Synthesis and Structure–Activity Relationship of 3-Substituted Benzamide, Benzo[*b*]furan-7-carboxamide, 2,3-Dihydrobenzo[*b*]furan-7-carboxamide, and Indole-5-carboxamide Derivatives as Selective Serotonin 5-HT_4 Receptor Agonists

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The title compounds (6—9) were prepared and evaluated for serotonin 5-HT_4 agonistic activity in *in vitro* tests. Introducing a propyl or allyl group at the 3-position of benzamide caused only a slight enhancement of agonistic activity. Construction of the benzo[*b*]furan skeleton and 2,3-dihydrobenzo[*b*]furan skeleton caused a significant enhancement of the activity. 4-Amino-*N*-[2-(1-azabicyclo[3.3.0]octan-5-yl)ethyl]-5-chloro-2-methylbenzo[*b*]furan-7-carboxamide (7b) hemifumarate was as potent as cisapride. 4-Amino-*N*-[2-(1-azabicyclo[3.3.0]octan-5-yl)ethyl]-5-chloro-2,3-dihydro-2-methylbenzo[*b*]furan-7-carboxamide (8a) hemifumarate, 4-amino-*N*-[2-(1-azabicyclo-[3.3.0]octan-5-yl)ethyl]-5-chloro-2,3-dihydro-2-ethylbenzo[*b*]furan-7-carboxamide (8c) hemifumarate, and 4-amino-*N*-[2-(1-azabicyclo[3.3.0]octan-5-yl)ethyl]-5-chloro-2,3-dihydro-2,3-dimethylbenzo[*b*]furan-7-carboxamide (8d) hemifumarate were more potent than cisapride. Furthermore, 8a hemifumarate was free from dopamine D_1, D_2, serotonin 5-HT_1, 5-HT_2 and muscarine M_1, M_2 receptor binding activity in the *in vitro* tests. On the other hand, construction of the indole skeleton caused a remarkable decrease in activity.

Key words benzo[*b*]furan-7-carboxamide; serotonin 5-HT_4 agonistic activity; structure–activity relationship; 2,3-dihydrobenzo[*b*]furan-7-carboxamide

Metoclopramide[2)] (**1**) and cisapride[3)] (**2**) are clinically used as gastroprokinetic agents. Their gastroprokinetic action is accepted to be due to agonistic activity at a serotonin receptor subtype (5-HT_4).[4)] These agents, however, have dopamine D_2 receptor antagonistic activity, which is responsible for unfavorable side effects such as extrapyramidal disorder and cryptorrhea (lactation and prolactinemia). To moderate these side effects, various benzamide derivatives, for instance, mosapride[5)] (**3**), zacopride[6)] (**4**), and so on, have been synthesized (Chart 1). These derivatives were mainly obtained by modification of the *tert*-amine side chain on metoclopramide (**1**). Many kinds of *tert*-amine side chains were examined in the benzamide series, and it was suggested that azabicyclo derivatives were more potent and selective for serotonin 5-HT_4 agonism.[7)] On the other hand, little work has been done on the influence of the substituents at the 3-position of benzamide derivatives on 5-HT_4 agonistic activity, except for the report on SB 204070[8)] (**5**).

In the present study, with the aim of finding more potent and selective analogs, we first selected the 2-(1-azabicyclo-[3.3.0]octan-5-yl)ethyl group[9)] as the azabicyclo moiety.[10)] Next, we designed new 3-substituted benzamides, benzo[*b*]furan-7-carboxamide, 2,3-dihydrobenzo[*b*]-furan-7-carboxamide, and indole-5-carboxamide derivatives, having the 2-(1-azabicyclo[3.3.0]octan-5-yl)ethyl group as the azabicyclo moiety (Chart 2). As a result of *in vitro* screening tests, 4-amino-*N*-[2-(1-azabicyclo[3.3.0]-octan-5-yl)ethyl]-5-chloro-2,3-dihydro-2-methylbenzo-[*b*]furan-7-carboxamide (**8a**) hemifumarate was found to be more potent than cisapride in 5-HT_4 agonistic activity and to be free from dopamine D_1, D_2, serotonin 5-HT_1, 5-HT_2, and muscarine M_1 and M_2 receptor binding activity. In addition, we report the structure–activity relationship (SAR) of these compounds for 5-HT_4 receptor agonistic activity.

Chemistry

The requisite benzoic acid derivatives (**12a**—**e**) were prepared by the methods depicted in Chart 3. The treatment of methyl 4-acetylamino-2-hydroxybenzoate (**10**)[11)] with ethyl iodide followed by chlorination with *N*-chlorosuccinimide (NCS) gave methyl 4-acetylamino-5-chloro-2-ethoxybenzoate (**11a**). Alkaline hydrolysis of **11a** gave 4-amino-5-chloro-2-ethoxybenzoic acid (**12a**). The 3-allyl group was introduced by the Claisen rearrangement of the 2-allyloxy-5-chloro derivative. The rearranged

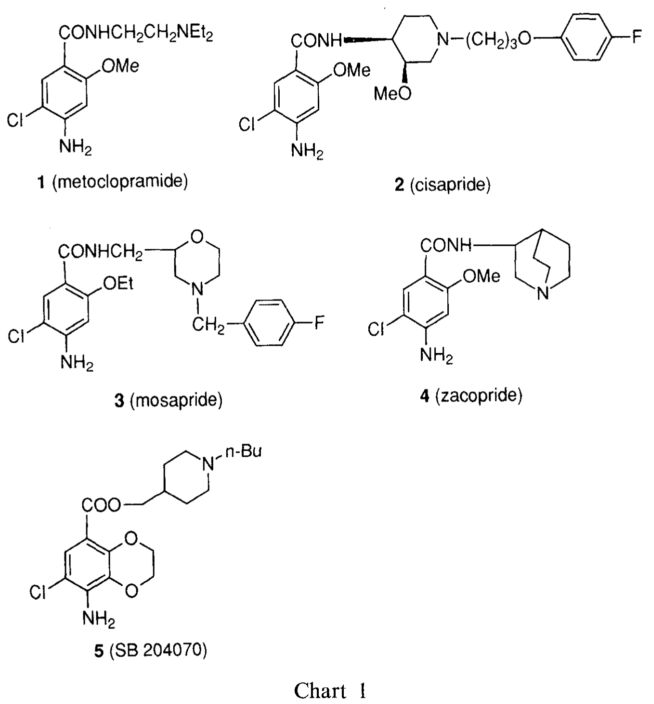

Chart 1

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phenolic product was alkylated with alkyl halide to give methyl 4-acetylamino-3-allyl-5-chloro-2-alkoxybenzoate (**11b, c**). Alkaline hydrolysis of **11b, c** gave 3-allyl-2-alkoxy-4-amino-5-chlorobenzoic acids (**12b, c**). The 3-propyl derivatives (**11d, e**) were prepared by a catalytic hydrogenation of the 2-alkoxy-3-allylbenzoates, which were derived from **13a** by the Claisen rearrangement followed by the alkylation of the resulting phenolic group, with 5% Pd–C catalyst. Chlorination at the 5-position and alkaline hydrolysis of the acetylamino and ester groups gave 2-alkoxy-4-amino-5-chloro-3-propylbenzoic acid (**12d, e**).

The benzo[*b*]furan-7-carboxylic acid derivatives (**22a—c**), which have a cyclic structure between the 3-carbon and 2-oxygen of the benzoic acids, were prepared as shown in Chart 4. The Claisen-type rearrangement reaction of

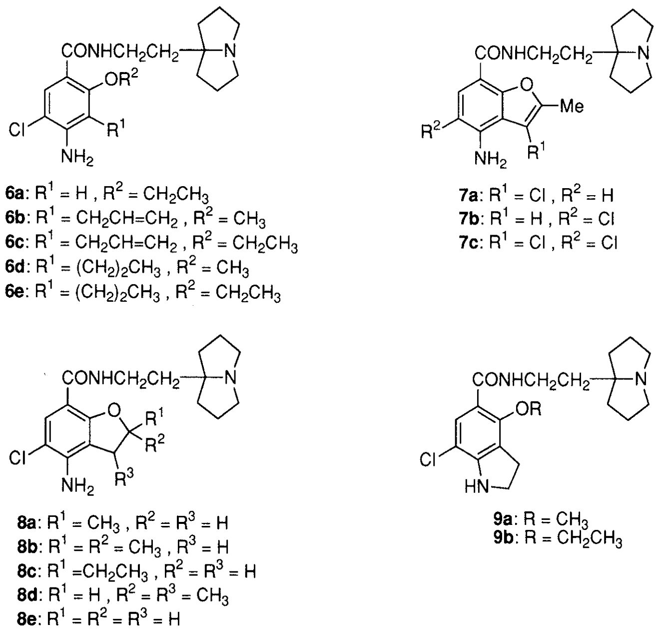
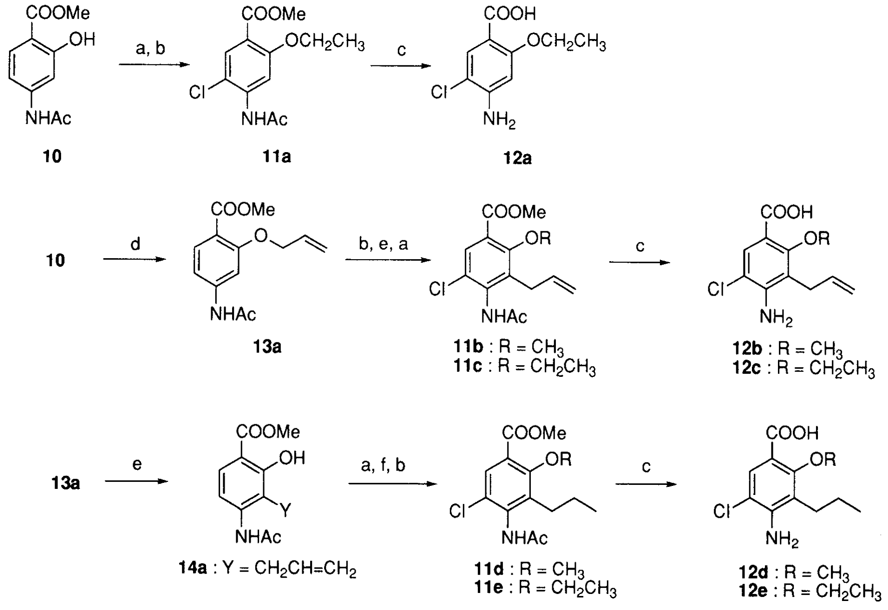


Chart 2

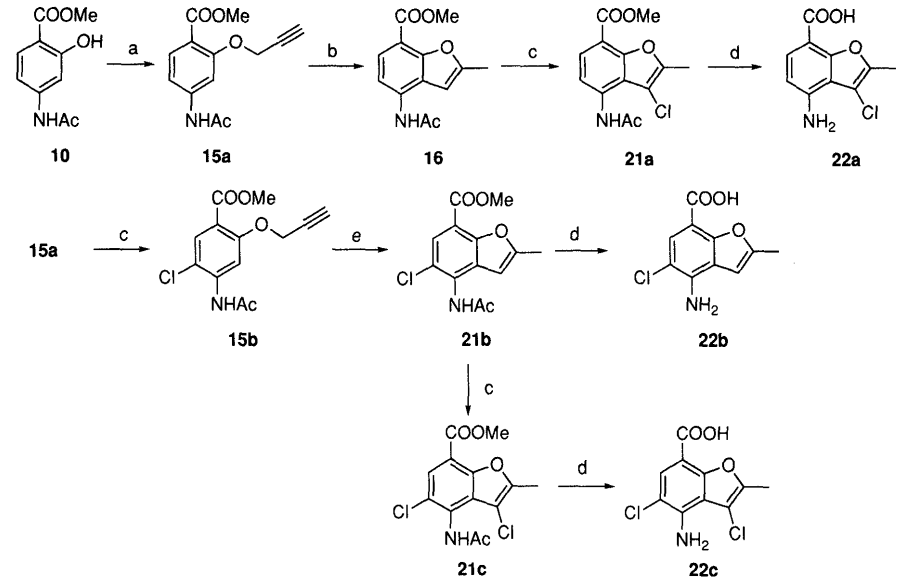
methyl 4-acetylamino-2-propargyloxybenzoate (**15a**) in 1,2-dichlorobenzene gave methyl 4-acetylamino-2-methylbenzo[*b*]furan-7-carboxylate (**16**) in 45.3% yield together with methyl 5-acetylamino-2*H*-1-benzopyran-8-carboxylate (**17**), methyl 1-acetyl-4-hydroxy-2-methyl-1*H*-indole-5-carboxylate (**18**), methyl 1-acetyl-1,2-dihydro-5-hydroxyquinoline-6-carboxylate (**19**), and methyl 5-hydroxyquinoline-6-carboxylate (**20**) as minor products. The chlorination at the 3-position and alkaline hydrolysis of **16** gave 4-amino-3-chloro-2-methylbenzo[*b*]furan-7-carboxylic acid (**22a**). In the case of chlorination of **16**, the 3-position was chlorinated, but not the 5-position. This was confirmed by the disappearance of the proton peak at the 3-position in the ^{1}H-NMR spectrum of **21a**. The Claisen-type rearrangement reaction of methyl 4-acetylamino-5-chloro-2-propargyloxybenzoate (**15b**) in *N*-methylpyrrolidone, which was prepared from **15a** by chlorination, gave methyl 4-acetylamino-5-chloro-2-methylbenzo[*b*]furan-7-carboxylate (**21b**) in 38% yield, together with methyl 5-acetylamino-5-chloro-2*H*-1-benzopyran-8-carboxylate (**23**) as a minor product. The alkaline hydrolysis of **21b** gave 4-amino-5-chloro-2-methylbenzo[*b*]furan-7-carboxylic acid (**22b**). Chlorination at the 3-position of **21b** followed by alkaline hydrolysis of **21c** gave 4-amino-3,5-dichloro-2-methylbenzo[*b*]furan-7-carboxylic acid (**22c**).

The 2,3-dihydrobenzo[*b*]furan-7-carboxylic acid derivatives (**26a—e**) were synthesized according to Chart 5. The thermal rearrangement reaction of methyl 4-acetylamino-2-(alkenyloxy)benzoates (**13a—d**) in *N*-methylpyrrolidone, which were prepared from **10** with alkenyl chloride, gave methyl 4-acetylamino-2-hydroxy-3-alkenylbenzoates (**14a—d**). Compounds **14a—d** were cyclized to the methyl 4-acetylamino-2,3-dihydrobenzo[*b*]furan-7-carboxylate derivatives (**24a—d**) under acid conditions. Chlorination of **24a—d** followed by alkaline hydrolysis gave the 4-amino-2,3-dihydrobenzo[*b*]furan-7-carboxylic



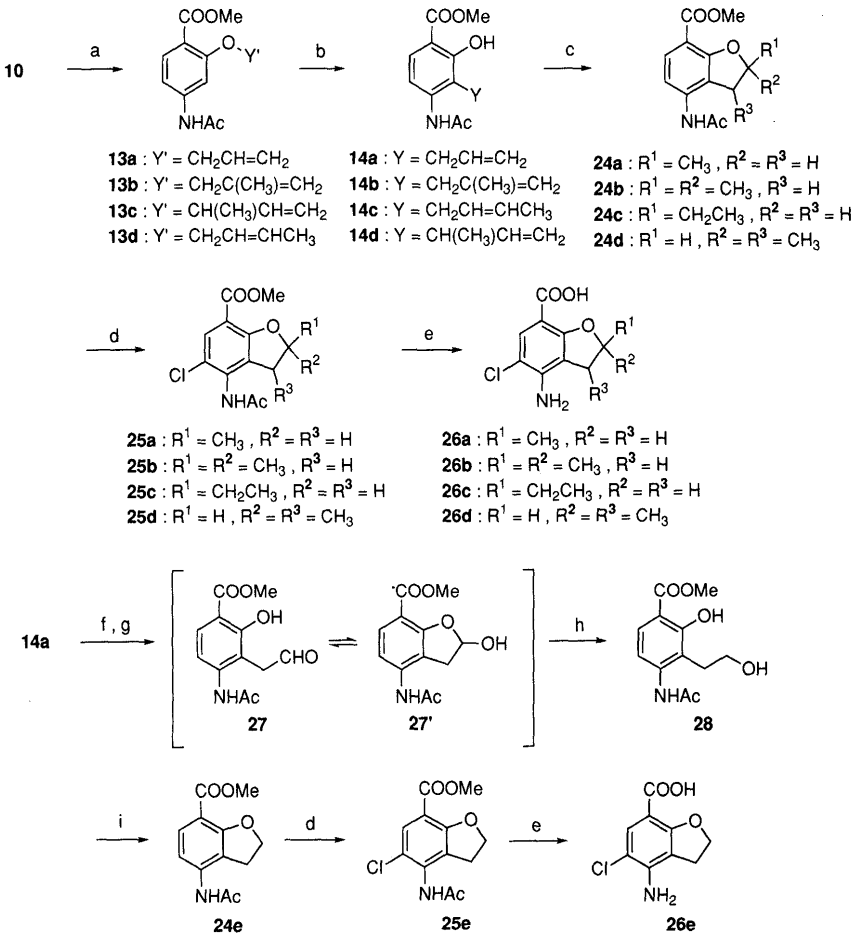
Reagents: a CH_3I or CH_3CH_2I, K_2CO_3 ; b *N*-chlorosuccinimide (NCS) ; c 4N NaOH;
d $BrCH_2CH{=}CH_2$, K_2CO_3 ; e *N*-methylpyrrolidone, Δ; f H_2, 5% Pd-C

Chart 3



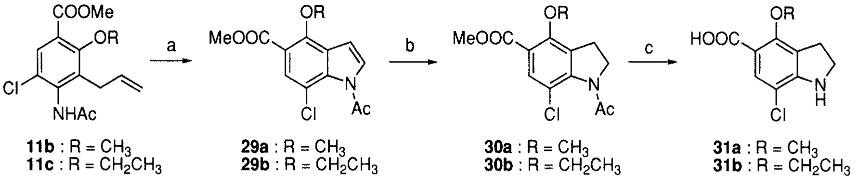
Reagents: a $BrCH_2C{\equiv}CH$, K_2CO_3 ; b 1,2-dichlorobenzene, Δ; c NCS ; d 4N NaOH;
e *N*-methylpyrrolidone, Δ

Chart 4



Reagents: a alkenyl halide , K_2CO_3 ; b *N*-methylpyrrolidone, Δ; c 97% H_2SO_4; d NCS; e 4N NaOH
f OsO_4 , $KClO_3$; g $NaIO_4$; h $NaBH_4$; i DEAD, Ph_3P

Chart 5



Reagents: a OsO_4, Na_2O_2 ; b H_2, 5% Pd-C ; c 4N NaOH

Chart 6

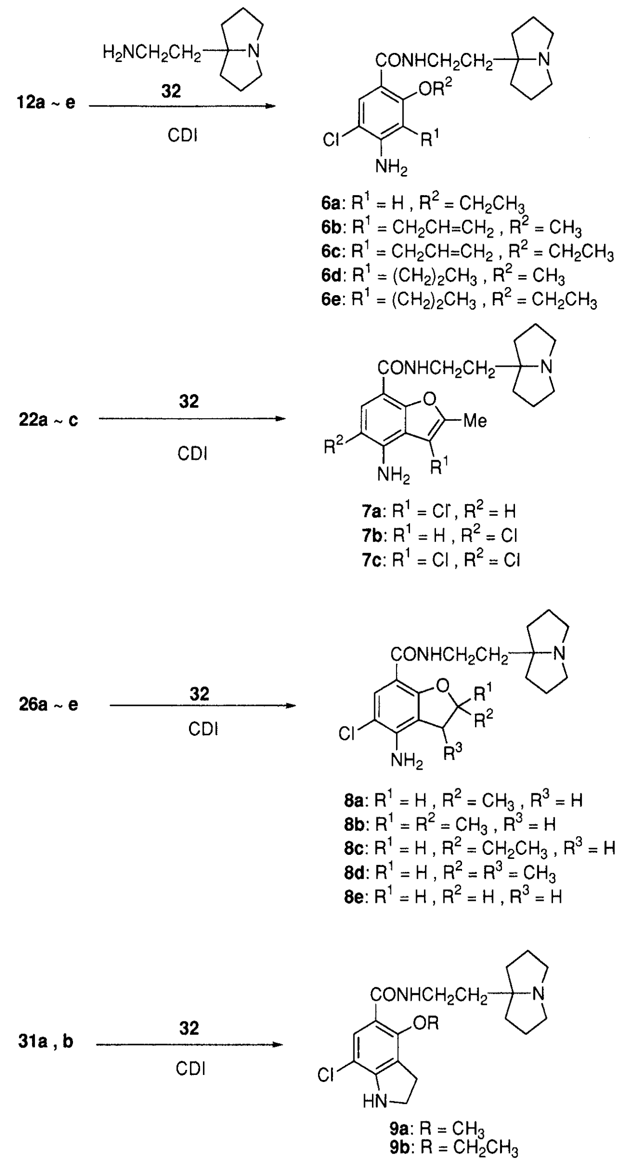


Chart 7

acid derivatives (**26a**—**d**). Next, a 2,3-dihydrobenzo[*b*]-furan derivative (**26e**) was prepared *via* processes starting with oxidative cleavage of the double bond of **14a**. Methyl 4-acetylamino-3-formylmethyl-2-hydroxybenzoate (**27**) was obtained by adding $NaIO_4$ after the treatment of **14a** with OsO_4. The ^{1}H-NMR spectrum of **27** in DMSO-d_6 showed that **27** was a balanced mixture with methyl 4-acetylamino-2,3-dihydro-2-hydroxybenzo[*b*]furan-7-carboxylate (**27′**) in the ratio of **27**:**27′** = 1:1. The reduction of the mixture of **27** and **27′** with $NaBH_4$ afforded 4-acetylamino-2-hydroxy-3-(2-hydroxyethyl)-benzoate (**28**) as a single product. Cyclization by the dehydration reaction of **28** gave methyl 4-acetylamino-2,3-dihydrobenzo[*b*]furan-7-carboxylate (**24e**). The chlorination of **24e** followed by alkaline hydrolysis gave 4-amino-2,3-dihydrobenzo[*b*]furan-7-carboxylic acid (**26e**).

The synthesis of the indole-5-carboxamide derivatives (**31a, b**), which have a cyclic structure between the 3-carbon and 4-nitrogen atoms of the benzoic acid derivatives is shown in Chart 6. The treatment of **11b, c** with OsO_4 in the presence of Na_2O_2 gave methyl 1-acetyl-4-alkoxy-7-chloroindole-5-carboxylates (**29a, b**). Catalytic hydrogenation of **29a, b** followed by alkaline hydrolysis gave 4-alkoxy-7-chloroindole-5-carboxylic acids (**31a, b**).

5-(2-Aminoethyl)-1-azabicyclo[3.3.0]octane[10] (**32**) was synthesized from 5-cyanomethyl-1-azabicyclo[3.3.0]octane.[9]

Finally, the reaction of **12a**—**e**, **22a**—**c**, **26a**—**e**, and **31a, b** with **32** in the presence of 1,1′-carbonyldiimidazole (CDI) afforded the corresponding **6a**—**e**, **7a**—**c**, **8a**—**e**, and **9a, b** which were led to the hemifumarates for the biological tests (Chart 7, Table 1).

Pharmacological Results

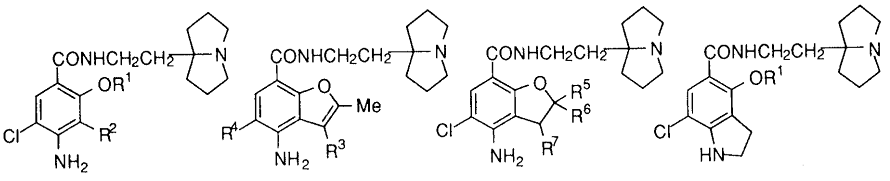
The 5-HT_4 receptor agonistic activity of the obtained compounds was checked in accordance with the method described by Baxter *et al.*,[12] using cisapride as the control compound. The results are shown in Table 1. The EC_{50} of compound **6a**, which has no substituent at the 3-position was 1.9 μM. The 5-HT_4 agonistic activity was enhanced by introduction of an alkyl group (**6b**—**e**) into the 3-position of the benzamide skeleton. The EC_{50} was 0.36—0.55 μM, and there was a slight difference in the activity between the propyl group and allyl group.

The agonistic activity was enhanced by converting the benzamide skeleton into a benzo[*b*]furan-7-carboxamide skeleton (**7a, b**). The EC_{50} was of nanomolar order, but the introduction of a chloro group into the 3-position and the removal of the chloro group at the 5-position caused the activity to decrease (**7a, c**).

2,3-Dihydrobenzo[*b*]furan-7-carboxamide derivatives also showed high activity. As for the substituent at the 2-position, a methyl group or an ethyl group was effective, and the EC_{50} values were 0.030 μM (**8a**) and 0.018 μM (**8c**), respectively. There was a slight difference in activity between the methyl group (**8a**) and ethyl group (**8c**). However, the activity was reduced by introducing two methyl groups at the 2-position (**8b**). The substituent at the 3-position on the 2,3-dihydrobenzo[*b*]furan-7-carboxamide skeleton had a slight effect on the 5-HT_4 receptor agonistic activity (**8d**).

The agonistic activity was decreased by converting the benzamide skeleton into an indole-5-carboxamide skeleton (**9a, b**). The EC_{50} values were 4.6 μM (**9a**) and 4.5 μM (**9b**).

Table 1. Physicochemical and Pharmacological Data for Synthesized Compounds (**6**—**9**)



6a—**e** **7a**—**c** **8a**—**e** **9a, b**

No.	Substrate	mp (°C)	Formula[a]	EC_{50} (μM)
6a	$R^1=CH_3$, $R^2=H$	152—154	$C_{18}H_{26}ClN_3O_2$	1.9
6b	$R^1=CH_3$, $R^2=CH_2CHCH_2$	84—88	$C_{20}H_{28}ClN_3O_2 \cdot 1/2C_4H_4O_4$	0.48
6c	$R^1=CH_2CH_3$, $R^2=CH_2CHCH_2$	82—85	$C_{21}H_{30}ClN_3O_2 \cdot 1/2C_4H_4O_4$	0.45
6d	$R^1=CH_3$, $R^2=CH_2CH_2CH_3$	152—161	$C_{20}H_{30}ClN_3O_2 \cdot 1/2C_4H_4O_4$	0.55
6e	$R^1=CH_2CH_3$, $R^2=CH_2CH_2CH_3$	92—96	$C_{21}H_{32}ClN_3O_2 \cdot 1/2C_4H_4O_4$	0.36
7a	$R^3=Cl$, $R^4=H$	240 (dec.)	$C_{19}H_{24}ClN_3O_2 \cdot 1/2C_4H_4O_4$	2.0
7b	$R^3=H$, $R^4=Cl$	244 (dec.)	$C_{19}H_{24}ClN_3O_2 \cdot 1/2C_4H_4O_4$	0.037
7c	$R^3=Cl$, $R^4=Cl$	242 (dec.)	$C_{19}H_{23}Cl_2N_3O_2 \cdot 1/2C_4H_4O_4$	0.80
8a	$R^5=CH_3$, $R^6=R^7=H$	236 (dec.)	$C_{19}H_{26}ClN_3O_2 \cdot 1/2C_4H_4O_4$	0.030
8b	$R^5=R^6=CH_3$, $R^7=H$	189—191	$C_{20}H_{28}ClN_3O_2$	0.30
8c	$R^5=CH_2CH_3$, $R^6=R^7=H$	192 (dec.)	$C_{20}H_{28}ClN_3O_2 \cdot 1/2C_4H_4O_4$	0.018
8d	$R^5=R^7=CH_3$, $R^6=H$	228 (dec.)	$C_{20}H_{28}ClN_3O_2 \cdot 1/2C_4H_4O_4$	0.013
8e	$R^5=R^6=R^7=H$	124—125	$C_{18}H_{24}ClN_3O_2$	0.30
9a	$R^1=CH_3$	207 (dec.)	$C_{19}H_{26}ClN_3O_2 \cdot 1/2C_4H_4O_4$	4.6
9b	$R^1=CH_2CH_3$	215 (dec.)	$C_{20}H_{28}ClN_3O_2 \cdot 1/2C_4H_4O_4$	4.5
Cisapride				0.042
Mosapride				2.3

a) All elemental analyses for C, H and N were within $\pm 0.3\%$ of the calculated values.

In the radioligand binding assays (Table 2), **8a** showed no affinity at a concentration of 100 μM for the dopamine D_1, D_2 and serotonin 5-HT_1, 5-HT_2 binding sites in the rat brain synaptic membranes and weak affinity for the muscarine M_1, and M_2 binding sites with IC_{50}'s of 1.2 and 19.8 μM, respectively. Cisapride had high dopamine D_2 and serotonin 5-HT_2 binding affinities with IC_{50}'s of 0.63 and 0.003 μM, respectively, and weak dopamine D_1 and serotonin 5-HT_1 binding affinities with IC_{50}'s of 5.3 and 12 μM, respectively. Mosapride also had a high serotonin 5-HT_2 binding affinity with an IC_{50} of 0.524 μM.

Table 2. ^{3}H-Labeled Ligand Binding Profile of **8a**, Cisapride, and Mosapride in Rat Brain Synaptic Membranes

Binding Site	IC_{50} (μM)		
	8a	Cisapride	Mosapride
5-HT_1	>100	11.5	24.2
5-HT_2	88	0.0027	0.524
D_1	>100	5.28	>100
D_2	>100	0.627	>100
M_1	1.2	>10	>10
M_2	19.8	>10	>10

Discussion

The SARs associated with substituents on the 3-position of benzamide were examined. The substituents had only a slight effect on affinity for the serotonin 5-HT_4 binding site. The introduction of a propyl or allyl group at the 3-position of the benzamide skeleton slightly enhanced the agonistic activity, although these compounds were less potent than cisapride. There was little difference in activity between the propyl group and allyl group, and so, it appears that introducing a bulky group at the 3-position did not reduce the agonistic activity.

The SARs of the benzo[*b*]furan and 2,3-dihydrobenzo[*b*]furan skeletons were then examined. The benzo[*b*]furan-7-carboxamide derivatives and 2,3-dihydrobenzo[*b*]furan-7-carboxamide derivatives were similar in lipophilicity to the compounds substituted at the 3-position of benzamide, although the agonistic activity was more potent than that of the benzamide derivatives, mosapride and cisapride. The agonistic activity of **7b** was similar to that of **8a**. Consequently, it is thought that both the lipophilicity of the compounds and π electrons of the substituent at the 3-position of the benzamide skeleton and benzo[*b*]furan skeleton have only a slight effect on the activity, and that flexibility of the substituent at the 3-position on a benzamide skeleton enhances the agonistic activity. In the 2,3-dihydrobenzo[*b*]furan skeleton, introduction of a mono methyl or ethyl group at the 2-position enhanced the activity. It is thought that the directionality, but not the bulkiness, of a substituent at the 2-position is important for agonistic activity. Furthermore, introduction of a methyl group at the 3-position enhanced the activity. On the other hand, in the benzo[*b*]furan skeleton, introduction of a chloro group at the 3-position caused a remarkable decrease in activity. This implies that introduction of an electron-withdrawing group at the 3-position of the benzo[*b*]furan skeleton reduces the activity.

Construction of an indole skeleton from the propyl group at the 3-position and the amino group of benzamide caused a remarkable decrease in activity. Steric bulk around the amino group seems to be undesirable for agonistic activity.

In the radioligand binding assay, cisapride had a high dopamine D_2 binding affinity. This high affinity is consistent with its dopamine D_2 antagonistic character. Mosapride had no dopamine D_2 binding affinity, but had a high serotonin 5-HT_2 binding affinity. On the other hand, **8a** hemifumarate had weak muscarine M_1 and M_2 binding affinities, although these binding affinities were in contrast to its 5-HT_4 agonistic affinity.

In conclusion, some benzo[*b*]furan-7-carboxamide derivatives and 2,3-dihydrobenzo[*b*]furan-7-carboxamide derivatives showed more potent 5-HT_4 agonistic activity than mosapride and cisapride. Compound **8a** hemifumarate was found to possess a potent 5-HT_4 agonistic affinity and to be free from dopamine D_1, D_2, serotonin 5-HT_1, 5-HT_2 and muscarine M_1, M_2 receptor binding activities *in vitro*.

Experimental

Chemistry All melting points were determined on a Yanagimoto micromelting point apparatus without correction. IR spectra were recorded on a Perkin Elmer 1600. Mass spectra were obtained on a JEOL JMS-SX 120A spectrometer. ^{1}H- (270 MHz) NMR spectra were recorded on a JEOL JNM-GSX 270 in $CDCl_3$ or DMSO-d_6. Chemical shifts are expressed as δ values (ppm) with tetramethylsilane as an internal standard, and coupling constants (J values) are given in hertz (Hz).

Methyl 4-Acetylamino-5-chloro-2-ethoxybenzoate (11a) A mixture of methyl 4-acetylamino-2-hydroxybenzoate (**10**) (24.0 g, 115 mmol), ethyl iodide (20.2 g, 158 mmol), and potassium carbonate (31.7 g, 230 mmol) in *N*,*N*-dimethylformamide (DMF, 240 ml) was stirred for 24 h at 20—30 °C. The reaction mixture was poured into ice-water (400 ml), and the resultant precipitate was collected by filtration and recrystallized from ethanol to give 26.8 g (98.4%) of methyl 4-acetylamino-2-ethoxybenzoate as prisms. mp 145—146 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7.3 Hz, CH_3), 2.19 (3H, s, CH_3), 3.86 (3H, s, CH_3), 4.09 (2H, q, J=7.3 Hz, CH_2), 6.84 (1H, dd, J=2.0, 8.8 Hz, C5-H), 7.58 (1H, br s, C3-H), 7.65 (1H, br s, CONH), 7.78 (1H, d, J=8.8 Hz, C6-H). IR (KBr) cm^{-1}: 1698, 1604 (C=O). High-resolution MS m/z: Calcd for $C_{12}H_{15}NO_4$: 237.1001. Found: 237.1013.

A mixture of the obtained benzoate (25.0 g, 105 mmol) and NCS (14.8 g, 111 mmol) in DMF (150 ml) was stirred for 3 h at 70 °C. The cooled reaction mixture was concentrated *in vacuo* and poured into ice-water (200 ml). The resultant precipitate was collected by filtration to give 26.8 g (98.4%) of **11a** as a needle.

Physicochemical data are summarized in Table 3.

Methyl 4-Acetylamino-2-allyloxybenzoate (13a) A mixture of methyl 4-acetylamino-2-hydroxybenzoate (**10**) (80.0 g, 382 mmol), potassium carbonate (52.9 g, 382 mmol), 3-bromo-1-propene (50.6 g, 421 mmol), and tetra *n*-butylammonium chloride (5.31 g, 19.1 mmol) in acetonitrile (350 ml) was refluxed for 22 h. The cooled reaction mixture was concentrated *in vacuo*, and the residue was treated with water (100 ml). The resulting precipitate was collected by filtration to give 91.0 g (95.5%) of **13a** as a powder. mp 112—114 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s, $COCH_3$), 3.87 (3H, s, OCH_3), 4.6—4.7 (2H, m, CH_2), 5.2—5.7 (2H, m, CH_2), 5.8—6.3 (1H, m, CH), 6.81 (1H, dd, J=1.9, 8.6 Hz, C5-H), 7.44 (1H, br s, CONH), 7.62 (1H, d, J=1.9 Hz, C3-H), 7.80 (1H, d, J=8.8 Hz, C6-H). IR (KBr) cm^{-1}: 1710, 1591 (C=O). High-resolution MS m/z: Calcd for $C_{13}H_{15}NO_4$: 249.1001. Found: 249.0989.

Methyl 4-Acetylamino-3-allyl-5-chloro-2-methoxybenzoate (11b) A mixture of **13a** (7.49 g, 30.1 mmol) and NCS (3.80 g, 28.5 mmol) in DMF (7.0 ml) was stirred for 21 h at 70 °C. The cooled reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 2) to give 6.50 g (72.4%) of methyl 4-acetylamino-2-allyloxy-5-chlorobenzoate as a powder. mp 102—103 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s, $COCH_3$), 3.88 (3H, s, OCH_3), 4.6—4.7 (2H, m, CH_2), 5.32 (1H, dd, J=1.5, 10.2 Hz, CH_2), 5.56 (1H, dd, J=1.5, 17.1 Hz, CH_2), 6.0—6.1 (1H, m, CH), 7.74 (1H, br s, CONH), 7.75 (1H, s, C3-H), 8.31 (1H, s, C6-H).

A solution of the obtained benzoate (13.0 g, 45.9 mmol) in *N*-methylpyrrolidone (50.0 ml) was refluxed for 2 h, then poured into ice-water. The resultant precipitate was collected by filtration, and recrystallized from ethanol to give 8.00 g (61.5%) of methyl 4-acetylamino-3-allyl-5-chloro-2-hydroxybenzoate as a powder. mp 188—189 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.22 (3H, s, $COCH_3$), 3.4—3.5 (2H, m, CH_2), 3.96 (3H, s, OCH_3), 5.0—5.1 (2H, m, CH_2), 5.8—5.9 (1H, m, CH), 6.94 (1H, br s, CONH), 7.85 (1H, s, C6-H), 11.08 (1H, s, OH). IR (KBr) cm^{-1}: 1686, 1666 (C=O). High-resolution MS m/z: Calcd for $C_{13}H_{14}ClNO_4$: 283.0611. Found: 283.0635.

A mixture of methyl 4-acetylamino-3-allyl-5-chloro-2-hydroxybenzoate (3.00 g, 10.6 mmol), methyl iodide (694 μl, 10.6 mmol), and potassium carbonate (2.92 g, 10.6 mmol) in DMF (30.0 ml) was stirred for 21 h at 70 °C. The reaction mixture was then poured into ice-water (150 ml), and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$: AcOEt : hexane = 1 : 4 : 5) to give 1.80 g (57.1%) of **11b** as needles.

Methyl 4-acetylamino-3-allyl-5-chloro-2-hydroxybenzoate (705 mg, 2.49 mmol) was similarly treated with ethyl iodide (700 μl, 8.14 mmol) to give 500 mg (64.5%) of **11c** as a powder.

Physicochemical data of **11b** and **11c** are summarized in Table 3.

Methyl 4-Acetylamino-3-allyl-2-hydroxybenzoate (14a) A solution of **13a** (90.0 g, 361 mmol) in *N*-methylpyrrolidone (90.0 ml) was refluxed for 1.5 h. The reaction mixture was poured into ice-water. The resultant precipitate was collected by filtration to give 85.4 g (94.9%) of **14a** as a powder. mp 186—188 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s, $COCH_3$), 3.5—3.6 (2H, m, CH_2), 3.94 (3H, s, CH_3), 5.0—5.2 (2H, m, CH_2), 5.8—6.1 (1H, m, CH), 7.42 (1H, br s, CONH), 7.70 (1H, br, C5-H), 7.92 (1H, d, J=8.8 Hz, C6-H), 11.25 (1H, s, OH). IR (KBr) cm^{-1}: 1656 (C=O). High-resolution MS m/z: Calcd for $C_{12}H_{15}NO_4$: 249.1001. Found: 249.1020.

Methyl 4-Acetylamino-5-chloro-2-methoxy-3-propylbenzoate (11d) Compound **14a** (5.00 g, 20.1 mmol) was alkylated in a similar procedure as employed in the synthesis of **11b** to give 3.33 g (63.1%) of methyl 4-acetylamino-3-allyl-2-methoxybenzoate as a powder. mp 128—129 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s, $COCH_3$), 3.5—3.6 (2H, m, CH_2), 3.8—4.0 (2H, m, CH_2), 3.80 (3H, s, CH_3), 3.90 (3H, s, CH_3), 5.11 (1H, d, J=17.6 Hz, CH_2), 5.23 (1H, d, J=10.3 Hz, CH_2), 5.9—6.0 (1H, m, CH), 7.41 (1H, br s, CONH), 7.79 (1H, d, J=8.8 Hz, C6-H), 7.92 (1H, d, J=8.8 Hz, C5-H). IR (KBr) cm^{-1}: 1731, 1659 (C=O). High-resolution MS m/z: Calcd for $C_{14}H_{17}NO_4$: 263.1157. Found: 263.1133.

A mixture of the obtained benzoate (600 mg, 1.90 mmol) and 10% Pd–C in $CHCl_3$ (10.0 ml) was stirred at room temperature under H_2 gas for 15 h. The reaction mixture was filtered and concentrated *in vacuo* to give 600 mg (99.9%) of methyl 4-acetylamino-2-methoxy-3-propylbenzoate as a powder. mp 105—106 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7.3 Hz, CH_3), 1.5—1.6 (2H, m, CH_2), 2.22 (3H, s, $COCH_3$), 2.62 (2H, t, J=5.9 Hz, CH_2), 3.83 (3H, s, CH_3), 3.91 (3H, s, CH_3), 7.10 (1H, br s, CONH), 7.74 (1H, br s, C6-H), 7.85 (1H, br s, C5-H). IR (KBr) cm^{-1}: 1731, 1656 (C=O). High-resolution MS m/z: Calcd for $C_{14}H_{19}NO_4$: 265.1314. Found: 263.1330.

A mixture of methyl 4-acetylamino-2-methoxy-3-propylbenzoate (410 mg, 1.55 mmol) and NCS (227 mg, 1.70 mmol) in DMF (2.0 ml) was stirred for 7 h at 70 °C. The reaction mixture was poured into ice-water (150 ml), and the resultant precipitate was collected by filtration to give

406 mg (100%) of **11d** as a powder.

Compound **14a** (5.00 g, 20.1 mmol) was similarly alkylated to give 3.33 g (63.1%) of methyl 4-acetylamino-3-allyl-2-ethoxybenzoate as a powder. mp 107—110 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7.3 Hz, CH_3), 2.15 (3H, s, $COCH_3$), 3.53 (2H, d, J=5.4 Hz, CH_2), 3.8—4.0 (2H, m, CH_2), 3.90 (3H, s, CH_3), 5.11 (1H, d, J=17.6 Hz, CH_2), 5.23 (1H, d, J=10.6 Hz, CH_2), 5.9—6.0 (1H, m, CH), 7.43 (1H, br s, CONH), 7.79 (1H, d, J=8.8 Hz, C6-H), 7.92 (1H, d, J=8.8 Hz, C5-H). IR (KBr) cm^{-1}: 1733, 1656 (C=O). High-resolution MS m/z: Calcd for $C_{15}H_{19}NO_4$: 277.1314. Found: 277.1302.

Catalytic hydrogenation of methyl 4-acetylamino-3-allyl-2-ethoxy benzoate gave methyl 4-acetylamino-2-methoxy-3-propylbenzoate as a powder. mp 113—114 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7.3 Hz, CH_3), 1.43 (3H, t, J=7.8 Hz, CH_3), 1.5—1.6 (2H, m, CH_2), 2.21 (3H, s, $COCH_3$), 2.61 (2H, t, J=5.9 Hz, CH_2), 3.89 (3H, s, CH_3), 3.93 (2H, q, J=6.8 Hz, CH_2), 7.08 (1H, br s, CONH), 7.71 (1H, d, J=8.8 Hz, C6-H), 7.85 (1H, br s, C5-H). IR (KBr) cm^{-1}: 1731, 1655 (C=O). High-resolution MS m/z: Calcd for $C_{15}H_{21}NO_4$: 279.1470. Found: 279.1453.

Then chlorination of methyl 4-acetylamino-2-methoxy-3-propylbenzoate gave 555 mg (98.8%) of **11e** as a powder.

Physicochemical data of **11d** and **11e** are summarized in Table 3.

Methyl 4-Acetylamino-2-propargyloxybenzoate (15a) A mixture of **10** (10.5 g, 50.2 mmol), propargyl bromide (6.58 g, 55.3 mmol), and potassium carbonate (6.92 g, 50.2 mmol) in acetonitrile (42.0 ml) was refluxed for 24 h, then poured into ice-water (80 ml). The resultant precipitate was collected by filtration to give 9.78 g (78.8%) of **15a** as a powder. mp 120—122 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s, CH_3), 2.54 (1H, t, J=1.4 Hz, CH), 3.87 (3H, s, CH_3), 4.79 (2H, d, J=1.4 Hz, CH_2), 6.99 (1H, dd, J=8.8, 2.0 Hz, C5-H), 7.47 (1H, br s, CONH), 7.66 (1H,

Table 3. Physicochemical Data for Synthesized Compounds (**11a—e**, **21a—c**, **25a—e**, **30a, b**)

Compd. No.	mp (°C)	IR (KBr) (cm^{-1})	High-resolution MS (m/z)	^{1}H-NMR ($CDCl_3$) δ (ppm)
11a	139—140	3236, 1694, 1686	Calcd for $C_{12}H_{14}ClNO_4$: 271.0611 Found: 271.0601	1.47 (3H, t, J=6.8 Hz, CH_3), 2.27 (3H, s, CH_3), 3.87 (3H, s, CH_3), 4.15 (2H, q, J=6.8 Hz, CH_2), 7.74 (1H, br s, CONH), 7.87 (1H, s, C3-H), 8.28 (1H, s, C6-H)
11b	114—116	3248, 1733, 1668	Calcd for $C_{14}H_{16}ClNO_4$: 297.0768 Found: 297.0752	2.21 (3H, s, $COCH_3$), 3.48 (2H, d, J=5.9 Hz, CH_2), 3.83 (3H, s, CH_3), 3.93 (3H, s, CH_3), 4.96(1H, d, J=10.2 Hz, CH_2), 5.08 (1H, d, J=17.1 Hz, CH_2), 5.8—6.0 (1H, m, CH), 6.90 (1H, br s, CONH), 7.84 (1H, s, C6-H)
11c	135—136	3266, 1732, 1667	Calcd for $C_{15}H_{18}ClNO_4$: 311.0924 Found: 311.0902	1.41 (3H, t, J=7.3 Hz, CH_3), 2.20 (3H, s, $COCH_3$), 3.48 (2H, d, J=5.4 Hz, CH_2), 3.91 (3H, s, CH_3), 3.94 (2H, q, J=7.3 Hz, CH_2), 4.96 (1H, dd, J=17.6, 1.9 Hz, CH_2), 5.07 (1H, d, J=10.3 Hz, CH_2), 5.8—5.9 (1H, m, CH), 6.93 (1H, br s, CONH), 7.83 (1H, d, J=8.5 Hz, C6-H)
11d	120—121	3442, 1728, 1656	Calcd for $C_{14}H_{18}ClNO_4$: 299.0924 Found: 299.0921	0.94 (3H, t, J=7.3 Hz, CH_3), 1.5—1.6 (2H, m, CH_2), 2.24 (3H, s, $COCH_3$), 2.63 (2H, t, J=7.8 Hz, CH_2), 3.84 (3H, s, CH_3), 3.92 (3H, s, CH_3), 6.89 (1H, br s, CONH), 7.78 (1H, br s, C6-H)
11e	120—121	3257, 1732, 1661	Calcd for $C_{15}H_{20}ClNO_4$: 313.1081 Found: 313.1075	0.95 (3H, t, J=7.3 Hz, CH_3), 1.43 (3H, t, J=7.3 Hz, CH_3), 1.5—1.6 (2H, m, CH_2), 2.25 (3H, s, $COCH_3$), 2.6—2.7 (2H, m, CH_2), 3.91 (3H, s, CH_3), 3.95 (2H, q, J=6.8 Hz, CH_2), 6.84 (1H, br s, CONH), 7.77 (1H, d, J=8.8 Hz, C6-H)
21a	198—200	3261, 1715, 1667	Calcd for $C_{13}H_{12}ClNO_4$: 281.0455 Found: 281.0433	2.27 (3H, t, J=7.3 Hz, CH_3), 2.52 (3H, t, J=7.3 Hz, CH_3), 3.97 (3H, t, J=7.3 Hz, CH_3), 7.91 (1H, d, J=9.3 Hz, C5-H), 8.26 (1H, d, J=9.3 Hz, C6-H), 8.60 (1H, br s, CONH)
21b	205 °C (dec.)	3259, 1714	Calcd for $C_{13}H_{12}ClNO_4$: 281.0455 Found: 281.0461	2.26 (3H, s, $COCH_3$), 2.53 (3H, s, CH_3), 3.98 (3H, s, CH_3), 6.66 (1H, s, C3-H), 7.51 (1H, br s, CONH), 7.89 (1H, br s, C6-H)
21c	224—225	3231, 1718, 1672	Calcd for $C_{13}H_{11}Cl_2NO_4$: 315.0065 Found: 315.0041	2.27 (3H, t, J=7.3 Hz, CH_3), 2.52 (3H, t, J=7.3 Hz, CH_3), 3.97 (3H, t, J=7.3 Hz, CH_3), 7.91 (1H, s, C6-H), 8.87 (1H, br s, CONH)
25a	197—201	3227, 1715, 1666	Calcd for $C_{13}H_{14}ClNO_4$: 283.0611 Found: 283.0615	1.52 (3H, d, J=6.5 Hz, CH_3), 2.24 (3H, s, $COCH_3$), 2.84 (1H, dd, J=7.8, 16.6 Hz, CH_2), 3.31 (1H, dd, J=8.8, 16.6 Hz, CH_2), 3.89 (3H, s, CH_3), 5.0—5.2 (1H, m, CH), 7.27 (1H, br s, CONH), 7.73 (1H, s, C6-H)
25b	181—183	3225, 1729, 1708	Calcd for $C_{14}H_{16}ClNO_4$: 297.0768 Found: 297.0771	1.52 (6H, s, CH_3), 2.23 (3H, s, CH_3), 3.01 (2H, s, CH_2), 3.87 (3H, s, CH_3), 7.27 (1H, br s, CONH), 7.72 (1H, s, C6-H)
25c	155—156	3237, 1711, 1669	Calcd for $C_{14}H_{16}ClNO_4$: 297.0768 Found: 297.0647	1.02 (3H, t, J=7.3 Hz, CH_3), 1.7—1.8 (2H, m, CH_2), 1.8—1.9 (2H, m, CH_2), 2.24 (3H, s, CH_3), 2.88 (1H, dd, J=9.3, 16.6 Hz, CH_2), 3.27 (1H, dd, J=9.3, 16.6Hz, CH_2), 3.89 (3H, s, CH_3), 4.9—5.0 (1H, m, CH), 7.26 (1H, br s, NH), 7.78 (1H, s, C6-H)
25d	131—139	3237, 1773, 1696	Calcd for $C_{14}H_{16}ClNO_4$: 297.0768 Found: 297.0773	0.99 (3H, d, J=6.8 Hz, CH_3), 1.23 (3H, d, J=6.8 Hz, CH_3), 1.48 (3H, d, J=6.8 Hz, CH_3), 1.51 (3H, d, J=6.8 Hz, CH_3), 2.25 (3H, s, CH_3), 3.4—3.5 (1H, m, CH), 3.6—3.7 (1H, m, CH), 3.89 (3H, s, CH_3), 4.5—4.6 (1H, m, CH), 5.0—5.1 (1H, m, CH), 7.25 (1H, br s, NH), 7.81 (1H, s, C6-H)
25e	217—218	3242, 1699, 1675	Calcd for $C_{12}H_{12}ClNO_4$: 269.0455 Found: 269.0432	2.24 (3H, s, $COCH_3$), 3.22 (2H, t, J=8.8 Hz, CH_2), 3.90 (3H, s, CH_3), 4.75 (2H, t, J=8.8 Hz, CH_2), 7.30 (1H, br s, CONH), 7.80 (1H, s C6-H)
30a	155—158	1708, 1676	Calcd for $C_{13}H_{14}ClNO_4$: 283.0611 Found: 283.0633	2.30 (3H, s, CH_3), 3.10 (2H, t, J=7.3 Hz, C3-H), 3.89 (3H, s, CH_3), 3.90 (3H, s, CH_3), 4.20 (1H, t, J=7.3 Hz, C2-H), 7.78 (1H, s, C6-H)
30b	99—101	1705, 1683	Calcd for $C_{14}H_{16}ClNO_4$: 297.0768 Found: 297.0672	1.43 (3H, t, J=7.3 Hz, CH_3), 2.31 (3H, s, CH_3), 3.09 (2H, t, J=7.3 Hz, C3-H), 3.89 (3H, s, CH_3), 4.03 (2H, q, J=7.3 Hz, CH_2), 4.19 (1H, t, J=7.3 Hz, C2-H), 7.79 (1H, s, C6-H)

d, J=2.0 Hz, C3-H), 7.82 (1H, d, J=8.8 Hz, C6-H). IR (KBr) cm^{-1}: 1693, 1601 (C=O). High-resolution MS m/z: Calcd for $C_{13}H_{13}NO_4$: 247.0844. Found: 247.0857.

Methyl 4-Acetylamino-2-methylbenzo[*b*]furan-7-carboxylate (16) A solution of **15a** (3.00 g, 12.1 mmol) in 1,2-dichlorobenzene (30.0 ml) was refluxed for 60 h. The reaction mixture was purified by silica gel column chromatography (MeOH : $CHCl_3$ = 1 : 50→1 : 20) to give 1.36 g (45.3%) of **16** as a powder, together with methyl 5-acetylamino-2*H*-1-benzopyran-8-carboxylate (**17**, 235 mg, 7.8%, as a powder), methyl 1-acetyl-4-hydroxy-2-methylindol-5-carboxylate (**18**, 91.0 mg, 3.0%, as a powder), methyl 1-acetyl-1,2-dihydro-5-hydroxyquinoline-6-carboxylate (**19**, 210 mg, 7.0%, as a powder), and methyl 5-hydroxyquinolin-6-carboxylate (**20**, 150 mg, 5.0%, as a powder). **16**: mp 185—186 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s, $COCH_3$), 2.53 (3H, s, CH_3), 3.98 (3H, s, CH_3), 6.41 (1H, s, CH), 7.36 (1H, br s, CONH), 7.86 (2H, br s, C5, 6-H). IR (KBr) cm^{-1}: 1726, 1661 (C=O). High-resolution MS m/z: Calcd for $C_{13}H_{13}NO_4$: 247.0844. Found: 247.0856. **17**: mp 160—163 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s, $COCH_3$), 3.87 (3H, s, CH_3), 4.82 (2H, d, J=2.1 Hz, C2-H), 5.9—6.0 (1H, m, C3-H), 6.47 (1H, d, J=9.8 Hz, C4-H), 7.22 (1H, br s, NH), 7.39 (1H, br s, C5-H), 7.66 (1H, d, J=8.8 Hz, C6-H). **18**: mp 125—128 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.62 (3H, d, J=1.5 Hz, CH_3), 2.72 (3H, s, CH_3), 3.96 (3H, s, CH_3), 6.61 (1H, J=1.5 Hz, C4-H), 7.51, 7.68 (2H, each d, J=8.8 Hz, C5, 6-H), 11.3 (1H, s, OH). **19**: mp 65—68 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s, CH_3), 3.96 (3H, s, CH_3), 4.43 (2H, dd, J=2.0, 4.4 Hz, C2-H), 6.07 (1H, dt, J=4.4, 9.3 Hz, C3-H), 6.78 (1H, d, J=8.8 Hz, C8-H), 6.94 (1H, J=9.3 Hz, C4-H), 7.70 (1H, d, J=8.8 Hz, C7-H), 11.1 (1H, s, OH). **20**: mp 114—118 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.03 (3H, s, CH_3), 7.45 (1H, dd, J=3.9, 8.3 Hz, C3-H), 7.56 (1H, d, J=9.3 Hz, C8-H), 8.02 (1H, J=9.3 Hz, C7-H), 8.73 (1H, dd, J=2.9, 8.3 Hz, C4-H), 8.98 (1H, dd, J=2.9, 3.9 Hz, C2-H).

Methyl 4-Acetylamino-3-chloro-2-methylbenzo[*b*]furan-7-carboxylate (21a) Compound **16** (300 mg, 1.21 mmol) was chlorinated with NCS in a similar procedure as employed in the synthesis of **11a**, to give 130 mg (38.0%) of **21a** as a powder.

Physicochemical data are summarized in Table 3.

Methyl 4-Acetylamino-5-chloro-2-propargyloxybenzoate (15b) Compound **15a** (10.0 mg, 40.5 mmol) was similarly converted to 11.0 g (96.5%) of **15b** as a powder. mp 135—136 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s, $COCH_3$), 2.56 (1H, t, J=2.5 Hz, CH), 3.88 (3H, s, CH_3), 4.82 (2H, d, J=2.5 Hz, CH_2), 7.77 (1H, br s, CONH), 7.90 (1H, s, C3-H), 8.46 (1H, s, C6-H). IR (KBr) cm^{-1}: 1727, 1710 (C=O). High-resolution MS m/z: Calcd for $C_{13}H_{12}ClNO_4$: 281.0455. Found: 281.0458.

Methyl 4-Acetylamino-5-chloro-2-methylbenzo[*b*]furan-7-carboxylate (21b) A solution of **15b** (3.00 g, 10.7 mmol) in *N*-methylpyrrolidone (5.0 ml) was refluxed for 5 h, then poured into ice-water, and extracted with $CHCl_3$ (30 ml × 3). The extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH : AcOEt = 1 : 9→1 : 5) to give 2.17 g (72.3%) of **21b** as needles, together with methyl 5-acetylamino-6-chloro-2*H*-1-benzopyran-8-carboxylate (**23**, 561 mg, 18.7%, as a powder). **23**: mp 173—174 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s, CH_3), 3.88 (3H, s, CH_3), 4.91 (2H, dd, J=2.0, 3.9 Hz, C2-H), 5.9—6.0 (2H, m, C3-H), 7.10 (1H, s, OH), 7.72 (1H, s, C6-H).

Physicochemical data of **21b** are summarized in Table 3.

Methyl 4-Acetylamino-3,5-dichloro-2-methylbenzo[*b*]furan-7-carboxylate (21c) A mixture of **21b** (800 mg, 2.84 mmol) and NCS (417 mg, 3.13 mmol) in DMF (8.0 ml) was stirred for 3 h at 70 °C, then cooled and poured into ice-water (150 ml). The resultant precipitate was collected by filtration and purified by silica gel column chromatography (AcOEt : hexane = 1 : 1) to give 750 mg (83.6%) of **21c** as a powder.

Physicochemical data of **21c** are summarized in Table 3.

Methyl 4-Acetylamino-2-alkenyloxybenzoate (13b—d) A solution of **10** (1.00 g, 4.78 mmol) in DMF (2.00 ml) was treated with 60% NaH (211 mg, 5.26 mmol). The mixture was stirred for 30 min at room temperature, and then alkenyl chloride (5.26 mmol) was added to it. The whole was stirred for 48 h at 70 °C, cooled, poured into ice-water (80 ml), and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 2) to give **13b—d** (79.4—95.4%) as a powder.

Methyl 4-Acetylamino-2-(2-methyl-2-propenyloxy)benzoate (13b) mp 107—110 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.82 (3H, s, CH_3), 2.19 (3H, s, CH_3), 3.87 (3H, s, CH_3), 4.47 (2H, s, CH_2), 4.99 (2H, s, CH_2), 5.20 (2H, s, CH_2), 6.83 (1H, dd, J=2.0, 8.3 Hz, C5-H), 7.62 (2H, br s, C3-H), 7.78 (1H, br s, NH), 7.80 (1H, d, J=8.3 Hz, C6-H). IR (KBr) cm^{-1}: 1722, 1670 (C=O). High-resolution MS m/z: Calcd for $C_{14}H_{17}NO_4$: 263.1157. Found: 263.1136.

Methyl 4-Acetylamino-2-(1-methyl-2-propenyloxy)benzoate (13c) mp 105—110 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, d, J=6.3 Hz, CH_3), 2.18 (3H, s, CH_3), 3.86 (3H, s, CH_3), 4.86 (1H, q, J=6.3 Hz, CH), 5.17 (1H, d, J=9.3 Hz, CH_2), 5.35 (1H, d, J=17.1 Hz, CH_2), 5.9—6.0 (1H, m, CH), 6.80 (1H, dd, J=2.0, 8.3 Hz, CH), 7.3—7.4 (1H, m, C5-H), 7.75 (1H, br s, NH), 7.80 (1H, d, J=8.3 Hz, C6-H). IR (KBr) cm^{-1}: 1795 (C=O). High-resolution MS m/z: Calcd for $C_{14}H_{17}NO_4$: 263.1157. Found: 263.1131.

Methyl 4-Acetylamino-2-(2-butenyloxy)benzoate (13d) The ^{1}H-NMR spectrum showed that **13d** was a mixture of geometrical isomers (*cis* : *trans* = 2 : 1). IR (KBr) cm^{-1}: 1722, 1676 (C=O). High-resolution MS m/z: Calcd for $C_{14}H_{17}NO_4$: 263.1157. Found: 263.1163. *cis*-Isomer: ^{1}H-NMR ($CDCl_3$) δ: 1.74 (3H, t, J=1.0 Hz, CH_3), 2.19 (6H, s, CH_3), 3.86 (6H, s, CH_3), 4.53 (2H, d, J=7.9 Hz, CH_2), 5.6—5.8 (2H, m, CH), 6.84 (1H, dd, J=2.5, 5.4 Hz, C3-H), 7.54 (1H, br s, NH), 7.62 (1H, br s, C5-H), 7.80 (1H, d, J=8.8 Hz, C6-H). *trans*-Isomer: ^{1}H-NMR ($CDCl_3$) δ: 1.72 (3H, t, J=1.0 Hz, CH_3), 2.19 (6H, s, CH_3), 3.86 (6H, s, CH_3), 4.68 (2H, d, J=4.4 Hz, CH_2), 5.6—5.8 (1H, m, CH), 5.8—6.0 (1H, m, CH), 6.81 (1H, dd, J=2.5, 5.4 Hz, C3-H), 7.54 (1H, br s, NH), 7.60 (1H, br s, C5-H), 7.78 (1H, d, J=8.8 Hz, C6-H).

Methyl 4-Acetylamino-2-hydroxy-3-alkenylbenzoate (14b—d) The Claisen rearrangement of compounds **13b—d** (5.00 g, 20.1 mmol) was conducted in a similar procedure as employed in the synthesis of **14a** to give **14b—d** (59.6—74.6%), each as a powder.

Methyl 4-Acetylamino-2-hydroxy-3-(2-methyl-2-propenyl)benzoate (14b) mp 162—163 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.74 (3H, s, CH_3), 2.14 (3H, s, CH_3), 3.93 (3H, s, CH_3), 3.50 (2H, s, CH_2), 4.83 (2H, s, CH_2), 4.94 (2H, s, CH_2), 6.83 (1H, dd, J=2.0, 8.3 Hz, C5-H), 7.6—7.8 (3H, m, CONH, C5-H, C6-H). IR (KBr) cm^{-1}: 3303 (OH), 1662 (C=O). High-resolution MS m/z: Calcd for $C_{14}H_{17}NO_4$: 263.1157. Found: 263.1173.

Methyl 4-Acetylamino-2-hydroxy-3-(2-butenyl)benzoate (14c) mp 158—160 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.7—1.8 (3H, m, CH_3), 2.16 (3H, s, CH_3), 3.4—3.5 (2H, m, CH_2), 3.93 (3H, s, CH_3), 5.5—5.6 (2H, m, CH), 7.54 (1H, br s, NH), 7.8—7.9 (2H, m, C5, 6-H), 11.2 (1H, s, OH). IR (KBr) cm^{-1}: 3356 (OH), 1698, 1658 (C=O). High-resolution MS m/z: Calcd for $C_{14}H_{17}NO_4$: 263.1157. Found: 263.1152.

Methyl 4-Acetylamino-2-hydroxy-3-(1-methyl-2-propenyl)benzoate (14d) mp 62—68 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, d, J=6.8 Hz, CH_3), 2.09 (6H, s, CH_3), 3.93 (6H, s, CH_3), 4.4—4.5 (1H, m, CH), 5.3—5.4 (1H, m, CH_2), 5.8—5.9 (1H, m, CH), 6.2—6.3 (1H, m, CH), 7.7—7.8 (2H, br m, C5, 6-H), 8.01 (1H, br s, NH), 11.4 (1H, s, OH). IR (KBr) cm^{-1}: 3205 (OH), 1674, 1648 (C=O). High-resolution MS m/z: Calcd for $C_{14}H_{17}NO_4$: 263.1157. Found: 263.1169.

Cyclization of 14a—d A solution of **14a—d** (40.1 mmol) in 97% H_2SO_4 (50.0 ml) was stirred at 20—25 °C for 30 min, poured onto ice (500 g), and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was triturated with diethyl ether. The resulting precipitate was collected by filtration to give **24a—d**.

Methyl 4-Acetylamino-2,3-dihydro-2-methylbenzo[*b*]furan-7-carboxylate (24a) Yield 86.1% as a powder. mp 138—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.52 (3H, d, J=7.4 Hz, CH_3), 2.20 (3H, s, $COCH_3$), 2.72 (1H, dd, J=7.3, 15.1 Hz, CH_2), 3.48 (1H, dd, J=6.8, 15.1 Hz, CH_2), 3.87 (3H, s, CH_3), 5.0—5.2 (1H, m, CH), 7.12 (1H, br s, CONH), 7.45 (1H, d, J=8.3 Hz, C5-H), 7.73 (1H, d, J=8.3 Hz, C6-H). IR (KBr) cm^{-1}: 3343 (NH), 1706, 1692 (C=O). High-resolution MS m/z: Calcd for $C_{13}H_{15}NO_4$: 249.1001. Found: 249.1031.

Methyl 4-Acetylamino-2,3-dihydro-2,2-dimethylbenzo[*b*]furan-7-carboxylate (24b) Yield 100% as a powder. mp 143—145 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (6H, s, CH_3), 2.19 (3H, s, CH_3), 2.91 (2H, s, CH_2), 3.86 (3H, s, CH_3), 7.30 (1H, br s, CONH), 7.46 (1H, d, J=7. 9 Hz, C5-H), 7.72 (1H, d, J=7.9 Hz, C6-H). IR (KBr) cm^{-1}: 3319 (NH), 1691 (C=O). High-resolution MS m/z: Calcd for $C_{14}H_{17}NO_4$: 263.1157. Found: 263.1129.

Methyl 4-Acetylamino-2-ethyl-2,3-dihydrobenzo[*b*]furan-7-carboxylate (24c) Yield 11.3% as a powder. **24c**: mp 85—87 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.3 Hz, CH_3), 1.7—1.8 (2H, m, CH_2), 1.9—2.0 (2H, m, CH_2), 2.21 (3H, s, CH_3), 2.76 (1H, dd, J=7.3, 15.6 Hz, CH_2), 3.19 (1H, dd, J=9.3, 15.6 Hz, CH_2), 4.9—5.0 (1H, m, CH), 3.93 (3H, s, CH_3), 6.99 (1H, br s, NH), 7.33 (1H, d, J=6.3 Hz, C5-H), 7.74

(1H, d, J=6.3 Hz, C6-H). IR (KBr) cm^{-1}: 3336 (NH), 1710, 1672 (C=O). High-resolution MS m/z: Calcd for $C_{14}H_{17}NO_4$: 263.1157. Found: 263.1177. Methyl 5-acetylamino-3,4-dihydro-2-methyl-2H-1-benzopyran-8-carboxylate (**36**) was obtained in 40.3% as a powder together with compound **24c**. **36**: mp 163—164 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, d, J=6.4 Hz, CH_3), 1.7—1.8 (2H, m, CH_2), 2.1—2.2 (2H, m, CH_2), 2.20 (3H, s, CH_3), 2.6—2.7 (2H, m, CH_2), 3.86 (3H, s, CH_3), 4.1—4.2 (1H, m, CH), 7.00 (1H, br s, NH), 7.53 (1H, d, J=6.3 Hz, C5-H), 7.70 (1H, d, J=6.3 Hz, C6-H).

Methyl 4-Acetylamino-2,3-dihydro-2,3-dimethylbenzo[*b*]furan-7-carboxylate (24d) Yield 59.8% as a powder. mp 156—160 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, J=6.8 Hz, CH_3), 1.28 (3H, d, J=6.8 Hz, CH_3), 1.44 (3H, d, J=6.8 Hz, CH_3), 1.54 (3H, d, J=6.8 Hz, CH_3), 2.21 (6H, s, CH_3), 2.22 (6H, s, CH_3), 3.1—3.2 (1H, m, CH), 3.32 (1H, m, CH), 3.88 (6H, s, CH_3), 4.6—4.7 (1H, m, CH), 4.9—5.0 (1H, m, CH), 6.99 (1H, br s, NH), 7.4—7.5 (2H, m, C5-H), 7.5—7.6 (2H, m, C5-H), 7.75 (1H, d, J=8.8Hz, C5-H), 7.76 (1H, d, J=8.8 Hz, C6-H). IR (KBr) cm^{-1}: 3343 (NH), 1697 (C=O). High-resolution MS m/z: Calcd for $C_{14}H_{17}NO_4$: 263.1157. Found: 263.1162.

Methyl 4-Acetylamino-2-hydroxy-3-(2-hydroxyethyl)benzoate (28) Osmium tetroxide (600 mg, 2.36 mmol) was added to a mixture of **14a** (15.0 g, 60.0 mmol) in diethyl ether (400 ml) and water (400 ml). The reaction mixture was stirred for 10 min at 20—25 °C, and then sodium periodate (25.0 g, 117 mmol) was added to it. The whole was stirred for 12 h at 20—25 °C. The resultant precipitate was collected by filtration to give 14.0 g (92.6%) of a mixture of methyl 4-acetylamino-3-formylmethyl-2-hydroxybenzoate (**27**) and methyl 4-acetylamino-2,3-dihydro-2-hydroxybenzo[*b*]furan-7-carboxylate (**27′**). The mixture of **27** and **27′**: mp 179—180 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.32 (3H, s, CH_3), 2.83 (1H, d, J=17.6 Hz, C3-H), 3.19 (2H, br s, CH_2), 3.26 (1H, dd, J=7.3, 17.6 Hz, C3-H), 3.88 (3H, s, CH_3), 5.92 (1H, t, J=6.8 Hz, C2-H), 6.57 (1H, t, J=6.8 Hz, C2-OH), 7.61, 7.70 (2H, each d, J=8.7 Hz, C5, 6-H), 10.6 (1H, s, CHO).

Sodium borohydride (2.11 g, 55.8 ml) was added to a slurry of the mixture of **27** and **27′** (14.0 g, 55.7 mmol) in methanol (200 ml) with ice-cooling, and the reaction mixture was stirred for 2 h at 20—25 °C.

Table 4. Physicochemical Data for Synthesized Compounds (**12a—e**, **22a—c**, **26a—e**, **31a, b**)

Compd. No.	Yeild (%)	mp (°C)	IR (KBr) (cm^{-1})	High-resolution MS (m/z)	^{1}H-NMR ($CDCl_3$) δ (ppm)
12a	86.9	165—166	3377, 1675	Calcd for $C_9H_{10}ClNO_3$: 215.0349 Found: 215.0334	1.33 (3H, t, J=7.3 Hz, CH_3), 2.15 (3H, s, CH_3), 3.99 (2H, q, J=7.3 Hz, CH_2), 5.97 (2H, br s, NH_2), 6.45 (1H, s, C3-H), 7.58 (1H, d, J=8.5 Hz, C6-H), 11.6 (1H, br s, COOH)
12b	70.3	107—110	3392, 1702	Calcd for $C_{11}H_{12}ClNO_3$: 241.0506 Found: 241.0508	3.45 (2H, d, J=5.9 Hz, CH_2), 3.87 (3H, s, CH_3), 4.68 (2H, br s, NH_2), 5.1—5.2 (1H, m, CH_2), 5.2—5.3 (1H, m, CH_2), 5.9—6.0 (1H, m, CH), 8.02 (1H, s, C6-H), 10.88 (1H, br s, COOH)
12c	98.4	71—73	3389, 1697	Calcd for $C_{12}H_{14}ClNO_3$: 255.0662 Found: 255.0648	1.40 (3H, t, J=5.9 Hz, CH_3), 3.45 (2H, d, J=5.9 Hz, CH_2), 3.94 (3H, s, CH_3), 3.99 (2H, q, J=5.9 Hz, CH_2), 4.68 (2H, br s, NH_2), 5.1—5.2 (1H, m, CH_2), 5.2—5.3 (1H, m, CH_2), 5.9—6.0 (1H, m, CH), 8.01 (1H, s, C6-H), 10.98 (1H, br s, COOH)
12d	93.8	147—148	3378, 1702	Calcd for $C_{11}H_{14}ClNO_3$: 243.0662 Found: 243.0675	1.03 (3H, t, J=7.3 Hz, CH_3), 1.5—1.7 (2H, m, CH_2), 2.5—2.6 (2H, m, CH_2), 3.86 (3H, s, CH_3), 4.62 (2H, br s, NH_2), 7.96 (1H, s, C6-H), 11.20 (1H, br s, COOH)
12e	96.1	100—101	3361, 1713	Calcd for $C_{12}H_{16}ClNO_3$: 257.0819 Found: 257.0807	1.03 (3H, t, J=7.3 Hz, CH_3), 1.35 (3H, t, J=5.9 Hz, CH_3), 1.5—1.7 (2H, m, CH_2), 2.5—2.6 (2H, m, CH_2), 3.99 (2H, q, J=5.9 Hz, CH_2), 4.62 (2H, br s, NH_2), 7.95 (1H, s, C6-H), 11.20 (1H, br s, COOH)
22a	76.9	240 (dec.)	3385, 1675	Calcd for $C_{10}H_8ClNO_3$: 225.0193 Found: 225.0201	2.39 (3H, s, CH_3), 6.17 (2H, br s, NH_2), 6.46 (1H, d, J=8.3 Hz, C5-H), 7.56 (1H, d, J=8.3 Hz, C6-H)
22b	81.8	244 (dec.)	3393, 1661	Calcd for $C_{10}H_8ClNO_3$: 225.0193 Found: 225.0217	2.43 (3H, s, CH_3), 6.51 (2H, br s, NH_2), 6.82 (1H, s, C3-H), 7.56 (1H, s, C6-H)
22c	46.2	260 (dec.)	3358, 1680	Calcd for $C_{10}H_7Cl_2NO_3$: 258.9803 Found: 258.9800	2.44 (3H, s, CH_3), 6.20 (2H, br s, NH_2), 7.63 (1H, s, C6-H)
26a	93.1	170—172	3381, 1686	Calcd for $C_{10}H_{10}ClNO_3$: 227.0349 Found: 227.0357	1.57 (3H, d, J=5.9 Hz, CH_3), 2.67 (1H, dd, J=6.9, 14.7 Hz, CH_2), 3.20 (1H, dd, J=9.3, 14.7 Hz, CH_2), 4.23 (2H, br s, NH_2), 5.2—5.3 (1H, m, CH), 7.78 (1H, s, C6-H)
26b	89.6	176—178	3359, 1686	Calcd for $C_{11}H_{12}ClNO_3$: 241.0506 Found: 241.0501	1.60 (6H, s, CH_3), 2.89 (2H, s, CH_2), 4.41 (2H, br s, NH_2), 7.80 (1H, s, C6-H)
26c	95.2	113—122	3404, 1672	Calcd for $C_{11}H_{12}ClNO_3$: 241.0506 Found: 241.0487	0.96 (3H, t, J=7.3 Hz, CH_3), 1.5—1.6 (2H, m, CH_2), 2.66 (1H, dd, J=6.9, 14.7 Hz, CH_2), 3.22 (1H, dd, J=9.3, 14.7 Hz, CH_2), 4.21 (2H, br s, NH_2), 5.2—5.3 (1H, m, CH), 7.79 (1H, s, C6-H)
26d	71.0	161—165	3362, 1679	Calcd for $C_{11}H_{12}ClNO_3$: 241.0506 Found: 241.0491	1.16, 1.34, 1.47, 1.56 (6H, each d, J=6.3 Hz, CH_3), 3.0—3.1, 3.2—3.4 (1H, each m, C3-H), 4.49 (2H, br s, NH_2), 4.7—4.8, 5.0—5.1 (1H, each m, C2-H), 7.79, 7.81 (1H, each s, C6-H), 9.66 (1H, br s, COOH)
26e	90.3	256—257	3409, 1683	Calcd for $C_9H_8ClNO_3$: 213.0193 Found: 213.0181	3.10 (2H, t, J=8.8 Hz, CH_2), 4.43 (1H, br s, NH_2), 4.86 (2H, t, J=8.8 Hz, CH_2), 7.79 (1H, s C6-H)
31a	88.1	141—143	3333, 1667	Calcd for $C_{10}H_{10}ClNO_3$: 227.0349 Found: 227.0375	3.31 (2H, t, J=8.3 Hz, C3-H), 3.81 (2H, t, J=8.3 Hz, C2-H), 4.03 (3H, s, CH_3), 4.48 (1H, br s, NH), 7.91 (1H, s, C6-H)
31b	83.1	101—103	3330, 1664	Calcd for $C_{11}H_{12}ClNO_3$: 241.0506 Found: 241.0512	3.31 (2H, t, J=8.3 Hz, C3-H), 3.81 (2H, t, J=8.3 Hz, C2-H), 4.14 (2H, q, J=8.3 Hz, CH_3), 4.48 (1H, br s, NH), 7.91 (1H, s, C6-H)

After ice-cooling, the reaction mixture was acidified with 6 N HCl and the resultant precipitate was collected by filtration to give 9.30 g (65.9%) of **28** as a powder. mp 211—212 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.17 (3H, s, $COCH_3$), 2.95 (2H, t, J=5.4 Hz, CH_2), 3.93 (3H, s, CH_3), 3.98 (2H, t, J=5.4 Hz, CH_2), 7.57 (1H, d, J=8.9 Hz, C5-H), 7.73 (1H, d, J=8.9 Hz, C6-H), 9.15 (1H, br s, CONH), 11.2 (1H, s, OH). IR (KBr) cm^{-1}: 3343 (NH), 3278 (OH), 1666 (C=O). High-resolution MS m/z: Calcd for $C_{12}H_{15}NO_5$: 253.0950. Found: 253.0933.

Methyl 4-Acetylamino-2,3-dihydrobenzo[*b*]furan-7-carboxylate (24e) Diethyl azodicarboxylate (6.30 ml, 40.0 mmol) was added to a mixture of **28** (9.20 g, 36.30 mmol) and triphenylphosphine (10.5 g, 40.0 mmol) in THF (150 ml), and the mixture was stirred for 1 h at 20—25 °C. The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 1→AcOEt) to give 7.41 g (86.7%) of **24e** as a powder. mp 138—139 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.21 (3H, s, $COCH_3$), 3.13 (2H, t, J=8.8 Hz, CH_2), 3.89 (3H, s, CH_3), 4.76 (2H, t, J=8.8 Hz, CH_2), 7.04 (1H, br s, CONH), 7.47 (1H, d, J=8.8 Hz, C5-H), 7.75 (1H, d, J=8.8 Hz, C6-H). IR (KBr) cm^{-1}: 3343 (NH), 1706, 1692 (C=O). High-resolution MS m/z: Calcd for $C_{12}H_{13}NO_4$: 235.0844. Found: 235.0833.

Chlorination of 24a—e Compounds **24a—e** were converted to **25a—e** (64.9—99.4%) as a powder in a similar chlorination procedure as employed in the synthesis of **11a**.

Physicochemical data of **25a—e** are summarized in Table 3.

Methyl 1-Acetyl-7-chloro-4-methoxy-1*H*-indole-5-carboxylate (29a) A solution of 2.5% osmium tetroxide in 1-butanol (0.20 ml, 0.0196 mmol) was added to a solution of **11b** (1.00 g, 3.36 mmol) in a mixture of dioxane (30 ml) and water (10 ml), and the solution was stirred for 1 h at 20—25 °C. Then, sodium peroxide (1.50 g, 7.00 mmol) was added to it little by little, and the mixture was stirred for 3.5 h at 20—25 °C. Cyclohexane and water were added, and the whole was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in trifluoroacetic acid (10 ml), stirred for 15 min, and diluted with dichloromethane (100 ml). The solution was washed with water, 5% $NaHCO_3$, and water successively, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 2) to give 729 mg (77.1%) of **29a** as a powder. mp 118—121 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.70 (3H, s, CH_3), 3.94 (3H, s, CH_3), 4.03 (3H, s, CH_3), 6.84 (1H, d, J=3.4 Hz, C3-H), 7.45 (1H, d, J=3.4 Hz, C2-H), 7.85 (1H, s, C6-H). IR (KBr) cm^{-1}: 1735, 1686 (C=O). High-resolution MS m/z: Calcd for $C_{13}H_{12}ClNO_4$: 281.0455. Found: 281.0433.

Table 5. Physicochemical Data for Synthesized Compounds (**6a—e**, **7a—c**, **8a—e**, **9a, b**)

Compd. No.	Yield (%)	IR (KBr) (cm^{-1})	^{1}H-NMR (DMSO-d_6) δ (ppm)
6a	88.4	3389, 1649	1.48 (3H, t, J=6.8 Hz, CH_3), 1.6—1.9 (10H, m, CH_2), 2.5—2.7 (2H, m, CH_2), 3.0—3.2 (2H, m, CH_2), 3.4—3.6 (2H, m, CH_2), 4.11 (2H, q, J=6.8 Hz, CH_2), 4.33 (2H, br s, NH_2), 6.27 (1H, s, C3-H), 8.03 (1H, br s, CONH), 8.10 (1H, s, C6-H)[b]
6b[a]	93.6	3376, 1630	1.6—2.0 (10H, m, CH_2), 2.7—2.8 (2H, m, CH_2), 3.1—3.4 (6H, m, CH_2), 3.69 (3H, s, CH_3), 4.9—5.1 (2H, m, =CH_2), 5.47 (2H, br s, NH_2), 5.8—6.0 (1H, m, CH), 6.45 (1H, s, CH, fumaric acid), 7.51 (1H, s, C6-H), 8.30 (1H, br s, CONH)
6c[a]	88.9	3384, 1621	1.1—2.0 (13H, m, CH_2, CH_3), 2.7—2.8 (2H, m, CH_2), 3.1—3.4 (6H, m, CH_2), 3.7—3.8 (2H, m, CH_2), 5.0—5.1 (2H, m, =CH_2), 5.45 (2H, br s, NH_2), 5.8—6.0 (1H, m, CH), 6.45 (1H, s, CH, fumaric acid), 7.48 (1H, s, C6-H), 8.29 (1H, br s, CONH)
6d[a]	66.7	3375, 1621	0.94 (3H, t, J=7.3 Hz, CH_3), 1.4—1.6 (2H, m, CH_2), 1.6—1.9 (10H, m, CH_2), 2.5—2.6 (2H, m, CH_2), 2.7—2.8 (2H, m, CH_2), 3.2—3.5 (4H, m, CH_2), 3.63 (3H, s, CH_3), 5.49 (2H, br s, NH_2), 6.45 (1H, s, CH, fumaric acid), 7.43 (1H, s, C6-H), 8.30 (1H, br s, CONH)
6e[a]	63.4	3371, 1645	0.95 (3H, t, J=7.3 Hz, CH_3), 1.34 (3H, t, J=7.3 Hz, CH_3), 1.3—1.9 (10H, m, CH_2), 2.4—2.6 (2H, m, CH_2), 2.6—3.8 (2H, m, CH_2), 3.0—3.6 (4H, m, CH_2), 3.76 (2H, q, J=7.3 Hz, CH_2), 5.47 (2H, br s, NH_2), 6.44 (1H, s, CH, fumaric acid), 7.39 (1H, s, C6-H), 8.18 (1H, m, CONH)
7a[a]	100	3439, 1638	1.6—1.9 (10H, m, CH_2), 2.42 (3H, s, CH_3), 2.7—2.9 (2H, m, CH_2), 3.1—3.5 (4H, m, CH_2), 5.88 (2H, br s, NH_2), 6.46 (1H, d, J=8.8 Hz, C5-H), 6.46 (1H, s, CH, fumaric acid), 7.52 (1H, d, J=8.8 Hz, C6-H), 8.15 (1H, br s, CONH)
7b[a]	91.3	3443, 1657	1.6—1.9 (10H, m, CH_2), 2.46 (3H, s, CH_3), 2.6—2.8 (2H, m, CH_2), 3.1—3.2 (2H, m, CH_2), 3.4—3.5 (2H, m, CH_2), 6.19 (1H, br s, NH_2), 6.46 (1H, s, C3-H), 6.85 (1H, s, CH, fumaric acid), 7.55 (1H, s, C6-H), 8.26 (1H, br s, CONH)
7c[a]	64.0	3397, 1644	1.6—1.9 (10H, m, CH_2), 2.45 (3H, s, CH_3), 2.6—2.8 (2H, m, CH_2), 3.1—3.2 (2H, m, CH_2), 3.4—3.5 (2H, m, CH_2), 5.88 (1H, br s, NH_2), 6.47 (1H, s, CH, fumaric acid), 7.62 (1H, s, C6-H), 8.35 (1H, br s, CONH)
8a[a]	83.6	3397, 1648	1.44 (3H, d, J=6.4 Hz, CH_3), 1.6—1.9 (10H, m, CH_2), 2.62 (1H, dd, J=7.3, 15.6 Hz, C3-H), 2.7—2.8 (2H, m, CH_2), 3.1—3.2 (3H, m, CH_2), 3.3—3.4 (2H, m, CH_2), 5.10 (1H, m, C2-H), 5.75 (2H, br s, NH_2), 6.44 (1H, s, CH, fumaric acid), 7.48 (1H, s, C6-H), 7.89 (1H, s, CONH)
8b	90.1	3323, 1622	1.54 (6H, s, CH_3), 1.5—1.9 (10H, m, CH_2), 2.5—2.7 (2H, m, CH_2), 2.84 (2H, s, C3-H), 2.9—3.1 (2H, m, CH_2), 3.4—3.6 (2H, m, CH_2), 4.15 (2H, br s, NH_2), 7.76 (1H, br s, CONH), 7.88 (1H, s, C6-H)[b]
8c[a]	53.8	3396, 1627	0.96 (3H, t, J=7.3 Hz, CH_3), 1.6—1.9 (12H, m, CH_2), 2.7—2.8 (3H, m, CH_2, CH), 3.0—3.7 (6H, m, CH_2), 4.93 (1H, m, C2-H), 5.72 (1H, br s, NH_2), 6.46 (1H, s, CH, fumaric acid), 7.47 (1H, s, C6-H), 7.82 (1H, br s, CONH)
8d[a]	85.9	3395, 1640	0.99, 1.19, 1.32, 1.45 (6H, each d, J=6.8 Hz, CH_3), 1.6—1.9 (10H, m, CH_2), 2.6—2.8 (2H, m, CH_2), 3.1—3.7 (5H, m, CH_2, C3-H), 4.5—4.6, 4.8—4.9 (1H, each m, C2-H), 5.68, 5.75 (2H, each br s, NH_2), 6.45 (1H, s, CH, fumaric acid), 7.45, 7.50 (1H, each s, C6-H), 7.89, 7.98 (1H, each br s, CONH)
8e	80.0	3395, 1625	1.5—1.9 (10H, m, CH_2), 2.5—2.7 (2H, m, CH_2), 2.9—3.1 (2H, m, CH_2), 3.05 (2H, t, J=8.8 Hz, C3-H), 3.4—3.6 (2H, m, CH_2), 4.21 (2H, br s, NH_2), 4.74 (2H, t, J=8.8 Hz, C2-H), 7.87 (1H, s, C6-H), 8.28 (1H, br s, CONH)[b]
9a[a]	43.1	3406, 1602	1.6—1.9 (10H, m, CH_2), 2.7—2.8 (2H, m, CH_2), 3.1—3.9 (8H, m, CH_2), 3.82 (3H, s, CH_3), 6.14 (2H, br s, NH_2), 6.45 (1H, s, CH, fumaric acid), 7.48 (1H, s, C6-H), 8.26 (1H, m, CONH)
9b[a]	91.7	3379, 1645	1.29 (3H, t, J=6.8 Hz, CH_3), 1.6—1.9 (10H, m, CH_2), 2.7—2.8 (2H, m, CH_2), 3.0—3.6 (8H, m, CH_2), 4.03 (2H, q, J=6.8 Hz, CH_2), 6.13 (2H, br s, NH_2), 6.45 (1H, s, CH, fumaric acid), 7.45 (1H, s, C6-H), 8.12 (1H, br s, CONH)

a) Hemifumarate. *b*) $CDCl_3$.

Methyl 1-Acetyl-7-chloro-4-ethoxy-1*H*-indole-5-carboxylate (29b) Compound **11c** (1.66 g, 5.33 mmol) was converted to 1.16 g (73.9%) of **29b** in a similar procedure as employed in the synthesis of **29a** as a powder. mp 98—101 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7.3 Hz, CH_3), 2.71 (3H, s, CH_3), 3.91 (3H, s, CH_3), 4.01 (2H, q, J=7.3 Hz, CH_2), 6.85 (1H, d, J=3.4 Hz, C3-H), 7.45 (1H, d, J=3.4 Hz, C2-H), 7.83 (1H, s, C6-H). IR (KBr) cm^{-1}: 1734, 1684 (C=O). High-resolution MS m/z: Calcd for $C_{14}H_{14}ClNO_5$: 295.0611. Found: 295.0633.

Methyl 1-Acetyl-7-chloro-2,3-dihydro-4-methoxy-1*H*-indole-5-carboxylate (30a) A mixture of **29a** (729 mg, 2.59 mmol), 5% Pd–C, methanol (100 ml), and acetic acid (2.0 ml) was stirred at room temperature under H_2 gas for 48 h and then filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (AcOEt : hexane = 3 : 2) to give 566 mg (77.1%) of **30a** as a powder.

Compound **29b** (760 mg, 2.57 mmol) was similarly converted to 460 mg (60.1%) of **30b** as a powder.

Physicochemical data of **30a** and **30b** are summarized in Table 3.

General Procedure of Alkaline Hydrolysis A mixture of a methyl benzoate (**11a—e**), a methyl benzo[*b*]furan-7-carboxylate (**21a—c**), a methyl 2,3-dihydrobenzo[*b*]furan-7-carboxylate (**25a—e**), or a methyl indole-5-carboxylate derivative (**30a, b**), 4 N NaOH, and methanol was refluxed for 2 h. The cooled reaction mixture was neutralized with 4 N HCl (4.0 ml), and the resultant precipitate was collected by filtration to give the corresponding **12a—e**, **22a—c**, **26a—e**, or **31a, b**.

Physicochemical data are summarized in Table 4.

4-Amino-*N*-[2-(1-azabicyclo[3.3.0]octan-5-yl)ethyl]-5-chloro-2,3-dihydro-2-methylbenzo[*b*]furan-7-carboxamide (8a) CDI (2.43 g, 22.0 mmol) was added to a solution of **26a** (5.00 g, 22.0 mmol) in dry THF (50 ml) little by little, and the mixture was stirred for 1 h. Then, a solution of 5-(2-aminoethyl)-1-azabicyclo[3.3.0]octane (3.08 g, 22.0 mmol) in dry THF (10 ml) was added. The whole was refluxed for 1 h, cooled, and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$. This solution was washed with saturated $NaHCO_3$ and then water, and concentrated *in vacuo*. The residue was purified by alumina column chromatography ($CHCl_3$) to give 6.68 g (83.6%) of **8a** as a powder. A solution of fumaric acid (1.07 g, 9.20 mmol) in ethanol (9.0 ml) was added to a solution of **8a** (6.68 g, 18.4 mmol) in ethanol (39 ml), and the mixture was stirred for 6 h. The resultant precipitate was collected by filtration to give 7.59 g (98.0%) of **8a** hemifumarate as a powder.

Other compounds for the biological tests (**6—9**) were prepared in a similar manner to that described above. Physicochemical data are summarized in Tables 1 and 5.

Serotonin 5-HT$_4$ Receptor Agonistic Activity The 5-HT$_4$ receptor agonistic activity was tested by using the methodology of Baxter *et al.*[12] Briefly, tatunica muscularis mucosae (TMM) preparation was obtained from rat esophagus, and the responses to the cumulative addition of the compounds were expressed as percentage relaxation of the carbachol-induced tone. The potency of agonistic activity was estimated in terms of the concentration giving 50% relaxation (EC_{50}).

Radioligand Binding Assay The test compounds at the concentrations of 1, 10, and 100 μM were tested in binding assays using rat brain synaptic membranes for competition with the following ligands at their respective binding sites: 5-HT$_1$,[13] [^{3}H]5-HT in the forebrain; 5-HT$_2$,[14] [^{3}H]ketanserin in the frontal cortex; dopamine D_1,[15] [^{3}H]SCH23390 in the striatum; dopamine D_2,[14] [^{3}H] spiperon in the striatum; muscarine M^1,[16] [^{3}H]pirenzapine in the frontal cortex; muscarine M_2,[15] [^{3}H]quinuclidinyl benzilate (QNB) in the frontal cortex. Each assay was started by addition of the tissue preparation and terminated by rapid filtration through Whatman GF/B glass-fiber filters under reduced pressure. The filters were transferred to scintillation vials, and the scintillator ACS II was added, then the radioactivity in the filters was counted. The IC_{50} values of the test compounds (the concentrations causing 50% inhibition of ^{3}H-labeled ligand specific binding) were determined by probit analysis.

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References and Notes

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