5-HT_3 Receptor Antagonists. 2. 4-Hydroxy-3-quinolinecarboxylic Acid Derivatives

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A series of 4-hydroxy-3-quinolinecarboxylic acid derivatives (6) and 4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxylic acid derivatives (7) were designed and synthesized as 5-HT_3 receptor antagonists. Molecular modeling studies suggested that the 3-carbonyl moiety in 6 was almost coplanar to the plane of an aromatic ring, but in 7 there was a 30° deviation. 4-Hydroxy substitution in quinoline derivatives enhanced affinity for the 5-HT_3 receptors, and *endo*-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-hydroxy-3-quinolinecarboxamide (**6f**) exhibited the most potent activity in the Bezold–Jarisch (B-J) reflex test (ED_{50} = 0.1 μg/kg, iv) among quinoline derivatives 6. Although 4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxamide derivatives (**7a**) exhibited higher affinity (e.g., **7d**: K_i = 0.48 nM) for the 5-HT_3 receptors than ondansetron (K_i = 7.6 nM) or granisetron (K_i = 2.1 nM), these amides showed less potent activity in the B-J reflex test than the reference compounds. Interestingly, the ester derivatives **7c**, **7f**, and **7h** eliminated affinity for the 5-HT_3 receptors. These unusual structure–activity relationships and the deviation of the 3-carbonyl moiety from the plane of an aromatic ring suggest that the active conformation of **7a** might be different from the proposed one for the preceding 5-HT_3 antagonists. Thus, **6f** was chosen for further studies. No receptor binding for a variety of ligands was significantly antagonized by **6f**. Comparing the ratios of the ED_{50} value in the B-J reflex test (rat, iv) with the LD_{50} value in acute lethal toxicity (mouse, iv), **6f** was proved to have a 600-fold wider margin of safety than ondansetron. Compound **6f** dose-dependently attenuated both the incidence and frequency of emetic episodes induced by cisplatin in the dog (ED_{50} = 14 μg/kg, iv) more potently than ondansetron (ED_{50} = 210 μg/kg, iv). Compound **6f** (KF-20170) is now under further investigation as a drug for treating gastrointestinal disorder.

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] Recently, the 5-HT_3 receptor has attracted considerable attention 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] zacopride (**3**),[9] and ICS 205-930 (**4a**),[10] which have been shown to be effective in the control of cancer chemotherapy-induced emesis, an event suggested to be modulated by the 5-HT_3 receptors in the area postrema.[11]

Recently, many papers[12-14] described the important factors for high affinity toward the 5-HT_3 receptors, one of which is the coplanarity between an aromatic ring and a carbonyl moiety. However, according to our molecular modeling studies about 1-alkyl-2-oxo-1,2-dihydroquinoline-4-carboxylic acid derivatives (**5**), which possess high affinity for the 5-HT_3 receptors, their minimum-energy conformation did not have such a coplanarity.[14] The ethylene moiety in ondansetron (**1**)[7] or the intramolecular hydrogen bond between N atom at the 2-position and H atom of the amide group in granisetron (**2**)[8] or between O atom of the methoxy group and H atom of the amide group in zacopride (**3**)[9] can be considered to contribute toward maintaining the planarity between an aromatic ring and a carbonyl moiety. We therefore introduced such a hydrogen bond into the quinoline derivatives in order to obtain coplanar compounds and examine their structure–activity relationships.

We designed compounds **6a**, in which H atom of the hydroxy group at the 4-position (acidic proton) and O atom of the carbonyl group at the 3-position could form an intramolecular hydrogen bond,[15] and further, compounds **7a**, in which besides the above hydrogen bond, another hydrogen bond might exist between O atom of the carbonyl group at the 2-position and H atom of the amide group at the 3-position.

This paper describes the synthesis, the molecular modeling studies, and the 5-HT_3 receptor antagonistic activity of a series of quinoline- and naphthyridine-3-carboxylic acid derivatives.

Chemistry

The general procedures for the preparation of the target compounds are shown in Scheme I. 3-Quinolinecarboxylic acid derivatives (**8**) were treated with $SOCl_2$ followed by the reaction with tropine or amines such as *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-ylamine,[16] *exo*-8-methyl-8-azabicyclo[3.2.1]oct-3-ylamine,[17] *endo*-9-methyl-9-azabicyclo[3.3.1]non-3-ylamine,[17] or *endo*-1-azabicyclo[3.3.1]non-4-ylamine[18] to afford target compounds **6** (*n*-BuLi as a base in method A and NaH as a base in method B) (Scheme I).

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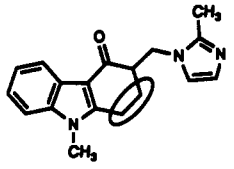

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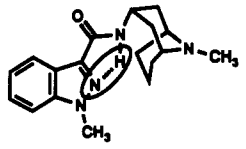

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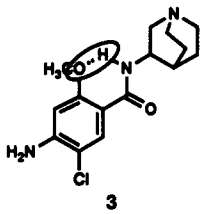

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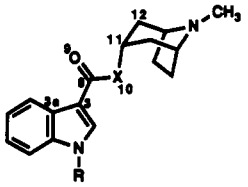
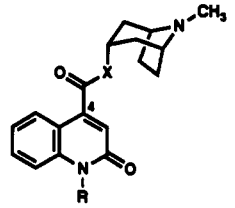
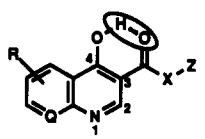




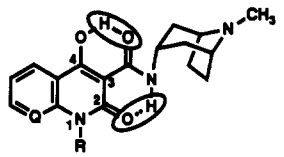
4a: R=H, X=O
4b: R=Me, X=O
4c: R=Me, X=NH

4

5

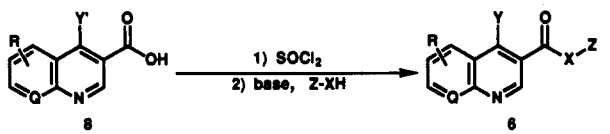


6a
(Z: bicyclo system)



7a

Scheme I



8

6

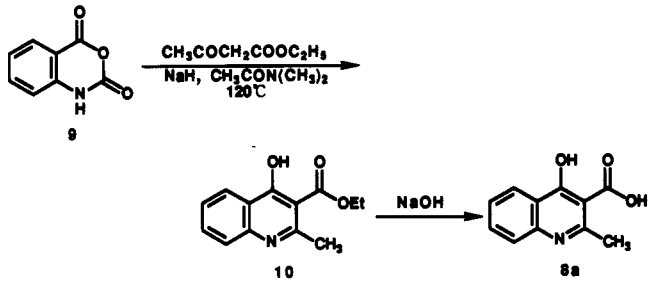
base : *n*-BuLi (Method A) or NaH (Method B)

Q = CH or N
X = O or NH
Y = H, OH, or Cl
Y' = H or OH
Z = bicyclo system

The starting carboxylic acids, 4-hydroxy-3-quinolinecarboxylic acid[19] and 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid,[20,21] were prepared according to the reported methods, respectively. 4-Hydroxy-2-methyl-3-quinolinecarboxylic acid (**8a**) was prepared by the reaction of isatoic anhydride (**9**) with ethyl acetoacetate followed by hydrolysis (Scheme II).

Compounds **6a** (6; Y = OH) are usually water soluble and sometimes could not be effectively extracted with organic solvents even at pH 7. This character made purification difficult for several compounds. Thus, **8b** (8; Q = CH, R = H, Y' = OH) was treated with an excess of $SOCl_2$ in the presence of several drops of DMF to afford 4-chloroquinoline-3-carbonyl chloride, which was then reacted with the amine to afford **6e** (Scheme III). Compound **6e** is more lipophilic than **6f** (Scheme III), and therefore could be easily extracted with $CHCl_3$ and further purified. Then, hydrolysis of **6e** easily occurred with 0.1 N HCl to afford **6f**. Compounds **6h**, **6i**, and **6l** were

Scheme II

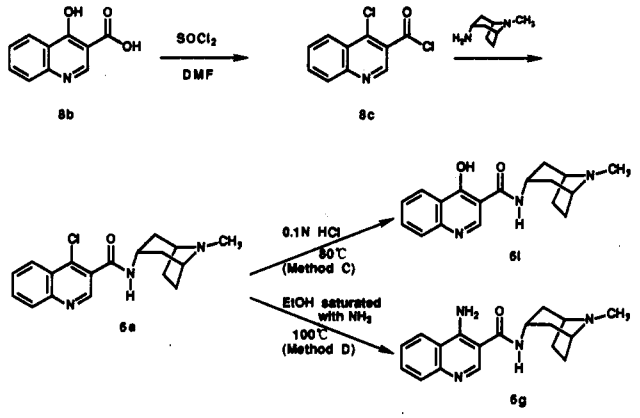


9

10

8a

Scheme III



8b

8c

6e

6l

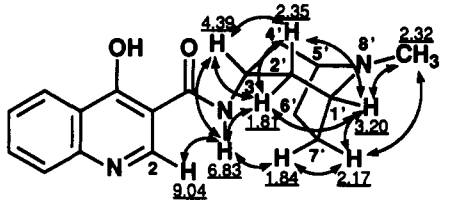
6g

similarly prepared from the 4-chloro derivatives. An 4-amino derivative **6g** was prepared from **6e** by ammonolysis (Scheme III).

Spectroscopic assignment of *endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amine or its amides has never been described in the literatures. Thus, we confirmed the stereochemical structure of **6f** using NOESY as shown in Figure 1. Observation of NOE between the amide hydrogen and hydrogen at the 6′-*endo*- or 7′-*endo*-position indicated the *endo* stereochemistry as illustrated in **6f**.

Compounds **6k** and **7(b–i)** were prepared from the corresponding ethyl esters **10** or **11** by the exchange reaction, respectively (Scheme IV). The starting ethyl esters, ethyl 4-hydroxy-2-methyl-3-quinolinecarboxylate (**10**)[22] and ethyl 1-*n*-butyl-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxylate,[23] were prepared according to the reported methods, respectively. Ethyl 4-hydroxy-2-oxo-1-phenyl-1,2-dihydro-1,8-naphthyridine-3-carboxylate (**11a**) was prepared as follows. Methyl 2-anilinonicotinate[24] (**12**) was treated with trichloromethyl chloroformate to afford azaisatoic anhydride derivative **13**,[25] which was then reacted with diethyl malonate to give ethyl ester **11a** (Scheme V). Ethyl 1-*n*-butyl-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (**11b**) was prepared similarly.

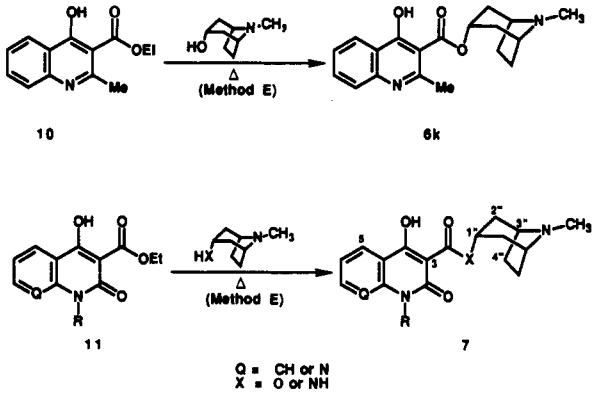
Since a number of tautomeric forms are possible for compounds **7**. We examined NMR spectra of **7e**. Assignment of ^{13}C signals were done by the HMQC (heteronuclear multiple quantum correlation) and the LSPD (long-range selective proton decoupling) techniques (see Experimental Section). The carbon (C-3) was proved to be quaternary by the HSQC (heteronuclear single quantum coherence) and the DEPT (distortionless enhancement by polarization transfer) techniques. The LSPD between the C-5 (δ_C 171.8 ppm) and the proton at the 4-OH group (δ_H 17.17 ppm) was observed. Thus a major tautomeric form of **7e** was elucidated as shown in Scheme IV.



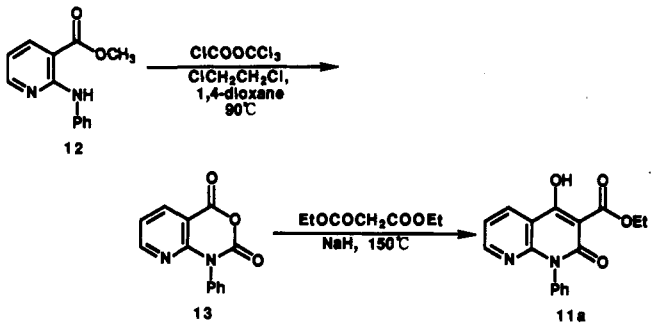
6f

Figure 1. Chemical shifts and NOE data of compound **6f**.

Scheme IV



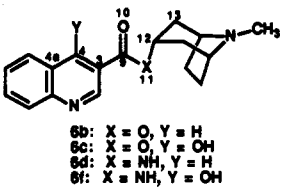
Scheme V

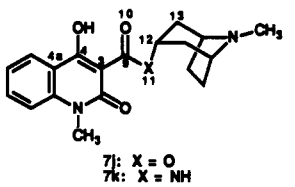


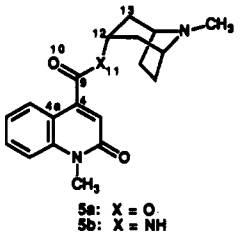
The physical and analytical data of all compounds are listed in Tables I and II.

Molecular Modeling Studies

To examine the validity of our drug design based upon the forced coplanarity of an aromatic group with a carbonyl group by an intramolecular hydrogen bond, molecular modeling studies for compounds **6b**, **6c**, **6d**, **6f**, **7j**, and **7k** were performed on an IRIS 4D/310 GTXB workstation with QUANTA 3.2/CHARMm 21.3.[26] A crystal structure of granisetron (**2**)[27] was retrieved from the Cambridge Structural Database[28] and modified with standard bond angles and lengths for initial structures of our compounds. Charge assignments of these molecules were performed using the charge templates in QUANTA. In the molecules with the 4-hydroxy group (**6c**, **6f**, **7j**, and **7k**), two sets of initial structures (the dihedral angle of C(4a)–C(4)–O–H = 180° or 0°) were used. These structures were then minimized using the adopted-basis Newton–Raphson technique[29,30] (nonbonded parameter cut off = 15 Å). A conformational search about rotatable bonds was performed at increments of 30° [C(9)–O(11) or C(9)–N(11), and O(11)–C(12) or N(11)–C(12)] and 20° [C(3)–C(9)]. The lower-energy conformers within 10 kcal/mol from the lowest-energy conformer were then minimized. Thus global energy minima were determined. The dihedral angles in the minimum-energy and lower-energy conformers of these compounds are shown in Table III, along with those of reference compounds **4b**, **4c**, **5a**, and **5b**.[14] From these calculations, H atom at the 4-hydroxy group was elucidated to be directed to O atom at the 3-carbonyl group in the minimum-energy conformers of **6c**, **6f**, **7j**, and **7k**.



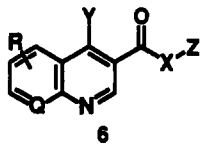




In contrast to the results in **5a** and **5b**,[14] an aromatic ring in **6b** was coplanar to a carbonyl moiety. Superimposition of **6b** with **5a** is shown in Figure 2, which suggests that the quinoline ring in **6b** interacts with the 5-HT$_3$ receptors in a different manner from that of the quinolone ring in **5a**. Introduction of a hydroxy group at the 4-position of the quinoline ring resulted in a very small deviation of the carbonyl moiety from the plane of an aromatic ring (Figure 3; compare **6c** and **6f** vs **6b** and **6d** in Table III, respectively) presumably due to small steric repulsion between the 4-hydroxy group and the 3-carbonyl group. Superimposition of **6f** with **6d** is shown in Figure 4. Observation of NOEs between the proton at the 2-position and the amide proton and between the proton at the 7′-position and the amide proton (Figure 1) is consistent with the minimum-energy conformation of **6f**. In 4-hydroxy-2-oxo-1,2-dihydroquinoline derivatives **7j** and **7k** (model compounds), the carbonyl moieties were calculated to be about 30° deviated from the plane of an aromatic ring (Figure 5). Superimposition of **7k** with **6f** is shown in Figure 6. However, the energy difference between the coplanar conformation, which is not a stable one, and the minimum-energy conformation of **7k** or **7j** was calculated to be ca. 1.1 or 0.6 kcal/mol. Thus, the molecules might easily populate the coplanar conformation during their interactions with the 5-HT$_3$ receptors. It is interesting to compare the conformation of **7** with that of the (2-alkoxybenzoyl)urea derivative, of which NMR and X-ray crystallography studies proved the coplanarity between a carbonyl moiety and an aromatic ring.[13e] From our calculations, it seems that the steric factor contributes to the determination of the minimum-energy conformation of these compounds **7** more dominantly than the ability to form the coplanarity by an intramolecular hydrogen bond.

Although the three-dimensional structures of **6b**, **6c**, **6d**, **6f**, **7j**, and **7k** were partly different from the expected structures, we examined 5-HT$_3$ receptor antagonistic activities of these compounds.

Table I. Quinoline or 1,8-Naphthyridine Type

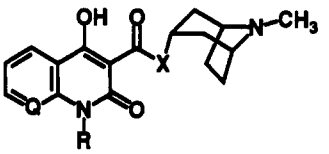


6

compd	Q	R	X	Y	Z	method	% yield[a]	mp, °C	formula	anal.[b]
6b	CH	H	O	H	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	A	34 (45)	288.0	$C_{18}H_{20}N_2O_2$·2HCl·2.4H_2O	C,H,N[d]
6c	CH	H	O	OH	*endo*-(8-methyl-azabicyclo[3.2.1]oct-3-yl)	A	21 (29)	278–280	$C_{18}H_{20}N_2O_3$·2HCl·H_2O	C,H,N
6d	CH	H	NH	H	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	B	22 (29)	187–191	$C_{18}H_{21}N_3O$·2HCl·H_2O	C,H,N
6e	CH	H	NH	Cl	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	B	31 (37)	181–184	$C_{18}H_{20}N_3OCl$·2HCl·2.1H_2O	C,H,N
6f	CH	H	NH	OH	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	C	73 (~100)	127.5–128.9	$C_{18}H_{21}N_3O_2$·$C_4H_4O_4$[c]·H_2O	C,H,N
6g	CH	H	NH	NH_2	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	D	76 (96)	282.5–288.5	$C_{18}H_{22}N_4O$·2HCl·H_2O	C,H,N
6h	CH	H	NH	OH	*exo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	C	73 (~100)	254.8–257.4	$C_{18}H_{21}N_3O_2$·$C_4H_4O_4$[c]·1.5H_2O	C,H,N
6i	CH	H	NH	OH	*endo*-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)	C	82 (~100)	130.1–132.0	$C_{18}H_{23}N_3O_2$·$C_4H_4O_4$[c]·H_2O	C,H,N
6j	CH	H	NH	OH	*endo*-(1-azabicyclo[3.3.1]non-4-yl)	B	64 (71)	128.8–129.6	$C_{18}H_{21}N_3O_2$·2$C_4H_4O_4$[c]·H_2O	C,H,N
6k	CH	2-CH_3	O	OH	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	E	42 (55)	149.0–150.5	$C_{18}H_{22}N_2O_3$·2HCl·0.5H_2O	C,H,N
6l	CH	2-CH_3	NH	OH	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	C	55 (89)	275.5–277.2	$C_{18}H_{23}N_3O_2$·$C_4H_4O_4$[c]·2H_2O·0.3AcOEt	C,H,N
6m	N	7-CH_3	O	OH	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	A	19	244.5–248.0	$C_{18}H_{21}N_3O_3$·0.8H_2O	C,H,N
6n	N	7-CH_3	NH	OH	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	B	31 (75)	275.3–276.7	$C_{18}H_{22}N_4O_2$·0.5$C_4H_4O_4$[c]·1.5H_2O	C,H,N

[a] Values in parentheses are the yields as a free base. [b] Analyses for the elements indicated were within ±0.4% of the theoretical values. [c] $C_4H_4O_4$, fumaric acid. [d] H: calcd, 6.55; found, 6.02.

Table II. 2-Oxo-1,2-dihydroquinoline or 2-Oxo-1,2-dihydro-1,8-naphthyridine Type



7

compd	Q	R	X	method	% yield[a]	mp, °C	formula	anal.[b]
7b	CH	H	NH	E	83 (91)	275.9–276.2	$C_{18}H_{21}N_3O_3$·$C_4H_4O_4$[c]·0.5H_2O	C,H,N
7c	CH	butyl	O	E	19 (59)	163.0–164.0	$C_{22}H_{28}N_2O_4$·$C_4H_4O_4$[c]·H_2O	C,H,N
7d	CH	butyl	NH	E	40 (47)	159.2–161.5	$C_{22}H_{28}N_3O_3$·2$C_4H_4O_4$[c]·H_2O	C,H,N
7e	CH	phenyl	NH	E	47 (75)	252.6–256.7	$C_{24}H_{25}N_3O_3$·$C_4H_4O_4$[c]·2.2H_2O	C,H,N[e]
7f	N	butyl	O	E	12 (79)	123.0–125.0	$C_{21}H_{27}N_3O_4$·$C_4H_4O_4$[c]·2H_2O	C,H,N
7g	N	butyl	NH	E	35 (72)	176.3–182.7	$C_{21}H_{28}N_4O_3$·$C_4H_4O_4$[c]	C,H,N
7h	N	phenyl	O	E	55	268.0–270.0	$C_{23}H_{23}N_3O_4$·0.5H_2O	C,H,N
7i	N	phenyl	NH	E	49 (60)	146.7–148.2	$C_{23}H_{24}N_4O_3$·$C_4H_4O_4$[c]·0.5H_2O·0.4C_3H_8O[d]	C,H,N

[a–c] See footnotes a–c in Table I. [d] C_3H_8O, isopropyl alcohol. [e] N: calcd, 7.81; found, 8.69.

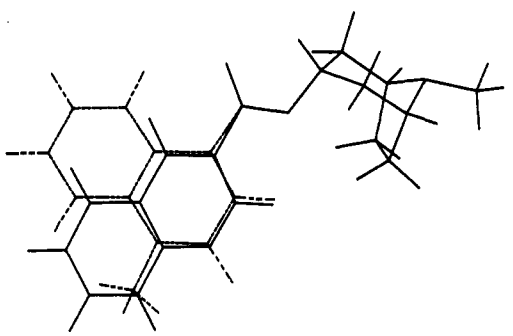


Figure 2. Superimposition of **6b** (solid line) with **5a** (dotted line) with the tropine moiety fitted together in the minimum-energy conformation.

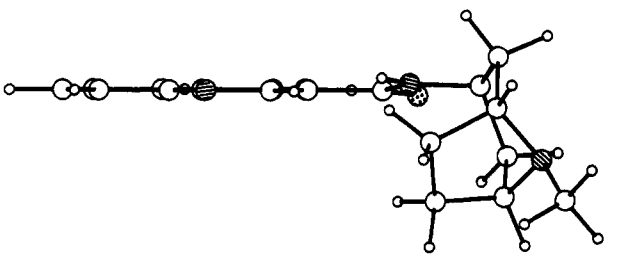


Figure 3. The energetic miinimum of **6f** viewed along the aromatic plane.

Pharmacological Results and Discussion

The 5-HT_3 receptors labeled by [^{3}H]quipazine in the neuroblastoma–glioma NG 108-15 cells[31,32] were reported to be similar to those labeled by the selective 5-HT_3 receptor antagonist, [^{3}H]GR 65630.[33] Thus, our compounds were evaluated for the 5-HT_3 receptor binding affinity versus [^{3}H]quipazine in NG 108-15 cells.

First, we evaluated quinoline derivatives **6** (Table IV). 4-Unsubstituted compound **6b** (ester) showed only low affinity for the 5-HT_3 receptors (K_i = 66 nM). 4-Unsubstituted and 4-amino-substituted amide derivatives **6d** and **6g** eliminated activity. The 4-chloro derivative **6e** (amide) showed low affinity. On the other hand, 4-hydroxy derivatives **6c** and **6f**, either an ester or an amide, exhibited high affinity (K_i = 6.1 and 1.5 nM, respectively) comparable to that of ondansetron (**1**; K_i = 7.6 nM) or granisetron (**2**; K_i = 2.1 nM). The presence of an intramolecular hydrogen bond in **6c** or **6f** was not supported by ^{1}H NMR studies. For example, the 4-hydroxy proton signal of **6c** or **6f** in DMSO-d_6 or $CDCl_3$ was not detected in the downfield region of the spectrum (δ_H 11–17 ppm). The intramolecular hydrogen bond in these compounds might be very weak. Molecular modeling studies of **6b**, **6c**, **6d**, and **6f**, suggest that an aromatic ring is almost coplanar to a carbonyl moiety regardless of the presence of a hydroxy group. Thus, the hydroxy group at the 4-position does not contribute to maintain the coplanarity between an aromatic ring and a carbonyl moiety and might interact directly with the 5-HT_3 receptors.

Table III. Conformational Analysis of **6b**, **6c**, **6d**, **6f**, **7j**, **7k**, **5a**, **5b**, **4b**, and **4c**

		dihedral angle (deg)			
compd	E (kcal/mol)	C(3)–C(9)[a]	C(9)–O or N(11)[b]	O or N(11)–C(12)[c]	C(4)–OH[d]
6b	0.00	−179.7	176.4	−72.0	
	0.17	0.8	176.6	−71.9	
6c	0.00	−178.4	176.5	−71.8	179.4
	0.90	17.6	176.8	−70.6	−170.9
	3.14	−179.3	176.7	−72.01	−49.3
6d	0.00	178.3	178.3	−73.2	
	0.79	−1.6	178.4	−73.2	
6f	0.00	173.6	178.0	−73.1	−178.6
	2.75	17.2	179.1	−74.6	−45.4
	2.90	24.9	179.9	−76.0	−146.6
7j	0.00	151.2	−174.5	−72.5	−179.1
	0.19	29.0	175.3	−72.1	179.3
	3.15	35.0	176.2	−72.3	−0.9
7k	0.00	150.6	−180.0	−72.5	−178.6
	2.62	146.2	−179.1	−72.4	−1.7
	3.0	38.0	178.6	−73.8	−2.3
	3.1	44.9	178.9	−73.4	−172.3

		dihedral angle (deg)		
compd	E (kcal/mol)	C(4)–C(9)[e]	C(9)–O or N(11)[f]	O or N(11)–C(12)[g]
5a	0.00	156.0	176.7	−72.2
	0.25	24.9	175.8	−73.0
	4.62	120.6	−12.2	−67.8
5b	0.00	149.2	178.2	−73.2
	1.52	40.5	179.2	−75.2
	3.40	117.2	−4.9	−103.3

		dihedral angle (deg)		
compd	E (kcal/mol)	C(3)–C(8)[h]	C(8)–O or N(10)[i]	O or N(10)–C(11)[j]
4b	0.00	178.8	176.0	−72.0
	0.04	8.7	178.8	−72.0
4c	0.00	178.3	178.7	−74.5
	1.40	12.0	179.6	−75.5

[a] C(4)–C(3)–C(9)–O or N(11). [b] C(3)–C(9)–O or N(11)–C(12). [c] C(9)–O or N(11)–C(12)–C(13). [d] C(4a)–C(4)–O–H. [e] C(4a)–C(4)–C(9)–O or N(11). [f] C(4)–C(9)–O or N(11)–C(12). [g] C(9)–O or N(11)–C(12)–C(13). [h] C(3a)–C(3)–C(8)–O or N(10). [i] C(3)–C(8)–O or N(10)–C(11). [j] C(8)–O or N(10)–C(11)–C(12).

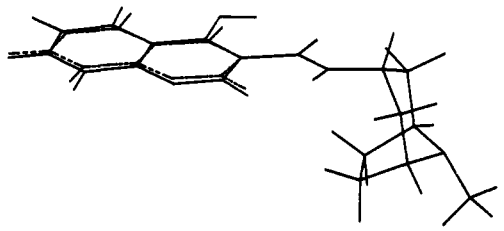


Figure 4. Superimposition of **6f** (solid line) with **6d** (dotted line) with the tropine moiety fitted together in the minimum-energy conformation.

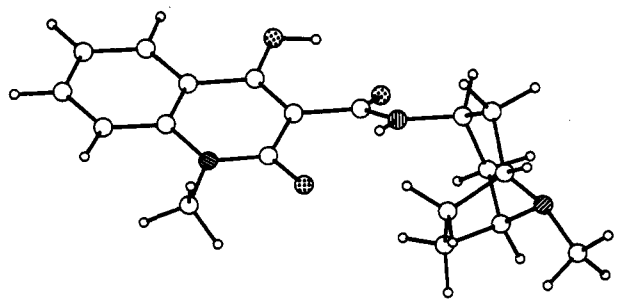


Figure 5. The energetic minimum of **7k**.

Replacement of the bicyclo system from an *endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl) group (**6f**) to an *exo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl) (**6h**), an *endo*-(9-methyl-9-azabicyclo[3.3.1]non-3-yl) (**6i**), or an *endo*-(1-azabicyclo[3.3.1]non-4-yl) group (**6j**) resulted in the reduction of affinity. Introduction of a methyl group in the 2-position (**6k** and **6l** vs **6c** and **6f**, respectively) also decreased affinity. Steric constrains restrict substitution in the quinoline ring as was demonstrated in the indole derivatives.[13c,d,34] Further, replacement of the 6-6 ring system from an quinoline ring (**6c** and **6f**) to a 1,8-naphthyridine ring (**6m** and **6n**) resulted in the loss of affinity. In this series, a quinoline ring seems to be essential.

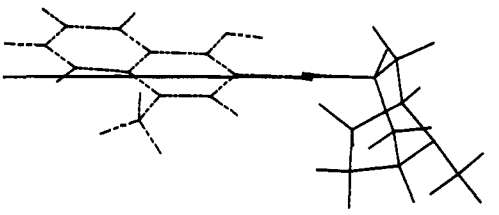
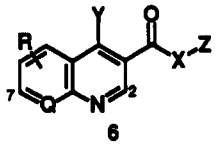


Figure 6. Superimposition of **6f** (solid line) with **7k** (dotted line) with the tropine moiety fitted together in the minimum-energy conformation.

Next, we evaluated 4-hydroxy-2-oxo-1,2-dihydroquinoline derivatives **7** (Table V). The amides **7b**, **7d**, **7e**, **7g**, and **7i** exhibited high affinity. Particularly, the quinoline derivatives **7d** and **7e** exhibited higher affinity (K_i = 0.48 and 1.4 nM, respectively) than ondansetron (**1**) or granisetron (**2**). As was demonstrated in a series of compounds **5**,[14] there was some bulk tolerance at the 1-position (**7d**, R = *n*-Bu; **7e**, R = phenyl). In ^{1}H NMR spectra of **7d** and **7e**, the 4-hydroxy proton signals were observed in the downfield (δ 16.94 and 17.7, respectively). As above, these data suggest the presence of a hydrogen bond between H atom of the 4-hydroxyl group and O atom of the 3-carbonyl group in **7d** and **7e**. However, in other compounds (**7b**, **7g**, and **7i**), such a downfield proton signal was not observed. These results and modeling studies suggest that the hydrogen bond in **7** is very weak and cannot force the coplanarity of an aromatic group with a carbonyl group. On the other hand, the esters in compounds **7** (**7c**, **7f**, and **7h**) eliminated affinity for the 5-HT$_3$ receptors. This result is very different from that in **5**, where the esters were 100-fold more active than the amides. In both cases, the carbonyl moiety at the 3- or 4-position is speculated to be about 30° deviated from the plane of an aromatic ring by molecular modeling studies. Thus, *the difference in their structure–activity relationships suggest that the active conformation of 7 seems to be different from that of 5 and both should also be different from the proposed one of the preceding 5-HT$_3$ receptor antagonists.*[12,13]

Looking at the binding data of these compounds, the in vivo 5-HT$_3$ receptor antagonistic activity was examined for their ability to inhibit the 5-HT induced bradycardia [Bezold–Jarisch (B-J) reflex test[35]] in rats (Tables IV and V). 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 right ventricle wall.[36] In this test, compounds **7** showed less potent activity than ondansetron, although **7d** and **7e** showed higher affinity to the 5-HT$_3$ receptors in receptor binding than ondansetron. Turconi et al. described the good correlation between binding affinity and activity in the B-J reflex test with respect to their compounds.[37] Since these compounds **7** were stable at pH 7 (buffer) for several hours and did not shown partial agonistic activity (data not shown), this result was very surprising. Pharmacokinetic

Table IV. 5-HT_3 Receptor Binding Affinity, Antagonism of Bezold-Jarisch Reflex, and Acute Lethal Toxicity (1)

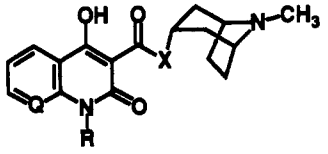


6

compd	Q	R	X	Y	Z	binding affinity,[a] K_i[b] (nM)	B-J reflex inhibition,[c] ED_{50} (mg/kg, iv) at 5 min	acute lethal toxicity[d] LD_{50} (mg/kg, iv)
6b	CH	H	O	H	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	66 ± 5.9	0.37	
6c	CH	H	O	OH	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	6.1 ± 0.2	0.0017	113.9
6d	CH	H	NH	H	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	>100		
6e	CH	H	NH	Cl	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	85 ± 2.3		
6f	CH	H	NH	OH	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	1.5 ± 0.22	0.00010	21.4
6g	CH	H	NH	NH_2	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	>100		
6h	CH	H	NH	OH	*exo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	100 ± 4.7		
6i	CH	H	NH	OH	*endo*-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)	30 ± 1.2		
6j	CH	H	NH	OH	*endo*-(1-azabicyclo[3.3.1]non-4-yl)	18		
6k	CH	2-CH_3	O	OH	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	58		
6l	CH	2-CH_3	NH	OH	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	7.2	0.015	
6m	N	7-CH_3	O	OH	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	>100		
6n	N	7-CH_3	NH	OH	*endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)	>100		
1 (ondansetron)						7.6 ± 0.59	0.021	7.5
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] Number of determinations is four. [d] Number of determinations is three.

Table V. 5-HT_3 Receptor Binding Affinity, Antagonism of Bezold-Jarisch Reflex, and Acute Lethal Toxicity (2)



7

compd	Q	R	X	binding affinity[a] K_i[b] (nM)	B-J reflex inhibition[c] ED_{50} (mg/kg, iv) at 5 min	acute lethal toxicity[d] LD_{50} (mg/kg, iv)
7b	CH	H	NH	7.6 ± 0.28	0.22	88.0
7c	CH	butyl	O	>100		
7d	CH	butyl	NH	0.48 ± 0.041	0.29	47.0
7e	CH	phenyl	NH	1.4 ± 0.23	0.073	18.2
7f	N	butyl	O	>100		
7g	N	butyl	NH	6.4	>0.1	33.7
7h	N	phenyl	O	>100		
7i	N	phenyl	NH	14 ± 2.8		
1 (ondansetron)				7.6 ± 0.59	0.021	7.5
2 (granisetron)				2.1 ± 0.26	0.019	

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

studies of these compounds are in progress. On the other hand, some of compounds **6**, which possess high affinity for the 5-HT_3 receptors, showed potent activity. Particularly, activity of **6f** [ED_{50} (50% effective dose) = 0.10 μg/kg, iv] was 200-fold more potent than that of ondansetron (ED_{50} = 21 μg/kg, iv).

We also evaluated the selected compounds for their acute lethal toxicity (iv) in the mouse as an index of side effects (Tables IV and V). As the results indicate, all compounds tested showed weaker toxicity than ondansetron. Comparing the ratios of the ED_{50} value in the B-J reflex test with the LD_{50} (50% lethal dose) value in acute lethal toxicity, **6f** was proved to have a 600-fold wider margin of safety than ondansetron. Thus, **6f** was chosen for further studies.

The pharmacological specificity of comopund **6f** for 5-HT_3 recognition sites was examined by investigating **6f** in a wide variety of central nervous system binding assays. These include assays for serotonin receptors (5-HT_{1A}, [^{3}H]8-OH-DPAT, rat hippocampus; 5-HT_2, [^{3}H]SCH-23390, rat striatum; D_2, [^{3}H]spiperone, rat striatum) muscarinic receptors (M_1, [^{3}H]QNB, rat cerebral cortex; M_2, [^{3}H]QNB, rat heart), adenosine receptors (A_1, [^{3}H]-CHA, guinea pig cerebral cortex; A_2, [^{3}H]NECA, rat straitum), histamine receptors (H_1, [^{3}H]pyrilamine, guinea pig cerebellum; H_2, [^{3}H]tiotidine, guinea pig cerebral cortex), and adrenaline receptors (α_1, [^{3}H]WB4101, rat cerebral cortex; α_2, [^{3}H]clonidine, rat cerebral cortex; β, [^{3}H]dihydroalprenolol, rat cerebral cortex). The apparent affinities, measured as IC_{50} (concentration of 50% inhibition) values, for **6f** were larger than 10 μM, demonstrating that this compound was inactive at displacing binding to a number of central recognition sites. Thus, **6f** was identified to be a selective 5-HT_3 antagonist.

In beagle dogs, cisplatin (3 mg/kg) induced emesis 93.7 ± 6.8 min after intravenous administration and the number of emetic episodes was 19.4 ± 1.9 (n = 7) for 6 h. As shown in Table VI, **6f** dose-dependently attenuated both the incidence and frequency of emetic episodes induced by cisplatin (ED_{50} = 14 μg/kg, iv).[38] At doses of 0.1–0.3 mg/kg (iv), this compound reduced the number of emetic episodes by 80–100%, and at 0.3 mg/kg (iv), vomiting was

Table VI. Antiemetic Profile against Cisplatin-Induced Emesis in the Dog

compd[a]	dose (mg/kg)	route	n[b]	mean % reduction in emetic episodes	mean % increase in emetic latency
6f	0.01	iv	4	44**	14
	0.03	iv	4	54**	23
	0.1	iv	4	80***	116*
	0.3	iv	2	100	>284[c]
6f	0.1	po	4	64**	32*
	1.0	po	3	88***	142
1 (ondansetron)	0.1	iv	4	18	33*
	0.3	iv	4	61**	115**
	1.0	iv	2	100	>284[c]

[a] Administered 30 and 60 min prior to cisplatin (3 mg/kg, iv) for iv and po experiments, respectively. Mean number of emesis in control group (n = 7) is 19.4 ± 1.9, and mean minute of latency in control group is 93.7 ± 6.8; asterisks define significant difference from control group (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$). [b] n = number of dogs. [c] When dogs did not vomit, 360 min (duration of the study) was used to calculate the increase in emetic latency.

not observed until 360 min after cisplatin administration. Thus, 6f was clearly more potent than ondansetron (ED_{50} = 210 μg/kg, iv) and showed long duration of action. Further, 6f showed potent activity even after oral administration. Thus, 6f was proved to be a potent and long lasting antiemetic agent.

In conclusion, some of 4-hydroxy-3-quinolinecarboxylic acid derivatives showed high affinity for the 5-HT$_3$ receptors and exhibited potent activity in the B-J reflex test. Particularly, 6f was identified to be the most potent and selective 5-HT$_3$ antagonist. Thus, 6f (KF-20170) is now under further investigation as a drug for treating gastrointestinal disorder.

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 and ^{13}C NMR spectra were obtained on a JEOL JNM EX-270 FTNMR with Me_4Si as an internal standard, and mass spectra on a JEOL JMS-SX102 instrument (70 eV). 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 (Perkin-Elmer 2400CHN). Most of compounds were hygroscopic and could not be recrystallized in several solvents. Thus some were anlayzed by high resolution mass spectroscopy (JEOL JMS-SX 102 at 70 eV). High-performance liquid chromatography (HPLC) was carried out on a Hitachi L-6200 instrument with a YMC AM-312 ODS column, 150 mm × 6 mm.

Chemistry. The following procedures are representatives of the general methods that are described in the text. Purities of all compounds were examined by HPLC (mobile phase, 10–50% acetonitrile, and 0.5% acetic acid in H_2O; flow, 1–1.5 mL/min; UV detection at 254 nm) and proved to be more than 99%.

***endo*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl) 3-Quinolinecarboxlate Dihydrochloride (6b) (Method A).** A mixture of 3-quinolinecarboxylic acid (1.56 g, 9.01 mmol) and $SOCl_2$ (18 mL) was stirred at room temperature for 30 min. Excess of $SOCl_2$ was evaporated under reduced pressure, and anhydrous tetrahydrofuran (THF, 36 mL) was added (solution A). A 15% *n*-BuLi–hexane solution (9.5 mL, 15.35 mmol) was added to a mixture of tropine (2.18 g, 15.30 mmol) and anhydrous THF (6.3 mL) at 0 °C under an argon atmosphere, followed by stirring for further 15 min. After concentration of the mixture under reduced pressure, anhydrous THF (9 mL) and solution A were added dropwise. The mixture was stirred at room temperature for 3 h and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography with $CHCl_3$–MeOH (10:1) as eluent. The product was dissolved in a solvent mixture of $CHCl_3$ and MeOH, followed by addition of 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 6b as the hydrochloride (1.13 g, 34%): IR (KBr) 1734, 1637, 1029, 773 cm^{-1}; HRMS m/z 296.1536 (M^+), $C_{18}H_{20}N_2O_2$ requires 296.1525; ^{1}H NMR (DMSO-d_6) δ 9.37 (s, 1 H), 9.12 (s, 1 H), 8.33 (d, 1 H, J = 7.8 Hz), 8.21 (d, 1 H, J = 8.5 Hz), 8.01 (m, 1 H), 7.81 (m, 1 H), 5.27 (m, 1 H), 3.93 (m, 2 H), 2.70 (s, 3 H), 2.0–2.9 (m, 8 H).

***endo*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl) 4-Hydroxy-3-quinolinecarboxylate Dihydrochloride (6c) (Method A).** A mixture of 4-hydroxy-3-quinolinecarboxylic acid[19] (1.32 g, 7.00 mmol) and $SOCl_2$ (15 mL) was stirred at room temperature for 30 min. Excess of $SOCl_2$ was evaporated under reduced pressure, and anhydrous THF (30 mL) was added (solution A). A 15% *n*-BuLi–hexane solution (7.4 mL, 11.96 mmol) was added to a mixture of tropine (1.68 g, 11.90 mmol) and anhydrous THF (5 mL) at 0 °C under an argon atmosphere, followed by stirring for further 15 min. After concentration of the mixture under reduced pressure, anhydrous THF (7 mL) and solution A were added dropwise. The mixture was stirred at room temperature for 3 h and then concentrated under reduced pressure. The residue was purified by column chromatography of DIAION SP 207 (Mitsubishi Kasei Co., Ltd.) with a 20–80% aqueous MeOH solution as eluent. The product was dissolved in a solvent mixture of $CHCl_3$ and MeOH, followed by addition of 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 6c as the hydrochloride (0.56 g, 21%): IR (KBr) 3420 (br), 1690, 1642, 1583, 1429, 1024, 767 cm^{-1}; MS m/z 312 (M^+); ^{1}H NMR (DMSO-d_6) δ 10.76 (br s, 1 H), 8.56 (s, 1 H), 8.20 (d, 1 H, J = 7.7 Hz), 7.70 (m, 2 H), 7.42 (m, 1 H), 5.14 (m, 1 H), 3.86 (m, 2 H), 2.68 (s, 3 H), 1.8–2.9 (m, 8 H).

***endo*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl) 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (6m):** IR (KBr) 3420 (br), 1723, 1621, 1588, 1543, 1447, 799 cm^{-1}; HRMS m/z 327.1607 (M^+), $C_{18}H_{21}N_3O_3$ requires 327.1583; ^{1}H NMR (DMSO-d_6) δ 8.48 (s, 1 H), 8.42 (d, 1 H, J = 8.1 Hz), 7.35 (d, 1 H, J = 8.1 Hz), 5.06 (m, 1 H), 3.18 (m, 2 H), 2.60 (s, 3 H), 2.29 (s, 3 H), 1.6–2.4 (m, 8 H).

***endo-N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-3-quinolinecarboxamide Dihydrochloride (6d) (Method B).** A mixture of 3-quinolinecarboxylic acid (0.49 g, 2.83 mmol), $SOCl_2$ (1 mL), and several drops of dimethylformamide was stirred at room temperature for 1 h and then concentrated under reduced pressure (the acid chloride A). A solution of *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-ylamine[16] (0.79 g, 5.63 mmol) in anhydrous THF (15 mL) was added to a suspension of NaH (0.01 g, 4.17 mmol) in anhydrous THF (30 mL) at room temperature under an argon atmosphere, followed by stirring for further 1 h. The acid chloride A was portionwise added to this solution, and the mixture was stirred at room temperature for 12 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 with $CHCl_3$ (2 × 50 mL). 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 (25 mL). The precipitated crystals were collected by filtration and dried. The product was dissolved in MeOH, followed by addition of EtOAc saturated with HCl and EtOAc. The precipitated crystals were collected by filtration and dried to give compound 6d as the hydrochloride (0.23 g, 22%): IR (KBr) 1666, 1547, 1387, 1366, 1306, 780 cm^{-1}; MS m/z 295 (M^+); ^{1}H NMR (DMSO-d_6) δ 10.74 (br s, 1 H), 9.47 (s, 1 H), 9.25 (s, 1 H), 8.99 (m, 1 H), 8.20–8.41 (m, 2 H), 8.05 (m, 1 H), 7.85 (m, 1 H), 4.04 (m, 1 H), 3.86 (m, 2 H), 2.67 (s, 3 H), 2.0–2.9 (m, 8 H).

***endo-N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-chloro-3-quinolinecarboxamide Dihydrochloride (6e) (Method B).** A mixture of 4-hydroxy-3-quinolinecarboxylic acid[19] (0.76 g, 4.02 mmol), $SOCl_2$ (4 mL), and several drops of DMF was stirred at room temperature for 2 h and then concentrated under reduced pressure (the acid chloride A). A solution of *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-ylamine[16] (0.56 g, 3.99 mmol) in anhydrous THF (15 mL) was added to a suspension of NaH (0.01 g, 4.17

mmol) in anhydrous THF (30 mL) at room temperature under an argon atmosphere, followed by stirring for further 1 h. 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 extraction with $CHCl_3$ (2 × 50 mL). 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 (25 mL). The precipitated crystals were collected by filtration and dried. The product was dissolved in MeOH, followed by addition of EtOAc saturated with HCl and EtOAc. The precipitated crystals were collected by filtration and dried to give compound **6e** as the hydrochloride (0.51 g, 31%): IR (KBr) 1661, 1633, 1545, 1355 cm^{-1}; HRMS *m/z* 329.1285 (M^+), $C_{18}H_{20}N_3OCl$ requires 329.1295; ^1H NMR (DMSO-d_6) δ 10.80 (d, 1 H, *J* = 6.8 Hz), 8.91 (s, 1 H), 8.33 (d, 1 H, *J* = 8.3 Hz), 8.18 (d, 1 H, *J* = 8.4 Hz), 7.97 (m, 1 H), 7.87 (m, 1 H), 4.06 (m, 1 H), 3.85 (m, 2 H), 2.66 (s, 3 H), 1.9–2.9 (m, 8 H).

***endo-N*-(1-Azabicyclo[3.3.1]non-4-yl)-4-hydroxy-3-quinolinecarboxamide difumarate (6j)**: IR (KBr) 1710, 1653, 1516, 1476, 978, 766 cm^{-1}; HRMS *m/z* 311.1621 (M^+), $C_{18}H_{21}N_3O_2$ requires 311.1634; ^1H NMR (DMSO-d_6) δ 10.44 (s, 1 H), 8.75 (s, 1 H), 8.28 (d, 1 H, *J* = 7.6 Hz), 7.87 (d, 1 H, *J* = 3.7 Hz), 7.77 (m, 2 H), 7.50 (m, 1 H), 6.60 (s, 4 H), 4.21 (m, 1 H), 3.31–3.73 (m, 7 H), 1.83–2.21 (m, 6 H).

***endo-N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxamide hemifumarate (6n)**: IR (KBr) 1663, 1609, 1527, 1454, 1361, 1244, 810 cm^{-1}; MS *m/z* 326 (M^+); ^1H NMR (CF_3COOD) δ 9.39 (d, 1 H, *J* = 8.5 Hz), 9.35 (s, 1 H), 7.91 (d, 1 H, *J* = 8.5 Hz), 7.34 (s, 2 H), 6.57 (s, 2 H), 4.62 (d, 1 H, *J* = 6.1 Hz), 4.14 (m, 2 H), 3.09 (s, 3 H), 2.65 (s, 1 H), 2.36–3.05 (m, 8 H).

***endo-N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-hydroxy-3-quinolinecarboxamide Fumarate (6f) (Method C)**. A mixture of compound **6e** (free base, 0.68 g, 2.06 mmol) and 1 N HCl (180 mL) was stirred with heating at 80 °C for 13 h. Then, the solutioin was added to H_2O followed by washing with $CHCl_3$, and an aqueous saturated $NaHCO_3$ solution was added to adjust the pH of the solution to 7.5. Thereafter, this solution was extracted with $CHCl_3$, and dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. To the residue were added *i*-PrOH (40 mL) and fumaric acid (0.24 g, 2.07 mmol), followed by stirring at room temperature. Hexane (15 mL) was added to this solution with stirring, and the precipitated crystals were collected by filtration and dried to give compound **6f** as the fumarate (0.64 g, 73%): IR (KBr) 3400 (br), 1713, 1650, 1613, 1531, 1476, 1359, 759 cm^{-1}; MS *m/z* 311 (M^+); ^1H NMR (DMSO-d_6) δ 10.79 (d, 1 H, *J* = 7.3 Hz), 8.75 (s, 1 H), 8.29 (d, 1 H, *J* = 7.8 Hz), 7.69–7.75 (m, 2 H), 7.51 (m, 1 H), 6.55 (s, 2 H), 4.17 (m, 1 H), 3.73 (m, 2 H), 2.62 (s, 3 H), 1.80–2.55 (m, 8 H); ^1H NMR of a free base (**6f'**) (DMSO-d_6) δ 10.67 (d, 1 H, *J* = 7.9 Hz), 8.73 (s, 1 H), 8.28 (d, 1 H, *J* = 8.4 Hz), 7.75 (m, 1 H), 7.69 (d, 1 H, *J* = 8.4 Hz), 7.46 (m, 1 H), 4.10 (m, 1 H), 3.10 (m, 2 H), 2.21 (s, 3 H), 1.9–2.2 (m, 6 H), 1.61 (m, 2 H); ($CDCl_3$) δ 9.04 (s, 1 H), 8.27 (dd, 1 H, *J* = 8.4, 0.9 Hz), 8.12 (d, 1 H, *J* = 8.2 Hz), 7.82 (m, 1 H), 7.69 (m, 1 H), 6.83 (d, 1 H, *J* = 6.9 Hz), 4.39 (m, 1 H), 3.20 (m, 2 H), 2.35 (m, 2 H), 2.32 (s, 3 H), 2.17 (m, 2 h), 1.84 (m, 2 H), 1.81 (m, 2 H).

***exo-N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-hydroxy-3-quinolinecarboxamide fumarate (6h)**: IR (KBr) 3400 (br), 1645, 1623, 1552, 1519, 1467, 1356, 1289, 1195, 763 cm^{-1}; MS *m/z* 311 (M^+); ^1H NMR (DMSO-d_6) δ 10.03 (d, 1 H, *J* = 7.7 Hz), 8.71 (s, 1 H), 8.25 (d, 1 H, *J* = 7.9 Hz), 7.67–7.84 (m, 2 H), 7.47 (m, 1 H), 6.55 (s, 2 H), 4.26 (m, 1 H), 3.69 (m, 2 H), 2.57 (s, 3 H), 1.75–2.30 (m, 8 H).

***endo-N*-(9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-4-hydroxy-3-quinolinecarboxamide fumarate (6i)**: IR (KBr) 1657, 1643, 1531, 1476, 764 cm^{-1}; MS *m/z* 325 (M^+); ^1H NMR (DMSO-d_6) δ 10.07 (d, 1 H, *J* = 7.6 Hz), 8.74 (s, 1 H), 8.26 (d, 1 H, *J* = 8.4 Hz), 7.65–7.88 (m, 2 H), 7.48 (m, 1 H), 6.57 (s, 2 H), 4.38 (m, 1 H), 3.26 (m, 2 H), 2.59 (s, 3 H), 1.05–2.55 (m, 10 H).

***endo-N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-amino-3-quinolinecarboxamide Dihydrochloride (6g) (Method D)**. A mixture of compound **6e** (free form, 0.43 g, 1.30 mmol) and EtOH saturated with NH_3 (30 mL) was heated at 100 °C for 20 h in a sealed tube. After cooling, 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 alkalify the mixture, followed by twice extraction 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 EtOAc. The precipitated crystals were collected by filtration and dried. The product was suspended again in EtOAc, followed by addition of EtOAc saturated with HCl. The precipitated crystals were collected by filtration and dried to give compound **6g** as the hydrochloride (0.38 g, 76%): IR (KBr) 3430 (br), 1631, 1526, 1481, 1305, 768 cm^{-1}; MS *m/z* 310 (M^+); ^1H NMR (DMSO-d_6) δ 14.94 (br s, 1 H), 10.76 (m, 1 H), 9.84 (br s, 2 H), 9.11 (s, 1 H), 9.01 (d, 1 H, *J* = 2.8 Hz), 8.69 (d, 1 H, *J* = 8.2 Hz), 8.12 (d, 1 H, *J* = 7.6 Hz), 8.00 (m, 1 H), 7.74 (m, 1 H), 4.00 (m, 1 H), 3.84 (m, 2 H), 2.65 (s, 3 H), 1.95–2.75 (m, 8 H).

Ethyl 4-Hydroxy-2-methyl-3-quinolinecarboxylate (10). NaH (2.40 g, 100.0 mmol) was portionwise added to a mixture of ethyl acetoacetate (13..00 g, 99.9 mmol) and *N,N*-dimethylacetoamide (200 mL) under stirring at room temperature. To this solution was added a mixture of isatonic anhydride (19.50 g, 119.5 mmol) and *N,N*-dimethylacetoamide (150 mL) followed by stirring at 120 °C for 10 min. Then, the mixture was concentrated under reduced pressure, followed by addition of H_2O, and the mixture was subjected to ultrasonic waves. The precipitated crystals were collected by filtration and dried to give compound **10** (16.3 g, 71%): ^1H NMR (DMSO-d_6) δ 11.83 (br s, 1 H), 8.06 (d, 1 H, *J* = 8.0 Hz), 7.2–7.7 (m, 3 H), 4.24 (q, 2 H, *J* = 7.1 Hz), 2.40 (s, 3 H), 1.28 (t, 3 H, *J* = 7.1 Hz).

***endo-N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-hydroxy-2-methyl-3-quinolinecarboxamide fumarate (6l)**: IR (KBr) 1712, 1635, 1517, 1479, 983, 766 cm^{-1}; HRMS *m/z* 325.1774 (M^+), $C_{19}H_{23}N_3O_2$ requires 325.1790; ^1H NMR (DMSO-d_6) δ 11.03 (d, 1 H, *J* = 6.8 Hz), 8.21 (d, 1 H, *J* = 8.5 Hz), 7.70 (m, 2 H), 7.41 (m, 1 H), 6.55 (s, 2 H), 4.12 (m, 1 H), 3.74 (m, 2 H), 2.83 (s, 3 H), 2.63 (s, 3 H), 1.89–2.76 (m, 8 H).

***endo-N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-*n*-butyl-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxamide Difumarate (7d) (Method E)**. A mixture of ethyl 1-*n*-butyl-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxylate[23] (1.45 g, 5.01 mmol), *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-ylamine[16] (1.05 g, 7.49 mmol), and xylene (100 mL) was stirred with heating at 110 °C for 15 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 with $CHCl_3$ (2 × 50 mL). 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 EtOAc. The precipitated crystals were collected by filtration and dried. To this product were added *i*-PrOH (40 mL) and fumaric acid (0.27 g, 2.33 mmol), followed by stirring at room temperature. Hexane (15 mL) was added to this solution with stirring, and the precipitated crystals were collected by filtration and dried to give compound **7d** as the fumarate (1.02 g, 41%): IR (KBr) 3420 (br), 1720, 1641, 1561, 1483, 1408, 1276, 1167, 977, 789, 778 cm^{-1}; HRMS *m/z* 383.2206 (M^+), $C_{22}H_{29}N_3O_3$ requires 383.2209; ^1H NMR (DMSO-d_6) δ 16.94 (s, 1 H), 13.06 (br s, 4 H), 11.07 (d, 1 H, *J* = 7.3 Hz), 8.11 (d, 1 H, *J* = 8.1 Hz), 7.82 (m, 1 H), 7.65 (d, 1 H, *J* = 8.8 Hz), 7.39 (m, 1 H), 6.64 (s, 4 H), 4.19 (m, 1 H), 4.28 (t, 2 H, *J* = 7.5 Hz), 3.89 (m, 2 H), 2.70 (s, 3 H), 1.8–2.9 (m, 8 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 4-hydroxy-2-methyl-3-quinolinecarboxylate dihydrochloride (7k)**: IR (KBr) 3475 (br), 1727, 1661, 1642, 1583, 1492, 1423, 1316, 1222, 1153, 1020, 971 cm^{-1}; MS *m/z* 326 (M^+); ^1H NMR (DMSO-d_6) δ 12.33 (br s, 1 H), 10.65 (br s, 1 H), 8.09 (d, 1 H, *J* = 7.8 Hz), 7.55–7.80 (m, 2 H), 7.36 (m, 1 H), 5.15 (m, 1 H), 3.85 (m, 2 H), 2.66 (s, 3 H), 2.46 (s, 3 H), 1.8–2.9 (m, 8 H).

***endo-N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxamide fumarate (7b)**: IR (KBr) 3410 (br), 1655, 1649, 1558, 1489, 1402, 753 cm^{-1}; MS *m/z* 327 (M^+); ^1H NMR (DMSO-d_6) δ 11.90 (br s, 2 H), 11.05 (d, 1 H, *J* = 5.8 Hz), 7.98 (d, 1 H, *J* = 7.9 Hz), 7.70 (m, 1 H), 7.39 (d, 1 H, *J* = 7.9 Hz), 7.30 (m, 1 H), 6.57 (s, 2 H), 4.16 (m, 1 H), 3.67 (m, 2 H), 2.57 (s, 3 H), 1.88–2.51 (m, 8 H).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 1-*n*-butyl-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxylate fumarate (7c)**: IR (KBr) 3420 (br), 1657, 1619, 1562, 1497, 1408, 1323, 1171, 1023, 982, 766, 754 cm^{-1}; MS *m/z* 384 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 8.02 (d, 1 H, J = 8.1 Hz), 7.51 (m, 1 H), 7.30 (d, 1 H, J = 8.4 Hz), 7.08 (m, 1 H), 6.59 (s, 2 H), 5.06 (m, 1 H), 4.09 (t, 2 H, J = 7.1 Hz), 3.78 (m, 2 H), 2.67 (s, 3 H), 1.85–2.80 (m, 8 H), 1.54 (m, 2 H), 1.37 (m, 2 H), 0.92 (t, 3 H, J = 7.2 Hz).

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-4-hydroxy-2-oxo-1-phenyl-1,2-dihydro-3-quinolinecarboxamide fumarate (7e)**: IR (KBr) 3450 (br), 1629, 1554, 1483, 1405, 1353, 1268, 772, 737, 704 cm^{-1}; HRMS *m/z* 403.1877 (M$^+$), $C_{24}H_{25}N_3O_3$ requires 403.1896; ^{1}H NMR (DMSO-d_6) δ 17.17 (bs, 1 H), 10.80 (br s, 1 H), 8.15 (d, 1 H, J = 8.1 Hz), 7.55–7.72 (m, 4 H), 7.31–7.44 (m, 3 H), 6.63 (s, 2 H), 6.56 (d, 1 H, J = 8.7 Hz), 4.19 (m, 1 H), 3.83 (m, 2 H), 2.66 (s, 3 H), 1.97–2.71 (m, 8 H); ^{13}C NMR of a free base (7e′) (DMSO-d_6) δ 171.9 (C(4)), 169.7 (C(9)), 162.4 (C(2)), 140.5 (C(8a)), 136.7 (C(1′) in NPh group), 134.0 (C(7)), 130.0 (C(3′)), 129.1 (C(2′)), 128.9 (C(4′)), 124.3 (C(5)), 122.8 (C(6)), 115.9 (C(8)), 95.9 (C(3)), 60.8 (C(3″) in tropinyl group), 38.5 (C(1″)), 37.5 (NMe), 33.0 (C(2″)), 23.4 (C(4″)) (see Scheme IV).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 1-*n*-butyl-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate fumarate (7f)**: IR (KBr) 3430 (br), 1668, 1620, 1586, 1470, 1407, 1323, 1163, 1024, 973, 799, 777 cm^{-1}; MS *m/z* 385 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 8.46 (d, 1 H, J = 4.8 Hz), 8.26 (d, 1 H, J = 7.6 Hz), 7.07 (m, 1 H), 6.62 (s, 2 H), 5.03 (m, 1 H), 4.24 (t, 2 H, J = 7.3 Hz), 3.82 (m, 2 H), 2.69 (s, 3 H), 1.85–2.80 (m, 8 H), 1.56 (m, 2 H), 1.31 (m, 2 H), 0.90 (t, 3 H, J = 7.3 Hz).

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-*n*-butyl-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide fumarate (7g)**: IR (KBr) 3410 (br), 2960, 1633, 1588, 1564, 1481, 1407, 1279, 797, 648 cm^{-1}; MS *m/z* 384 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 10.93 (d, 1 H, J = 6.6 Hz), 8.82 (dd, 1 H, J = 4.6, 1.7 Hz), 8.46 (dd, 1 H, J = 7.8, 1.7 Hz), 7.44 (dd, 1 H, J = 7.8, 4.6 Hz), 6.64 (s, 2 H), 4.42 (t, 2 H, J = 7.3 Hz), 4.19 (m, 1 H), 3.90 (m, 2 H), 2.71 (s, 3 H), 2.03–2.73 (m, 8 H), 1.64 (m, 2 H), 1.36 (m, 2 H), 0.93 (t, 3 H, J = 7.3 Hz).

Ethyl 4-Hydroxy-2-oxo-1-phenyl-1,2-dihydro-1,8-naphthyridine-3-carboxylate (11a). A mixture of methyl 2-anilinonicotinate[24] (12; 15.3 g, 67.0 mmol), 1,2-dichloroethane (150 mL), and 1,4-dioxane (15 mL) was stirred with heating at 80 °C. To this solution was dropwise added trichloromethyl chloroformate (24.1 mL, 201.0 mmol) over 1 h followed by stirring at 90 °C for 1.5 h further. After cooling, active carbon (0.75 g) was added to the solution followed by stirring at 90 °C for 30 min. The mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to give 2,4-dioxo-1-phenyl-1,4-dihydro-2*H*-pyrid[2,3-*d*]oxazine (13; 15.9 g, 99%): ^{1}H NMR ($CDCl_3$) δ 8.3–8.6 (m, 2 H), 7.0–7.7 (m, 6 H).[25]

NaH (0.48 g, 20.0 mmol) was added to a mixture of compound 13 (4.00 g, 16.7 mmol) and diethyl malonate (25.3 mL, 166.6 mmol) at room temperature, followed by stirring with heating at 150 °C for 2.5 h. After cooling, EtOAc (100 mL) was added to the solution, and the mixture was subjected to ultrasonic waves. The precipitated crystals were collected by filtration and dissolved in H_2O, followed by addition of concentrated HCl to adjust the pH of the solution to 0.1–0.2. The precipitated crystals were collected by filtration, washed with H_2O, and dried to give compound **11a** (4.30 g, 83%): ^{1}H NMR (DMSO-d_6) δ 8.49 (dd, 1 H, J = 4.8, 1.8 Hz), 8.45 (dd, 1 H, J = 7.9, 1.8 Hz), 7.37–7.62 (m, 3 H), 7.32 (dd, 1 H, J = 7.9, 4.8 Hz), 7.23 (m, 2 H), 4.33 (q, 2 H, J = 7.1 Hz), 1.29 (t, 3 H, J = 7.1 Hz).

***endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 4-hydroxy-2-oxo-1-phenyl-1,2-dihydro-1,8-naphthyridine-3-carboxylate (7h)**: IR (KBr) 3400 (br), 1677, 1614, 1594, 1529, 1466, 1393, 1204, 1106, 1080, 1045, 1031, 975, 930, 798, 719 cm^{-1}; MS *m/z* 405 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 8.24 (d, 1 H, J = 7.7 Hz), 8.14 (d, 1 H, J = 4.6 Hz), 7.35–7.50 (m, 2 H), 7.31 (m, 1 H), 7.05–7.20 (m, 2 H), 6.99 (m, 1 H), 4.99 (m, 1 H), 3.70 (m, 2 H), 2.50 (s, 3 H), 1.85–2.75 (m, 8 H).

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-*n*-butyl-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide fumarate (7i)**: IR (KBr) 3400 (br), 1708, 1640, 1630, 1561, 1553, 1474, 1307, 982, 794, 736 cm^{-1}; HRMS *m/z* 404.1859 (M$^+$), $C_{23}H_{24}N_4O_3$ requires 404.1848; ^{1}H NMR (DMSO-d_6) δ 10.74 (d, 1 H, J = 7.3 Hz), 8.55 (d, 1 H, J = 4.6 Hz), 8.49 (d, 1 H, J = 7.9 Hz), 7.1–7.7 (m, 7 H), 6.53 (s, 2 H), 4.15 (m, 1 H), 3.53 (m, 2 H), 2.48 (m, 2 H), 1.36 (m, 3 H), 1.65–2.60 (m, 8 H).

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 NG108-15 cells was prepared according to the method of Neijt et al.[31] The receptor binding experiment was performed using [^{3}H]quipazine,[32] a high-affinity ligand to 5-HT$_3$ receptors. A membrane fraction obtained from 3×10^5 cells of NG108-15 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[39]) 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 NG108-15 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.[35] Male Wistar rats (230–330 g, Japan SLC) were anesthetized with urethane (1.25 g/kg, ip) and the trachea was 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 dissolved in saline 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. The ED_{50} values were calculated as the doses which reduced the 5-HT-induced bradycardia by 50%.

Acute Lethal Toxicity. Groups of five to seven male ddY mice weighing 19–21 g were given single intravenous injection of compounds in saline at several doses (0.2 mL per 20 g body weight) and were monitored for 7 days. LD_{50} values were calculated after 7 days by using probit analysis.

Cisplatin-Induced Emesis Assay.[38] Experiments were performed on adult male fasted beagle dogs (9–15 kg).

For Intravenous Experiment. On the day of the experiment, the dogs were fed dry dog food (Sanwa Kagaku; ED-1) and 60 min later given the test compound or saline (iv). Thirty minutes after intravenous injection, the dogs were given cisplatin (3 mg/kg, iv) which was dissolved by ultrasonication in physiological saline. This dose of cisplatin consistently evoked emesis, which was defined as productive regurgitation of stomach contents. Then, the dogs were monitored for 6 h. Repeated episodes of emesis occurring within 1 min were considered as a single episode.

For Oral Experiment. The dogs were given the test compound in capsule or a control capsule, and 15 min later fed dry dog food. Sixty minutes after the oral administration, the dogs were given cisplatin (3 mg/kg, iv) which was dissolved by sonication in saline. Then, the dogs were monitored for 6 h.

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