Synthesis and Evaluation of Novel 2-Oxo-1,2-dihydro-3-quinolinecarboxamide Derivatives as Serotonin 5-HT_4 Receptor Agonists

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A series of *N*-azabicycloalkyl-1-alkyl-2-oxo-1,2-dihydro-3-quinolinecarboxamides were synthesized and tested for serotonin 5-HT_4 receptor-stimulating effects in the regulation of electrically-evoked contraction in guinea pig muscle. Among them, *N*-azabicycloalkyl-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (8c, 9c, 10c, 11c, 12c) exhibited potent serotonin 5-HT_4 receptor-stimulating activity. The most potent compound, *N*-(*endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (8c, ED_{50}= 36.3 nM), was seven times as active as cisapride, while 8c had no affinity for 5-HT_{1A}, 5-HT_{1D}, D_2, muscarinic M_2 or muscarinic M_3 receptors even at 10 μM. Compound 8c stimulated digestive tract motility in conscious fed dogs (1.0 mg/kg *p.o.*).

Key words Quinolinecarboxamide; serotonin 5-HT_4 receptor-stimulating activity; structure–activity relationship

Serotonin (5-HT) is a neurotransmitter which is widely distributed in humans and has a remarkable variety of physiological effects. Seven subtypes of 5-HT receptors have been reported.[1,2] 5-HT_4 receptors[3] modulate cholinergic nerve-mediated contraction in the guinea pig ileum[4,5] and in the proximal colon, potentiate electrical field stimulation in the guinea pig ileum,[6] and induce of chloride secretion in rat distal colon.[7] These findings suggest that the 5-HT_4 receptors in the gut play roles in the induction and maintenance of gastrointestinal motility, and that 5-HT_4 receptor agonists activate gastrointestinal motor function and improve gastrointestinal dysfunction or conditions accompanied by motility failure. In fact, cisapride[8] and renzapride,[9] which stimulate 5-HT_4 receptors, are reported to increase gastrointestinal motor function and to improve gastrointestinal conditions such as heartburn, anorexia, bowel pain, and abdominal distension accompanied by chronic gastritis, diabetes mellitus or postoperative gastroparesis.

Three classes of compounds stimulating 5-HT_4 receptors are known,[10] 1) the indolealkylamines (5-HT, 5-methoxytryptamine), 2) the benzamides (metoclopramide,[11] cisapride, renzapride, zacopride[12,13]), and 3) the benzimidazolones (BIMU-8[14]) (Fig. 1). Generally, these agents act on other monoamine receptors as well. For example, cisapride and metoclopramide are used clinically as 5-HT_4 agonists, but both are apt to induce extrapyramidal syndrome as a result of D_2 receptor antagonism.[15,16] Mosapride is modified at a tertiary amine in order to reduce extrapyramidal syndrome.[17] There are many reports on the modification of tertiary amine moieties such as alkylamine, cyclic amine and azabicyclo structures. Among these amino moieties, azabicyclo structures exhibit potent and selective serotonin 5-HT_4 receptor-stimulating activity.[18] There are few reports, however, concerning modifications in the aromatic ring moiety of compounds stimulating 5-HT_4 receptors. In the present study, we report the synthesis and 5-HT_4 receptor-stimulating activity of 2-oxo-1,2-dihydro-3-quinolinecarboxamide derivatives having azabicycloamine structures with the aim of finding a new class of heterocyclic compounds that stimulate 5-HT_4 receptors.

Chemistry Compounds **5a**—**e** were prepared by the following synthetic pathway depicted in Chart 1. 2-Nitrobenzaldehyde **1** was condensed with diethyl malonate followed by a reduction of the nitro group to give 2-oxo-1,2-dihydro-3-quinolinecarboxylate **3**. Alkylation of **3** with appropriate

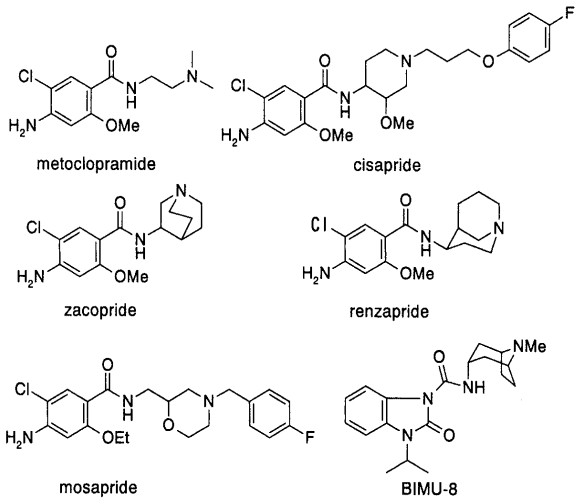

Fig. 1

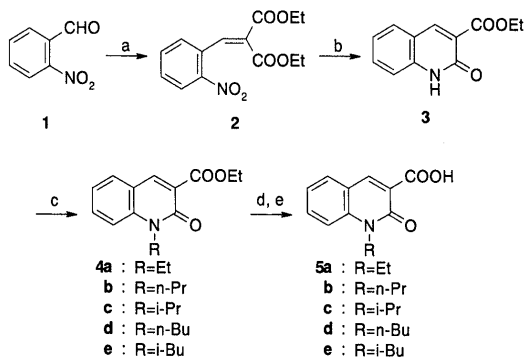

Chart 1

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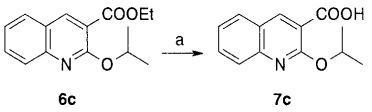
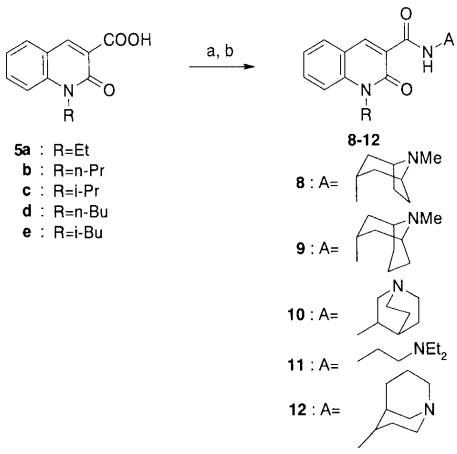
alkylhalides and sodium hydride in DMF led to a mixture of the *N*-alkyl isomers **4a**—**e** and *O*-alkyl isomers, which were separated by column chromatography. The *N*-alkyl isomers **4a**, **4b** and **4d** were obtained as major products. When isopropyl and isobutyl iodides were used as alkylating agents, *O*-alkyl isomers were obtained as the major products; the reaction of **3** and isopropyl iodide yielded the *N*-isopropyl isomer **4c** in 6.5% yield, along with the *O*-isopropyl isomer **6c** in 53.0% yield. Both isomers were hydrolyzed to the corresponding carboxylic acids (Chart 1 and Chart 2). Carboxylic acids **5c** and **7c** could be distinguished by IR spectra. Carboxylic acid **5c** exhibited absorption around 1734 cm^{-1}, whereas **7c** exhibited absorption around 1709 cm^{-1}. Treatment of carboxylic acids (**5a**—**e**) with thionyl chloride in toluene, followed by coupling with appropriate amines yielded the carboxamide derivatives (**8a**—**e**, **9c**, **10c**, **11c**, **12c**), as depicted in Chart 3.



Reagents: (a) NaOH, aq. MeOH

Chart 2



Reagents: (a) $SOCl_2$, toluene; (b) H_2N-A

Chart 3

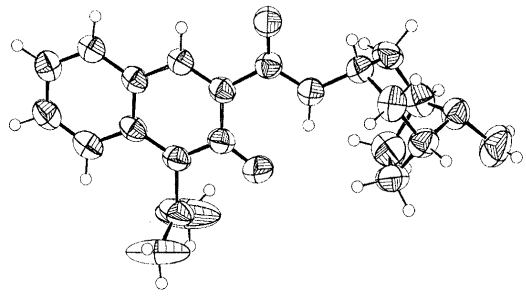


Fig. 2. X-Ray Structure of Compond **8c**

As mentioned above, alkylation yielded two isomers, *O*-alkyl and *N*-alkyl compounds. In order to clarify the structures of the alkylated compounds, compound **8c** was examined by X-ray crystallographic analysis. As shown in Fig. 2, **8c** was determined to be a *N*-isopropyl compound. Taking into account the IR spectra, **5a**, **5b**, **5d**, **5e** were shown to be *N*-alkyl isomers.

Results and Discussion

The 5-HT_4 receptor-stimulating activities of the carboxamide derivatives were evaluated in the regulation of electrically-evoked contractions in guinea pig muscle. The 50% effective doses (ED_{50}) of these compounds are shown in Table 1. Four azabicyclo structures, 8-azabicyclo[3.2.1]oct-3-yl (a), 9-azabicyclo[3.3.1]non-3-yl (b), 3-quinuclidinyl (c) and 1-azabicyclo[3.3.1]non-4-yl (e), and one straight chain, *N*,*N*-diethylaminoethyl (d), were selected for examination. Azabicyclo[3.3.1]non-3-yl (b) is an amine moiety of granisetron,[19] a 5-HT_3 receptor antagonist. We selected its 9-azabicyclo[3.3.1]non-3-yl moiety as an azabicyclo structure because of its structural similarity to 8-azabicyclo[3.2.1]octane. We selected the 8-azabicyclo[3.2.1]oct-3-yl (a) moiety as an amine moiety to examine the effect of alkyl substituents on the 1-position of the quinoline ring. 1-Alkyl groups strongly affect ED_{50} values. When operated with straight-chain alkyl groups, **8a** having an ethyl group showed potent activity (ED_{50}=138 nM). Branched-chain alkyl groups yielded better ED_{50} values than straight-chain alkyl groups. Iso-butyl (**8e**, ED_{50}=974 nM) and iso-propyl (**8c**, ED_{50}=36.3 nM) groups yielded better ED_{50} values than the corresponding *n*-butyl (**8d**, ED_{50}>3000 nM) and *n*-propyl (**8b**, ED_{50}=413 nM). The iso-propyl group appeared to be the best substituent for the 1-position. We next investigated the effect of the tertiary amine moiety. With iso-propyl as the alkyl group on the quinoline 1-position, all of five derivatives (**8c**, **9c**, **10c**, **11c**, **12c**) exhibited good 5-HT_4 receptor-stimulating activity. The

Table 1. Physicochemical Data and 5-HT_4 Receptor-Stimulating Activities of the Synthesized Compounds (**8a**—**e**, **9c**, **10c**, **11c** and **12c**)

Compound	mp (°C)	Recrystallization solvent	Formula	Calcd			Found			ED_{50} (nM)
				C	H	N	C	H	N	
8a	142—144	AcOEt	$C_{20}H_{25}N_3O_2 \cdot 0.4\,H_2O$	69.29	7.50	12.12	69.23	7.43	12.17	138
8b	151—153	AcOEt	$C_{21}H_{27}N_3O_2$	71.36	7.70	11.88	71.20	7.61	11.80	413
8c	173—177	AcOEt	$C_{21}H_{27}N_3O_2$	71.36	7.70	11.88	71.21	7.67	11.84	36.3
8d	150—152	AcOEt	$C_{22}H_{29}N_3O_2$	71.90	7.95	11.43	71.63	7.80	11.16	>3000
8e	234—237	IPA–hexane	$C_{22}H_{29}N_3O_2 \cdot C_4H_4O_4 \cdot 0.25\,H_2O$[a]	63.98	6.92	8.61	64.07	6.92	8.38	974
9c	184—187	AcOEt	$C_{22}H_{29}N_3O_2 \cdot 0.2\,H_2O$	71.21	7.99	11.32	70.97	7.93	11.20	122
10c	127—129	AcOEt	$C_{20}H_{25}N_3O_2 \cdot 0.3\,H_2O$	69.66	7.48	12.19	69.89	7.22	11.79	330
11c	209—213	MeOH–AcOEt	$C_{19}H_{27}N_3O_2 \cdot HCl \cdot 0.3\,H_2O$	61.46	7.76	11.31	61.70	7.46	11.23	433
12c	229—231	AcOEt	$C_{21}H_{27}N_3O_2$	71.36	7.69	11.88	71.07	7.60	11.69	390
Cisapride										271

a) Maleic acid salt.

Table 2. Physicochemical Data of the Synthesized Compounds (**8a—e**, **9c**, **10c**, **11c** and **12c**)

Compound	IR (KBr) (cm^{-1})	MS[a] (*m/z*)	^{1}H-NMR δ (ppm)
8a	3245, 2935, 1675, 1619, 1541	339 (M^+)	($CDCl_3$): 1.41 (3H, t, *J*=7.2 Hz), 1.75—1.88 (2H, m), 2.01—2.27 (4H, m), 2.27—2.45 (2H, m), 2.36 (3H, s), 3.25—3.35 (2H, m), 4.30 (1H, q, *J*=7.0 Hz), 4.44 (2H, q, *J*=7.2 Hz), 7.31 (1H, dt, *J*=1.6, 7.2 Hz), 7.43 (1H, d, *J*=8.6 Hz), 7.68 (1H, ddd, *J*=1.6, 7.2, 8.6 Hz), 7.77 (1H, dd, *J*=1.6, 7.2 Hz), 8.88 (1H, s), 10.62 (1H, d, *J*=7.4 Hz)
8b	3240, 2958, 2927, 1666, 1611, 1583, 1566, 1529	353 (M^+)	($CDCl_3$): 1.08 (3H, t, *J*=7.2 Hz), 1.70—1.95 (4H, m), 2.00—2.27 (4H, m), 2.27—2.48 (2H, m), 2.37 (3H, s), 3.15—3.30 (2H, m), 4.20—4.40 (3H, m), 7.30 (1H, dt, *J*=1.6, 7.2 Hz), 7.39 (1H, d, *J*=8.6 Hz), 7.67 (1H, ddd, *J*=1.6, 7.2, 8.6 Hz), 7.77 (1H, dd, *J*=1.6, 7.2 Hz), 8.88 (1H, s), 10.48 (1H, d, *J*=6.8 Hz)
8c	3263, 2961, 1673, 1616, 1585, 1568, 1528	353 (M^+)	($CDCl_3$): 1.68 (6H, d, *J*=7.2 Hz), 1.76—1.83 (2H, m), 2.00—2.40 (6H, m), 2.34 (3H, s), 3.10—3.28 (2H, m), 4.30 (1H, q, *J*=7.0 Hz), 5.40—5.90 (1H, br), 7.22—7.33 (1H, m), 7.55—7.70 (2H, m), 7.75 (1H, d, *J*=7.2 Hz), 8.83 (1H, s), 10.48 (1H, d, *J*=7.2 Hz)
8d	3240, 2955, 2928, 1668, 1612, 1585, 1567, 1527	367 (M^+)	($CDCl_3$): 1.02 (3H, t, *J*=7.2 Hz), 1.40—1.65 (2H, m), 1.65—1.95 (4H, m), 2.00—2.25 (4H, m), 2.25—2.45 (2H, m), 2.36 (3H, s), 3.15—3.30 (2H, m), 4.22—4.45 (3H, m), 7.30 (1H, dt, *J*=1.6, 7.2 Hz), 7.40 (1H, d, *J*=8.6 Hz), 7.67 (1H, ddd, *J*=1.6, 7.2, 8.6 Hz), 7.77 (1H, dd, *J*=1.6, 7.2 Hz), 8.88 (1H, s), 10.48 (1H, d, *J*=7.2 Hz)
8e	3436, 1713, 1673, 1618	367 (M^+) (Fab)	(DMSO-d_6): 0.92 (6H, d, *J*=7.5 Hz), 1.76—2.64 (12H, m), 3.48—3.65 (2H, m), 4.06—4.21 (1H, m), 4.29 (2H, d, *J*=7.5 Hz), 6.51 (2H, s), 7.32—7.43 (1H, m), 7.67—7.84 (2H, m), 7.99—8.09 (1H, m), 8.87 (1H, s), 10.46 (1H, d, *J*=8.8 Hz)
9c	3248, 2924, 1661, 1581, 1566, 1531	367 (M^+)	($CDCl_3$): 1.05—1.30 (2H, m), 1.68 (6H, d, *J*=7.2 Hz), 1.40—1.75 (3H, m), 1.90—2.20 (3H, m), 2.48—2.70 (2H, m), 2.57 (3H, s), 3.05—3.25 (2H, m), 4.40—4.65 (1H, m), 5.35—5.80 (1H, br), 7.23—7.35 (1H, m), 7.55—7.69 (2H, m), 7.74 (1H, d, *J*=7.8 Hz), 8.85 (1H, s), 9.83 (1H, d, *J*=7.4 Hz)
10c	3436, 2938, 1671, 1613, 1585, 1567, 1525	339 (M^+)	($CDCl_3$): 1.45—1.80 (3H, m), 1.68 (6H, d, *J*=7.0 Hz), 1.80—2.10 (2H, m), 2.65—3.12 (5H, m), 3.45 (1H, ddd, *J*=2.0, 9.4, 14.2 Hz), 4.10—4.28 (1H, m), 5.30—5.90 (1H, br), 7.24—7.35 (1H, m), 7.58—7.70 (2H, m), 7.77 (1H, d, *J*=7.8 Hz), 8.84 (1H, s), 10.31 (1H, d, *J*=7.2 Hz)
11c	3249, 2976, 2433, 1676, 1619, 1567, 1540	329 (M^+) (Fab)	(DMSO-d_6): 1.47 (6H, t, *J*=7.0 Hz), 1.67 (6H, d, *J*=7.0 Hz), 3.11—3.39 (6H, m), 3.92—4.08 (2H, m), 5.30—5.70 (1H, br), 7.26—7.38 (1H, m), 7.60—7.70 (2H, m), 7.75 (1H, d, *J*=7.8 Hz), 8.78 (1H, s), 10.28 (1H, t, *J*=5.6 Hz), 12.30—12.60 (1H, br)
12c	3258, 2933, 1672, 1615, 1584, 1567 1525	353 (M^+)	($CDCl_3$): 1.40—1.55 (1H, m), 1.68 (6H, d, *J*=7.0 Hz), 1.77—2.20 (6H, m), 2.90—3.30 (6H, m), 4.40—4.60 (1H, m), 5.40—5.90 (1H, br), 7.23—7.35 (1H, m), 7.56—7.70 (2H, m), 7.75 (1H, dd, *J*=1.0, 7.8 Hz), 8.85 (1H, s), 10.08 (1H, d, *J*=8.0 Hz)

a) EI mass spectra was measured, unless otherwise noted.

8-azabicyclo[3.2.1]oct-3-yl (a) group yielded the highest activity within synthesized compounds. Compound **8c** had 7 times the 5-HT_4 receptor-stimulating activity of cisapride (ED_{50}=271 nM).

Using **8c**, which had the highest 5-HT_4 receptor-stimulating activity, effects on digestive tract motility in conscious fed dogs were tested. Fig. 3 shows typical effects of **8c** (1.0 mg/kg *p.o.*). In the radioligand binding assay, **8c** had high affinity for the 5-HT_4 receptor which inhibited binding of [^{3}H] GR113808 on guinea pig striatum (IC_{50}=67.7 nM).[20] **8c** exhibited no affinity for dopamine D_2 receptors ([^{3}H] raclopride, rat striatum),[21] 5-HT_{1A} receptors ([^{3}H] 8OH-DPAT, guinea pig cortex),[22] 5-HT_{1D} receptors ([^{3}H] L-694247, guinea pig striatum),[23] muscarinic M_2 receptors ([^{3}H] NMS, rat heart),[24] or muscarinic M_3 receptors ([^{3}H] 4-DAMP, guinea pig bladder),[25] even at a concentration of 10 μM. Thus, Compound **8c** appears to be free of binding to these receptors.[26]

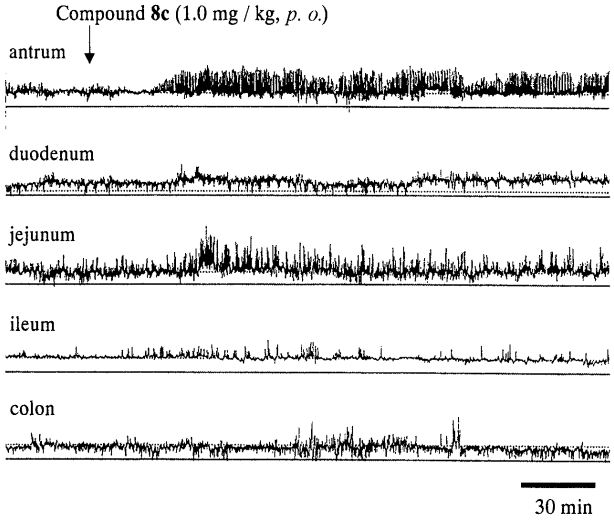
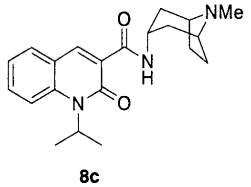


Fig. 3. Effect of **8c** on Digestive Tract Motility in Conscious Fed Dog

In conclusion, we investigated 2-oxo-1,2-dihydro-3-quinolinecarboxamide derivatives as possible 5-HT_4 receptor agonists. Of the compounds synthesized, *N-endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (**8c**) (Fig. 4) was optimal, and had 7 times the 5-HT_4 receptor-stimulating activity of cisapride, as measured by its effect on the regulation of electrically-evoked contractions in guinea pig muscle, and exhibited no 5-HT_{1A}, 5-HT_{1D}, D_2, muscarinic M_2 or muscarinic M_3 receptor binding. Compound **8c** thus exhibited high and specific 5-



8c

Fig. 4

HT_4 receptor-stimulating activity, and is a promising compound for the improvement of gastrointestinal dysfunction.

Experimental

Melting points were determined by a Buchi 535 melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1760 spectrometer. ^{1}H-NMR spectra were recorded on a Varian VXL-200 spectrometer. Chemical shifts are reported in ppm (δ) values, based on tetramethylsilane as an internal standard. MS were obtained on a JEOL JMS-SX102 spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400. TLC was performed on silica gel pre-coated plates (Merck, Kieselgel 60F-254). Column chromatography was performed over silica gel (Asahi glass, M. S. GEL. SIL.). 3-Amino-8-methyl-8-azabicyclo [3.2.1] octane (a),[27] 3-amino-9-azabicyclo [3.3.1] noane (b),[28] and 4-amino-1-azabicyclo[3.3.1]-nonane (e)[29] were synthesized according to references. 3-Aminoquinuclidine (c) and 2-diethylaminoethylamine (d) were purchased from Tokyo Kasei Organic Chemicals.

Ethyl 3-(2-Nitrophenyl)-2-ethoxycarbonylpropenate (2) Diethyl malonate (70.3 ml, 0.46 mol) and $NaHCO_3$ (58.4 g, 0.70 mol) were added to a solution of *o*-nitrobenzaldehyde **1** (70.0 g, 0.46 mol) in acetic anhydride (175 ml). The reaction mixture was stirred at 100 °C for 6 h. After being cooled, the reaction mixture was partitioned between AcOEt and water. The organic layer was washed successively with water, 5% Na_2CO_3 and brine, then dried over Na_2SO_4. The solvent was removed *in vacuo* to give a residue, which was triturated in EtOH to give 77.1 g (56.7%) of **2** as a pale yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7.2 Hz), 1.36 (3H, t, J=7.2 Hz), 4.08 (2H, q, J=7.2 Hz), 4.35 (2H, q, J=7.2 Hz), 7.39—7.48 (1H, m), 7.50—7.70 (2H, m), 8.20 (1H, s), 8.16—8.26 (1H, m). MS *m/z* (EI): 293 (M^+).

Ethyl 2-Oxo-1,2-dihydro-3-quinolinecarboxylate (3) Iron powder (53 g, 1.0 mol) was added to a pre-heated (80 °C) solution of **2** (46 g, 0.15 mol) in acetic acid. The reaction mixture was heated at 80 °C for 6.5 h, cooled and filtered through a Celite pad. The filtrate was evaporated *in vacuo* to leave a residue, which was purified by column chromatography using $CHCl_3$/MeOH=10 : 1 to give 21.3 g (62.5%) of **3** as a yellow solid. mp 175—179 °C (recrystallized from AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7.2 Hz), 4.46 (2H, q, J=7.2 Hz), 7.20—7.30 (1H, m), 7.50 (1H, d, J=7.8 Hz), 7.61 (1H, ddd, J=1.4, 7.0, 8.4 Hz), 7.65 (1H, d, J=8.0 Hz), 8.56 (1H, s), 12.51 (1H, s). IR (KBr) cm^{-1}: 3009, 2901, 1732, 1641, 1211. MS *m/z* (EI): 217 (M^+). *Anal.* Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.11; H, 5.24; N, 6.20.

Ethyl 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate (4c) and Ethyl 2-Isopropoxy-3-quinolinecarboxylate (6c) Compound **3** (40 g, 0.18 mol) and isopropyl iodide (62.6 g, 0.36 mol) were added to a suspension of sodium hydride (60% mineral oil suspension, 8.9 g, 0.38 mol) in DMF (200 ml). The reaction mixture was heated at 70 °C for 8 h. It was then diluted with water and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to afford a residue, which was purified by column chromatography using AcOEt/hexane=1 : 4 to give 3.1 g (6.5%) of **4c** as a yellow solid and 25.3 g (53.0%) of **6c** as a colorless oil. Physicochemical data of **4c** and **6c** are summarized in Tables 3 and 4.

Ethyl 1-alkyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate (4a, 4b, 4d, 4e) The syntheses of compounds **4a**, **4b**, **4d** and **4e** were conducted using procedures similar to that employed in the synthesis of **4c**. Chemical yield and physicochemical data of **4a**, **4b**, **4d** and **4e** are summarized in Tables 3 and 4.

1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylic Acid (5c) 5% NaOH solution (20 ml) was added to a solution of **4c** (1.55 g, 6.0 mmol) in MeOH (20 ml) at room temperature. The reaction mixture was stirred for 18 h and then acidified with concentrated HCl. The resulting precipitates were collected by filtration and dried under a vacuum to give 1.20 g (87.0%) of **5c** as a colorless powder. Physicochemical data of **5c** are summarized in Tables 3 and 4.

1-Alkyl-2-oxo-1,2-dihydro-3-quinolinecarboxylic Acid (5a, 5b, 5d, 5e) and 2-Isopropoxy-3-quinolinecarboxylic Acid (7c) The synthesis of compounds **5a**, **5b**, **5d**, **5e** and **7c** was conducted using procedures similar to that employed in the synthesis of **5c**. Chemical yield and physicochemical data of **5a**, **5b**, **5d**, **5e** and **7c** are summarized in Tables 3 and 4.

***N*-(*endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (8c)** A solution of **5c** (500 mg, 2.7 mmol) and thionyl chloride (5 ml) was heated at 100 °C for 1.5 h. The reaction mixture was concentrated to dryness *in vacuo*, and the residue was dissolved in toluene. The solvent was evaporated *in vacuo* again and the residue was dissolved in toluene. Then, 3-amino-8-methyl-8-azabicyclo[3.2.1]octane (404 mg, 2.8 mmol) in toluene (3 ml) was added to the above toluene solution, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then poured into 5% $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with brine, dried and evaporated *in vacuo*. The residue was purified by column chromatography using $CHCl_3$, then recrystallized from AcOEt to give 391 mg (51%) of **8c** as a colorless solid. Physicochemical data of **8c** are summarized in Tables 1 and 2.

1-Alkyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (8a, 8b, 8d, 9c, 10c, 12c) The synthesis of compounds **8a**, **8b**, **8d**, **9c**, **10c** and **12c** was conducted using procedures similar to that employed in the synthesis of **8c** to give **8a** (45.0%, colorless solid), **8b** (47.1%, colorless solid), **8d** (41.9%, colorless solid), **9c** (69.7%, colorless solid), **10c** (57.6%, colorless solid) and **12c** (20%, colorless solid). Physicochemical data of **8a**, **8b**, **8d**, **9c**, **10c** and **12c** are summarized in Tables 1 and 2.

***N*-(*endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isobutyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide Maleate (8e)** A solution of **5e** (720 mg, 2.9 mmol) and thionyl chloride (5 ml) was heated at 100 °C for 1.5 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was dissolved in toluene. The solvent was evaporated *in vacuo* again and the residue again dissolved in toluene. Then, 3-amino-8-methyl-8-azabicyclo-[3.2.1]octane (535 mg, 3.8 mmol) in toluene (3 ml) was added to the toluene solution and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into 5% $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with brine, dried and evaporated *in vacuo*. The residue was purified by column chromatography using $CHCl_3$/MeOH saturated with NH_3=20 : 1 to leave a solid (580 mg), which was dissolved in IPA (30 ml). A solution of maleic acid (158 mg, 1.4 mmol) was added to the solution and stirred at room temperature for 30 min. To the mixture was added hexane (100 ml), and the resulting precipitates were collected by filtration and recrystallized from IPA-hexane to give 405 mg (61.5%) of **8e** as a colorless solid. Physicochemical data of **8e** are summarized in Tables 1 and 2.

Table 3. Physicochemical Data of the Synthesized Compounds (**4a**—**e**, **5a**—**e**, **6c** and **7c**)

Compound	Yield (%)	Appearance	mp (°C)	Recrystallization solvent	Formula	Calcd			Found		
						C	H	N	C	H	N
4a	63.2	Pale yellow prism	73—74	AcOEt–hexane	$C_{14}H_{15}NO_3$	68.56	6.16	5.71	68.33	6.21	5.58
4b	75.4	Colorless gum	—	—	$C_{15}H_{17}NO_3$	—	—	—	—	—	—
4c	6.5	Pale yellow prism	54—57	AcOEt–hexane	$C_{15}H_{17}NO_3$	69.48	6.61	5.40	69.28	6.72	5.18
4d	50.6	Pale yellow prism	50—52	AcOEt–hexane	$C_{16}H_{19}NO_3$	70.31	7.01	5.12	70.11	7.03	4.97
4e	10.5	Pale yellow gum	—	—	$C_{16}H_{19}NO_3$	—	—	—	—	—	—
5a	87.6	Colorless solid	186—188	Acetone	$C_{12}H_{11}NO_3$	66.35	5.10	6.45	66.20	5.08	6.31
5b	87.9	Colorless solid	165—167	Acetone–H_2O	$C_{13}H_{13}NO_3$	67.52	5.67	6.06	67.47	5.60	6.01
5c	87.0	Colorless solid	167—169	Acetone–H_2O	$C_{13}H_{13}NO_3$	67.52	5.67	6.06	67.42	5.54	6.07
5d	94.3	Colorless needle	160—162	Acetone–H_2O	$C_{14}H_{15}NO_3$	68.56	6.16	5.71	68.35	6.10	5.51
5e	86.2	Colorless needle	167—169	Acetone–H_2O	$C_{14}H_{15}NO_3$	68.56	6.16	5.71	68.40	6.11	5.59
6c	53.0	Colorless oil	—	—	$C_{15}H_{17}NO_3$	—	—	—	—	—	—
7c	86.8	Colorless solid	103—104	AcOEt–hexane	$C_{13}H_{13}NO_3$	67.52	5.67	6.06	67.27	5.68	5.84

Table 4. Physicochemical Data of the Synthesized Compounds (**4a**—**e**, **5a**—**e**, **6c** and **7c**)

Compound	IR (KBr) (cm^{-1})	MS (EI) (*m/z*)	^{1}H-NMR (**4a**—**e**, **6c**: $CDCl_3$, **5a**—**e**, **7c**: DMSO-d_6) δ (ppm)
4a	1733, 1641	245 (M^+)	1.37 (3H, t, *J*=7.4 Hz), 1.43 (3H, t, *J*=7.4 Hz), 4.40 (2H, q, *J*=7.4 Hz), 4.44 (2H, q, *J*=7.4 Hz), 7.21—7.43 (2H, m), 7.60—7.72 (2H, m), 8.40 (1H, s)
4b	1738, 1651	259 (M^+)	1.05 (3H, t, *J*=7.4 Hz), 1.41 (3H, t, *J*=7.4 Hz), 1.68—1.90 (2H, m), 4.20—4.34 (2H, m), 4.92 (2H, t, *J*=7.4 Hz), 7.20—7.40 (2H, m), 7.59—7.72 (2H, m), 8.39 (1H, s)
4c	1732, 1646	259 (M^+)	1.42 (3H, t, *J*=7.4 Hz), 1.66 (6H, d, *J*=7.2 Hz), 4.41 (2H, q, *J*=7.4 Hz), 5.15—5.80 (1H, br), 7.17—7.27 (1H, m), 7.54—7.69 (3H, m), 8.30 (1H, s)
4d	1738, 1651	273 (M^+)	1.00 (3H, t, *J*=7.2 Hz), 1.42 (3H, t, *J*=7.2 Hz), 1.40—1.60 (2H, m), 1.65—1.84 (2H, m), 4.23—4.35 (2H, m), 4.43 (2H, q, *J*=7.2 Hz), 7.21—7.39 (2H, m), 7.58—7.70 (2H, m), 8.39 (1H, s)
4e	1739, 1654	273 (M^+)	1.00 (6H, d, *J*=7.5 Hz), 1.41 (3H, t, *J*=7.5 Hz), 2.27 (1H, septet, *J*=7.5 Hz), 4.21 (2H, d, *J*=7.5 Hz), 4.42 (2H, q, *J*=7.5 Hz), 7.20—7.40 (2H, m), 7.56—7.70 (2H, m), 8.38 (1H, s)
5a	1730, 1624	217 (M^+)	1.44 (3H, t, *J*=7.4 Hz), 4.49 (2H, q, *J*=7.4 Hz), 7.38—7.59 (2H, m), 7.76—7.89 (2H, m), 8.91 (1H, s), 14.62 (1H, s)
5b	1720, 1625	231 (M^+)	1.09 (3H, t, *J*=7.4 Hz), 1.75—1.96 (2H, m), 4.31—4.45 (2H, m), 7.38—7.55 (2H, m), 7.74—7.87 (2H, m), 8.92 (1H, s), 14.62 (1H, s)
5c	1734, 1631	231 (M^+)	1.71 (6H, d, *J*=7.2 Hz), 5.25—5.75 (1H, br), 7.36—7.45 (1H, m), 7.69—7.85 (3H, m), 8.88 (1H, s), 14.76 (1H, s)
5d	1737, 1622	245 (M^+)	1.02 (3H, t, *J*=7.4 Hz), 1.43—1.68 (2H, m), 1.70—1.89 (2H, m), 4.34—4.47 (2H, m), 7.39—7.56 (2H, m), 7.75—7.88 (2H, m), 8.92 (1H, s), 14.63 (1H, s)
5e	1737, 1627	245 (M^+)	1.02 (6H, d, *J*=7.5 Hz), 2.30 (1H, septet, *J*=7.5 Hz), 4.31 (2H, d, *J*=7.5 Hz), 7.37—7.55 (2H, m), 7.73—7.86 (2H, m), 8.92 (1H, s)
6c	1738, 1710, 1623	259 (M^+)	1.42 (3H, t, *J*=7.4 Hz), 1.46 (6H, d, *J*=7.2 Hz), 4.43 (2H, q, *J*=7.4 Hz), 5.64 (1H, septet, *J*=7.2 Hz), 7.39 (1H, ddd, *J*=1.2, 1.6, 7.8 Hz), 7.62—7.86 (3H, m), 8.54 (1H, s)
7c	1709, 1622	231 (M^+)	1.55 (6H, d, *J*=7.2 Hz), 5.88 (1H, septet, *J*=7.2 Hz), 7.49 (1H, ddd, *J*=1.2, 1.6, 7.8 Hz), 7.73—7.92 (3H, m), 9.01 (1H, s), 11.05—11.27 (1H, br)

***N*-(2-Diethylaminoethyl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide Hydrochloride (11c)** A solution of **5c** (500 mg, 2.7 mmol) and thionyl chloride (5 ml) was heated at 100 °C for 1.5 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was dissolved in toluene. The solvent was evaporated *in vacuo* again and the residue again dissolved in toluene. Then, 2-diethylaminoethylamine (330 mg) was added to the above toluene solution, and the reaction mixture stirred at room temperature for 1 h. The reaction mixture was then poured into 5% $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried and evaporated *in vacuo*. The residue was dissolved in EtOH (10 ml), then concentrated HCl (230 mg) was added. The mixture was evaporated *in vacuo* to afford a residue, which was recrystallized from MeOH–AcOEt to give 549 mg (69.3%) of **11c** as a colorless solid. Physicochemical data of **11c** are summarized in Tables 1 and 2.

Single-Crystal X-Ray Analysis of 8c Crystals of compound **8c** were grown from AcOEt as yellow prisms. Data was collected from a crystal with the dimensions 0.50×0.30×0.10 mm^3 on a Mac Science MXC18 diffractometer and corrected for Lorentz and polarization factors. The structure was determined by a direct method using the SHELXS86 program and refined using the crystan-GM program.[30] The final refinement was achieved by the full-matrix least-squares method, with anisotropic thermal parameters for all non-hydrogen atoms and fixed isotropic thermal parameters for hydrogen atoms. Crystal data: $C_{21}H_{27}N_3O_2$, M.W.=353.46, triclinic, space group *P*1, *a*=9.828 (2) Å, *b*=12.160 (3) Å, *c*=7.998 (4) Å, α=98.33 (3) Å, β=93.32 (3) Å, γ=90.26 (2) Å, *V*=944.0 (6) $Å^3$, *Z*=2, *Dc*=1.24 g/cm^3, F_{000}=380, temperature 15 °C, Cu$K\alpha$ (λ=1.54178 Å), 3157 observed reflections ($I>3.00\,\sigma$ (I)), 313 variable parameters, R=0.074, R_w=0.091.

Serotonin 5-HT$_4$ Receptor Agonistic Activity[31] Male guinea pigs of the Hartley strain (Nihon SLC Inc., Shizuoka) weighing 200—400 g were housed at 20—26 °C on a 12 h light/dark cycle with free access to food and water. Guinea pigs were killed by a blow to the head and by cutting of the carotid arteries. The ileum was excised 10—20 cm from the ileo-caecal junction and divided longitudinally into segments approximately 3 cm in length. The longitudinal muscle strips with the myenteric plexus attached were removed by gentle stroking with a cotton swab. The tissue was vertically suspended in an organ bath containing Krebs' solution (composition in mmol/l: NaCl, 120; KCl, 5.9; $NaHCO_3$, 15.5; NaH_2PO_4, 1.2; $CaCl_2$, 2.5; $MgCl_2$, 1.2; glucose, 11.5) aerated with a mixture of 95% O_2 and 5% CO_2 and maintained at 32 °C. Twitch responses were evoked by transmural electrical stimulation of the enteric cholinergic nerves using square-wave pulses (0.2 Hz, 1 ms pulse duration). Twitch responses were recorded isometrically with a resting tension of 0.8 g. The tissue was stimulated at supramaximal voltage to equilibration for 2—3 h. The twitch response was then decreased by voltage reduction. After obtaining a stable submaximal response, the tissue was exposed to 10 nmol/l of 5-HT. This concentration of 5-HT produced a sustained increase in the twitch response. Concentration–effect curves to agonists were constructed by exposing the strips to a cumulative addition of agonists. The responses to agonists were measured in terms of their ability to restore the twitch response to that obtained at supramaximal voltage.

Gastrointestinal Motility Dogs with strain gauge force transducers sutured to the serosa of the gastric antrum, small intestine or colon were prepared to measure circular muscle contractions. The experiments were started at least 14 d after surgery. The animals were deprived of food, but not water, for 18 h before each experiment. Before the application of test drugs, control recordings were performed in each dog. During this recording, a previously reported motility pattern, *i.e.*, alternating contractile and quiescent states, was confirmed at the antral site. Compound **8c** and vehicle were given 5—10 min after termination of the contractile state in the antrum, and a meal (100 kcal) was then given immediately.

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