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 LiBH₄ 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.

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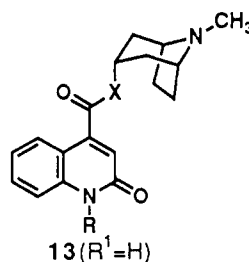
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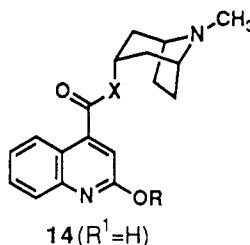
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Table I. *N*-Alkyl Type

compd	R	X	yield, %	mp, °C	formula	anal. ^a
18	H	O	6	303.0–306.0	C ₁₈ H ₂₀ N ₂ O ₃ ·HCl·0.6H ₂ O	C, H, N ^c
19	CH ₃	O	18	279.0–282.0	C ₁₉ H ₂₂ N ₂ O ₃ ·HCl·1.3H ₂ O	C, H, N
20	CH ₃ CH ₂	O	14	230.0–232.0	C ₂₀ H ₂₄ N ₂ O ₃ ·HCl·1.5H ₂ O	C, H, N
21	(CH ₃) ₂ CH	O	37	244.0–244.5	C ₂₁ H ₂₆ N ₂ O ₃ ·HCl·H ₂ O	C, H, N
22	CH ₃ (CH ₂) ₂	O	48	273.0–274.5	C ₂₁ H ₂₆ N ₂ O ₃ ·HCl·0.5H ₂ O	C, H, N
23	(CH ₃) ₂ CHCH ₂	O	29	262.0–263.5	C ₂₂ H ₂₈ N ₂ O ₃ ·HCl·0.5H ₂ O	C, H, N
24	CH ₃ (CH ₂) ₃	O	38	80–86	C ₂₂ H ₂₈ N ₂ O ₃ ·0.5HCl·1.8H ₂ O	C, H, N
25	(CH ₃) ₂ CH(CH ₂) ₂	O	28	68.5–69.0	C ₂₃ H ₃₀ N ₂ O ₃ ·HCl·1.5H ₂ O	C, H, N
26	CH ₃ (CH ₂) ₄	O	56	72.0–75.0	C ₂₃ H ₃₀ N ₂ O ₃ ·HCl·1.7H ₂ O	C, H, N
27	CH ₃ (CH ₂) ₅	O	42	146.5–147.5	C ₂₄ H ₃₂ N ₂ O ₃ ·HCl·H ₂ O	C, H, N
28	C ₆ H ₅ CH ₂	O	14	115.5–117.0	C ₂₅ H ₂₆ N ₂ O ₃ ·HCl·4H ₂ O	C, H, N
29	C ₆ H ₅	O	27	128.5–129.5	C ₂₄ H ₂₄ N ₂ O ₃ ·HCl·2H ₂ O	C, H, N
30	H	NH	23	231.8–235.2	C ₁₈ H ₂₁ N ₃ O ₂ ·C ₄ H ₄ O ₄ ^b ·H ₂ O	C, H, N
31	CH ₃	NH	23	254.5–255.5	C ₁₉ H ₂₃ N ₃ O ₂ ·C ₄ H ₄ O ₄ ^b	C, H, N ^d
32	CH ₃ (CH ₂) ₂	NH	22	239.7–242.2	C ₂₁ H ₂₇ N ₃ O ₂ ·C ₄ H ₄ O ₄ ^b ·0.3H ₂ O	C, H, N
33	CH ₃ (CH ₂) ₃	NH	36	217.8–219.0	C ₂₂ H ₂₉ N ₃ O ₂ ·C ₄ H ₄ O ₄ ^b	C, H, N
34	C ₆ H ₅	NH	51	251.2–256.2	C ₂₄ H ₂₅ N ₃ O ₂ ·C ₄ H ₄ O ₄ ^b	C, H, N ^e

^a Analyses for the elements indicated were within ±0.4% of the theoretical values. ^b C₄H₄O₄, 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

compd	R	X	yield, %	mp, °C	formula	anal. ^a
35	CH ₃	O	35	198.0–200.5	C ₁₉ H ₂₂ N ₂ O ₃ ·0.5C ₄ H ₄ O ₄ ^b ·H ₂ O	C, H, N
36	CH ₃ CH ₂	O	16	103.0–103.5	C ₂₀ H ₂₄ N ₂ O ₃ ·C ₄ H ₄ O ₄ ^b ·0.5H ₂ O	C, H, N
37	(CH ₃) ₂ CH	O	30	160.5–161.0	C ₂₁ H ₂₆ N ₂ O ₃ ·C ₄ H ₄ O ₄ ^b ·0.3H ₂ O	C, H, N
38	CH ₃ (CH ₂) ₂	O	15	154.0–162.0	C ₂₁ H ₂₆ N ₂ O ₃ ·C ₄ H ₄ O ₄ ^b ·0.5H ₂ O	C, H, N
39	(CH ₃) ₂ CHCH ₂	O	13	162.0–165.5	C ₂₂ H ₂₈ N ₂ O ₃ ·1.5C ₄ H ₄ O ₄ ^b ·0.5H ₂ O	C, H, N
40	CH ₃ (CH ₂) ₃	O	22	124.0	C ₂₂ H ₂₈ N ₂ O ₃ ·C ₄ H ₄ O ₄ ^b ·H ₂ O	C, H, N
41	CH ₃ (CH ₂) ₄	O	8	156.0–160.0	C ₂₃ H ₃₀ N ₂ O ₃ ·1.5C ₄ H ₄ O ₄ ^b ·0.5H ₂ O	C, H, N
42	CH ₃ (CH ₂) ₅	O	7	168.5–169.0	C ₂₄ H ₃₂ N ₂ O ₃ ·C ₄ H ₄ O ₄ ^b ·0.5H ₂ O	C, H, N
43	(CH ₃) ₂ CH	NH	13	122.7–127.5	C ₂₁ H ₂₇ N ₃ O ₂ ·C ₄ H ₄ O ₄ ^b ·1.5H ₂ O	C, H, N
44	CH ₃ (CH ₂) ₂	NH	30	189.8–191.3	C ₂₁ H ₂₇ N ₃ O ₂ ·C ₄ H ₄ O ₄ ^b	C, H, N ^c
45	CH ₃ (CH ₂) ₃	NH	20	196.8–198.1	C ₂₂ H ₂₉ N ₃ O ₂ ·C ₄ H ₄ O 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-HT₃ receptors characterized by [³H]ICS 205-930 binding assay.²⁵ The 5-HT₃ receptors labeled by [³H]quipazine in the above cells were reported to be similar to those labeled by the selective 5-HT₃ receptor antagonist, [³H]GR 65630.²⁶ Thus, compounds 18–51 were evaluated

for 5-HT₃ receptor binding affinity versus [³H]quipazine in NG 108-15 cells^{25,27} (Tables IV and V).

Most of the esters containing a tropane moiety, (18–29, 35–42), inhibited potently [³H]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-HT₃ 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 ₂ O ₃ ·HCl·1.8H ₂ O	C, H, N
47		12	121.5–122.0	C ₂₃ H ₃₀ N ₂ O ₃ ·HCl·2H ₂ O	C, H, N
48		46	155.9–158.8	C ₂₄ H ₃₃ N ₃ O ₂ ·C ₄ H ₄ O ₄ ^b ·1.5H ₂ O	C, H, N
49		40	178.5–180.0	C ₁₈ H ₂₀ N ₂ O ₂ ·2HCl·H ₂ O	C, H, N ^c
50		44	261–262	C ₁₈ H ₂₁ N ₃ O·C ₄ H ₄ O ₄ ^b ·0.5H ₂ O	C, H, N
51		9	hygroscopic	C ₂₂ H ₃₀ N ₂ O ₃ ·HCl·2.2H ₂ O	C, H, N

^{a, b} See footnotes 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-HT₃ 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 derivatives²⁸ 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.

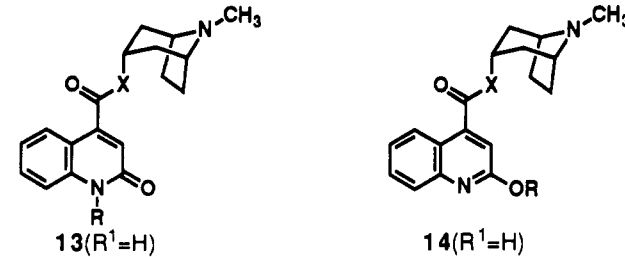
A 1,2,3,4-tetrahydroquinoline derivative 51, where the planarity of the area consisting of an aromatic ring and a carbonyl moiety was impaired by sp³-carbons at the 3- and 4-position of the ring, exhibited relatively low affinity for the 5-HT₃ receptors (K_i = 8.7 nM).

From these structure-activity relationships, the quinoline derivatives seem to interact with the 5-HT₃ 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

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Table IV. 5-HT₃ Receptor Binding Affinity and Antagonism of Benzold-Jarisch Reflex (1)


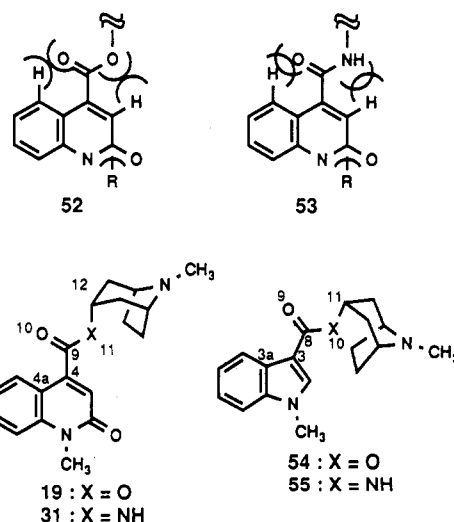
compd	R(13)	R(14)	X	5-HT ₃ receptor binding affinity: ^a <i>K_i</i> , ^b nM	inhibition of B-J reflex: ED ₅₀ ^c (mg/kg, iv) at 5 min
18	H		O	4.4 ± 0.09	0.017
19	CH ₃		O	2.6 ± 0.20	0.18
20	CH ₃ CH ₂		O	1.1 ± 0.07	0.022
21	(CH ₃) ₂ CH		O	0.32 ± 0.045	0.081
22	CH ₃ (CH ₂) ₂		O	0.45 ± 0.009	0.33
23	(CH ₃) ₂ CHCH ₂		O	0.47 ± 0.021	0.069
24	CH ₃ (CH ₂) ₃		O	0.68 ± 0.036	0.041
25	(CH ₃) ₂ CH(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 ₆ H ₅ CH ₂		O	1.3 ± 0.05	NT
29	C ₆ H 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 ₆ H ₄		NH	63 ± 9	NT
35		CH ₃	O	0.58 ± 0.015	5.64
36		CH ₃ CH ₂	O	0.88 ± 0.025	0.070
37		(CH ₃) ₂ CH	O	0.31 ± 0.021	1.62
38		CH ₃ (CH ₂) ₂	O	0.32 ± 0.006	6.78
39		(CH ₃) ₂ CHCH 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) ₂ CH	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 [³H]Quipazine-labeled 5-HT₃ 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 ED₅₀, 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-HT₃ 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-HT₃ receptors might be reduced. Recently, many papers^{18–21} described the important factors for high affinity for the 5-HT₃ receptors, one of which is the coplanarity between an aromatic ring and a carbonyl moiety.

Thus, studies on such structural properties for 5-HT₃ receptor antagonists 19, 31, 54, and 55, the latter two compounds of which are known to be potent 5-HT₃ receptor antagonists, were performed on an IRIS 4D/310 GTXB workstation with QUANTA 3.2/CHARMM 21.3.³¹ A

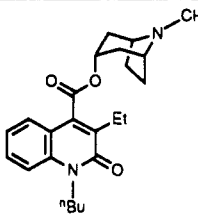
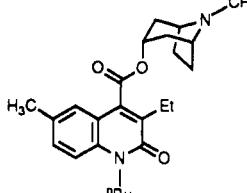
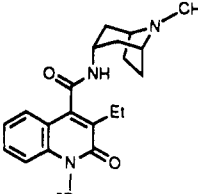
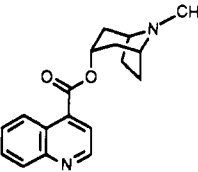
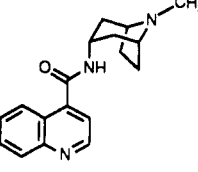
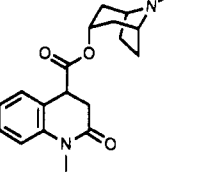


crystal structure of granisetron (2)³² was retrieved from the Cambridge Structural Database³³ and modified with

(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 5HT₃ Receptor. *J. Med. Chem.* 1987, 30, 1535–1537.

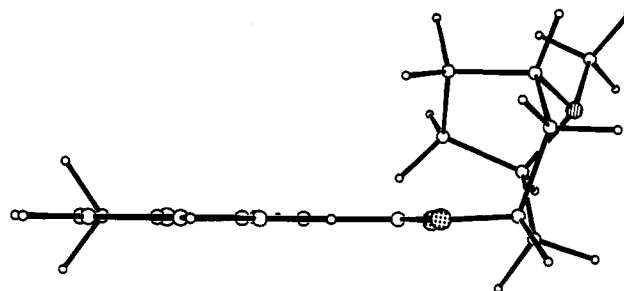
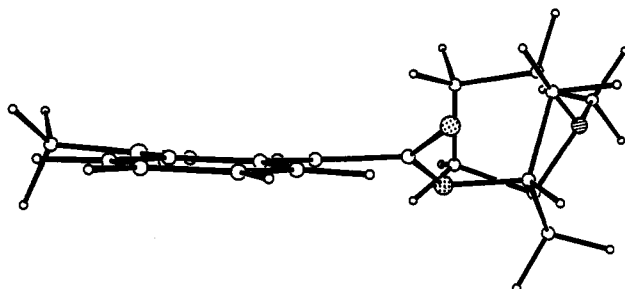
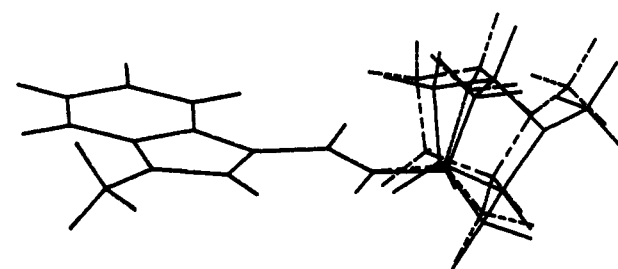
(31) QUANTA/CHARMM, Polygen Corp., 200 Fifth Ave., Waltham, MA 02254. (1986, 1987, 1988, 1991).

Table V. 5-HT₃ Receptor Binding Affinity and Antagonism of Bezold-Jarisch Reflex (2)

compd	structure	5-HT ₃ receptor binding affinity: ^a <i>K</i> _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-

**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.

basis Newton-Papson technique^{34,35} (nonbonded parameter cutoff = 15 Å).

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-HT₃ 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 tropane 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.

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

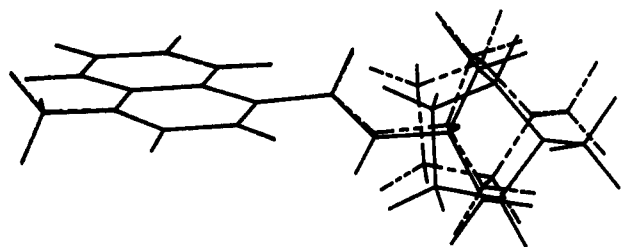


Figure 4. Superimposition of 19 (dotted line) and 31 (solid line) in the minimum-energy conformation.

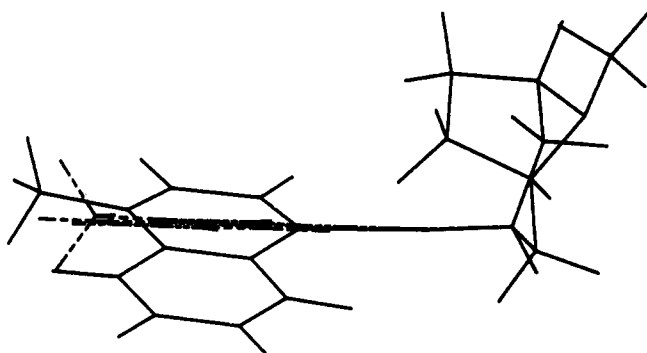


Figure 5. Superimposition of 19 (dotted line) and 54 (solid line) with the tropine moieties fitted together in the minimum-energy conformation.

populate the planar conformation during their interactions with the 5-HT₃ 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-HT₃ receptor antagonists.

With respect to the selected compounds, 5-HT₃ receptor antagonistic activity *in vivo* was examined by their ability to inhibit the 5-HT induced bradycardia [Bezold–Jarisch (B-J) reflex test³⁶] 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-HT₃ 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-HT₃ 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.

(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 Anesthetized Rats. *Br. J. Pharmacol.* 1986, 88, 319P.

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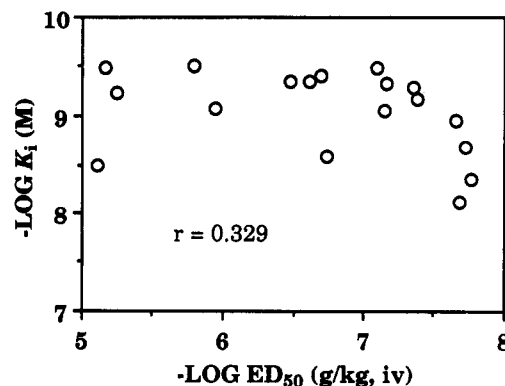


Figure 6. Correlation between the binding affinities ($-\log K_1$) and the activities in the Bezold–Jarisch reflex test ($-\log ED_{50}$).

These data indicate that activity in the B-J reflex test did not have good correlation with the K_1 values in the 5-HT₃ receptor binding test (Figure 6). Unlike the 5-HT₃ 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-HT₃ receptors. These results also suggest that our compounds interact with the 5-HT₃ receptors in a different way from that of the reported 5-HT₃ antagonists and that the heterogeneity of the 5-HT₃ 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-HT₃ 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-HT₃ receptors in a different way from that of the reported 5-HT₃ antagonists presumably due to the presence of the heterogeneity of the 5-HT₃ receptors between brain and heart.

Experimental Section

Proton nuclear magnetic resonance spectra (¹H NMR) were recorded on a JEOL JNM GX-270 FT NMR or a Hitachi R-90H FT NMR spectrometer with Me₄Si 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

(38) Nagel, A. A.; Rosen, T.; Rizzi, J.; Daffeh, J.; Guarino, K.; Nowakowski, J.; Vincent, L. A.; Heym, J.; McLean, S.; Seeger, T.; Connolly, M.; Schmidt, A. W.; Siok, C. Aromatic Thiazole Derivatives: Structurally Novel and Selective Serotonin-3 Receptor Antagonists. *J. Med. Chem.* 1990, 33, 13–16.

(39) Marica, A. V.; Peterson, A. S.; Brake, A. J.; Myers, R. M.; Julius, D. Primary Structure and Functional Expression of the 5-HT₃ Receptor, a Serotonin-Gated Ion Channel. *Science* 1991, 254, 432–437.

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 ($\text{DMSO}-d_6$) 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 ($\text{DMSO}-d_6$) 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 Et₂O 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^+), $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3$ requires 368.2100; ^1H NMR ($\text{DMSO}-d_6$) 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^+), $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3$ requires 312.1474; ^1H NMR ($\text{DMSO}-d_6$) 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^+), $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_3$ requires 326.1630; ^1H NMR ($\text{DMSO}-d_6$) 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 ($\text{DMSO}-d_6$) 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 ($\text{DMSO}-d_6$) 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 ($\text{DMSO}-d_6$) 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 ($\text{DMSO}-d_6$) 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 ($\text{DMSO}-d_6$) 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^+), $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_3$ requires 382.2256; ^1H NMR ($\text{DMSO}-d_6$) 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 ($\text{DMSO}-d_6$) 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^+), $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_3$ requires 402.1943; ^1H NMR ($\text{DMSO}-d_6$) 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 ($\text{DMSO}-d_6$) 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^+), $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_3$ requires 326.1630; ^1H NMR ($\text{DMSO}-d_6$) 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 ($\text{DMSO}-d_6$) 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-(isopropoxy)-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; ^1H NMR (DMSO- d_6) 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^+); ^1H 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^+); ^1H 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^+); ^1H 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), 6.56 (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; ^1H 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^+); ^1H 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^+), $C_{18}H_{20}N_2O_2 \cdot 2\text{HCl} \cdot \text{H}_2\text{O}$ requires 296.1525; ^1H NMR (DMSO- d_6) 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-ylamine²³ (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^+); ^1H 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^+); ^1H 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^+), $C_{19}H_{23}N_3O_2 \cdot \text{C}_4\text{H}_4\text{O}_4$ requires 325.1790; ^1H 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; ^1H 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.), $C_{21}H_{27}N_3O_2 \cdot \text{C}_4\text{H}_4\text{O}_4 \cdot 0.3\text{H}_2\text{O}$ 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^+), $C_{24}H_{25}N_3O_2 \cdot \text{C}_4\text{H}_4\text{O}_4$ requires 387.1947; ^1H 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-(isopropoxy)-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^+); ^1H 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^+), $C_{22}H_{27}N_3O_2 \cdot \text{C}_4\text{H}_4\text{O}_4$ requires 353.2104; ^1H 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), 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, 1328, 1238, 1195, 799, 761 cm^{-1} ; MS m/z 367 (M^+); ^1H 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^+); ^1H 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 H₂O, 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 H₂O, and dried to give compound 8a (3.96 g, 26%): ¹H NMR (CDCl₃) 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⁺), C₂₄H₃₂N₂O₃ requires 396.2413; ¹H 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). H₂O content 6.81% (method of K. Fischer), C₂₄H₃₂N₂O₃·HCl·1.8H₂O 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⁺); ¹H 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, Ac₂O (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 NaHCO₃ solution was added to the mixture. The precipitated crystals were collected by filtration, washed with H₂O, and dried to give 1-acetyl-5-methylisatin (4.84 g, 47%): ¹H NMR (CDCl₃) 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 H₂O, 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⁺); ¹H 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 LiBH₄ (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 H₂O 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 CHCl₃-MeOH (100:1) as eluent to give 1-(*n*-butyl)-4-(*n*-butyloxycarbonyl)-2-oxo-1,2,3,4-tetrahydroquinoline (1.88 g, 14%): ¹H NMR (CDCl₃) 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), H₂O (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 purified by silica gel column chromatography with CHCl₃-MeOH (10:1) as eluent to give compound 17 (1.73 g, 84%): ¹H 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⁺), C₂₂H₃₀N₂O₃ requires 370.2256; ¹H 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-HT₃ 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-HT₃ 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 [³H]quipazine,²⁶ a high affinity ligand for the 5-HT₃ receptors. A membrane fraction obtained from 3 × 10⁶ 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 [³H]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 72222¹⁰) from the total binding. The K_i values were derived from the IC₅₀ (concentration of 50% inhibition) values according to the method of Cheng and Prusoff.⁴⁰ The K_d value of [³H]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 anesthetized 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 ED₅₀ was calculated at the dose which reduced the 5-HT-induced bradycardia by 50%.

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