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Brief Article

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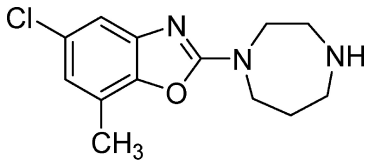


**6g**
Ki (5-$HT_3$ receptor) = 2.52 nM
anti-diarrhetic activity
$ID_{50}$ = 0.86 mg/kg, po

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# *Brief Articles*

## Orally Active Benzoxazole Derivative as 5-$HT_3$ Receptor Partial Agonist for Treatment of Diarrhea-Predominant Irritable Bowel Syndrome

Satoshi Yoshida,* Sojiro Shiokawa, Ken-ichi Kawano, Tomoko Ito, Hiroshi Murakami, Hisashi Suzuki, and Yasuo Sato

*Pharmaceutical Research Department Meiji Seika Kaisha, Ltd., 760 Morooka-Cho, Kohoku-ku, Yokohama 222-8567 Japan*

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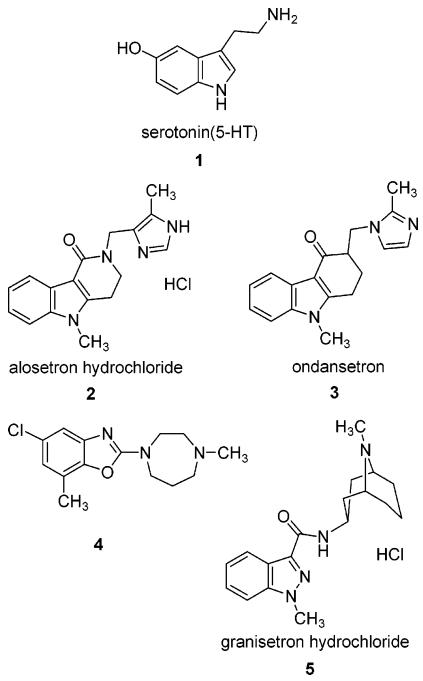
During our search for therapeutic agents to treat diarrhea-predominant IBS, we found that 2-substituted benzoxazole derivatives have a characteristic 5-$HT_3$ receptor partial agonist activity with high affinity. Some of these compounds showed high in vitro metabolical stability, and **6g** showed marked antidiarrhetic activity with little side effect of constipation in in vivo tests. Our results indicate that 5-$HT_3$ receptor partial agonists might be superior as therapeutic agents to the drugs currently used for IBS treatment.

### Introduction

5-Hydroxytryptamine (**1**, serotonin, 5-HT) is involved in various biological pathways.[1] Seven classes of 5-HT receptors are present in both the central and peripheral nervous systems.[2−5] Intensive studies have been focused on subtype-selective 5-HT receptor ligands, since they are not only attractive biological tools, but also novel candidates as therapeutic agents for a variety of diseases. Particular interest has been focused on the serotonin type 3 (5-$HT_3$) receptor,[6,7] because selective 5-$HT_3$ receptor antagonists effectively prevent the nausea and vomiting that commonly occur during cytotoxic cancer chemotherapy and/or radiation therapy. [8,9] Moreover, alosetron (**2**), a potent novel 5-$HT_3$ antagonist, was approved as the first therapeutic agent for diarrhea-predominant irritable bowel syndrome (IBS).[10] Although it possesses potent antidiarrhetic efficacy, it has several side effects, including constipation, which is seen in approximately 30% of patients treated.[11−13] Ondansetron[9] (**3**) improved stool consistency in patients with diarrhea-predominant IBS, but some of the patients reported discomfort and constipation.[14] In the treatment of diarrhea-predominant IBS, 5-$HT_3$ antagonists may potentially cause these side effects by inhibiting normal lower bowel function.[15] We proposed that 5-$HT_3$ receptor partial agonists might control gastroenteric motility without completely blocking 5-$HT_3$-sensitized nerve function.[16,17] This characteristic could make 5-$HT_3$ receptor partial agonists useful for the treatment of gastroenteric disorders, exemplified by IBS. In a previous study, our benzoxazole derivatives with a nitrogen-containing heterocyclic substituent at the 2-position were found to act as selective 5-$HT_3$ receptor partial agonists.[16,17] Among them, compound **4** showed high antidiarrhetic activity in an in vivo test ($ID_{50}$ = 0.3 mg/kg, sc) without preventing normal colonic function even at high doses of up to 30 mg/kg, sc.[16] Here, we describe our further efforts to find a drug candidate with high efficacy, particularly in in vivo tests. We found some analogues of 2-(1-piperazinyl)benzoxazole (**6b**, **6d**, **6f**) and 2-(1-homopiperazinyl)benzoxazole (**6g**) possessing similar or superior 5-$HT_3$ receptor affinity to the corresponding 2-(4-methyl-1-piperazinyl)benzoxazole derivatives (**6a**, **6c**, **6e**). Compounds which have an $NCH_3$-containing heterocyclic substituent, such as 4-methyl-1-piperazine, are known to be metabolized by P450 2D6 (CYP2D6) and other enzymes.[18] Therefore, we expected that benzoxazole derivatives with an NH-containing heterocyclic substituent would be candidate therapeutic agents with improved metabolic stability, if they retain favorable 5-$HT_3$ partial agonist characteristics.

**Chart 1**




* To whom correspondence should be addressed. Tel: +81-45-545-3133. Fax: +81-45-541-0667. E-mail: satoshi_yoshida@meiji.co.jp.

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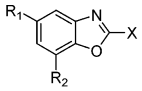
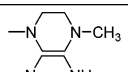
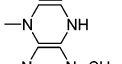
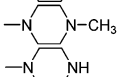
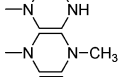
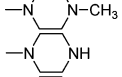
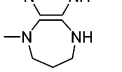
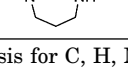
**Table 1**



| compd. | R1 | R2 | X | formula[a] | method | yield |
|---|---|---|---|---|---|---|
| **6a** | H | H |  | $C_{12}H_{15}N_3O$ | E | 85 |
| **6b** | H | H |  | $C_{11}H_{13}N_3O$ 1/3$H_2O$ | E | 72 |
| **6c** | $CH_3$ | $CH_3$ |  | $C_{14}H_{19}N_3O$ | ACD | 73 |
| **6d** | $CH_3$ | $CH_3$ |  | $C_{13}H_{17}N_3O$ | ACD | 72 |
| **6e** | Cl | $CH_3$ |  | $C_{13}H_{16}N_3OCl$ | BCD | 18 |
| **6f** | Cl | $CH_3$ |  | $C_{12}H_{14}N_3OCl$ | BCD | 56 |
| **6g** | Cl | $CH_3$ |  | $C_{13}H_{16}N_3OCl$ | BCD | 67 |

[a] Elemental analysis for C, H, N.

**Chemistry.** All synthesized compounds and the synthetic procedures are summarized in Table 1 and Scheme 1. Compounds substituted at the 5 and 7 positions of the benzoxazole ring were synthesized from commercially available or known *o*-nitrophenols. Reduction of the nitro group was performed by hydrogenation, and the obtained aminophenols were treated with carbon disulfide and potassium hydroxide in ethanol without isolation. [19] The cyclized thiol compounds were then coupled with amines by heating in toluene (compounds **6c**−**g**; procedure D). Compounds **6a** and **6b** were obtained by the coupling of 2-chlorobenzoxazole (**10**) with corresponding amines.

## Results and Discussion

To determine the characteristics of each compound, agonist activity for the 5-$HT_3$ receptor in the gut was examined in contraction tests using isolated guinea pig ileum.[20] Contraction induced by the test compounds was completely blocked by a 5-$HT_3$ receptor antagonist, granisetron (**5**).[8] The values of potency ($pD_2$) and intrinsic activity (ia; % efficacy ratio to the contraction obtained using 5-HT at 10 $\mu$M) presented are each the mean ± SEM of five independent determinations. Alosetron which did not induce a contractile response at all (no intrinsic activity) in this test could be identified as a 5-$HT_3$ receptor antagonist and is different from our compounds possessing a wide range of intrinsic activity.[21]

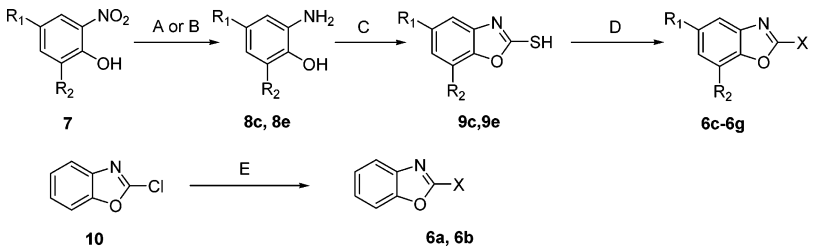
A radioligand binding assay using 5-$HT_3$ receptor[22] isolated from the rat cortex was also performed for all compounds. These results are summarized in Table 2. Comparison of $pD_2$ and $K_i$ values between the NH series (**6b**, **6d**, **6f**) and $NCH_3$ series (**6a**, **6c**, **6e**) clearly indicates that the compounds of the NH series generally show greater 5-$HT_3$ receptor partial agonist potency (higher $pD_2$ values) than those of the $NCH_3$ series. The influence of methyl substituents at the 5 and 7 positions of the benzoxazole nucleus seems to be similar in both series, i.e., this modification markedly improved the affinity for the 5-$HT_3$ receptor in both series (**6c**, **6d** vs. **6a**, **6b**). Further increase of the affinity was observed when a chlorine atom was introduced at the 5 position of the benzoxazole ring. Our previous study on the SAR of 2-(4-methylpiperazinyl)benzoxazole derivatives indicated that introduction of small lipophilic substituents such as $CH_3$ and Cl at the 5- and 7-position of the benzoxazole ring greatly increased the affinity for the 5-$HT_3$ receptor, [16] and this was also the case for the NH series. However, the influence of these substituents on the intrinsic activity was not the same in the two series. In the $NCH_3$ series, the 5,7-substituted compound **6c** (ia = 0.62) retains the intrinsic activity of the unsubstituted compound **6a** (ia = 0.62), while in the NH series, the 5,7-substituted compound **6d** (ia = 0.13) has only 25% of the intrinsic activity of the corresponding unsubstituted compound **6b** (ia = 0.59). Modification of the 5-methyl substituent to a 5-chloro substituent (compound **6e**) dramatically lowered the intrinsic activity in the $NCH_3$ series. However, in case of the NH series, the same modification led to retention of intrinsic activity (**6d**, ia = 0.13; **6f**, ia = 0.14). We consider that the intrinsic activity in both series is basically determined by the balance of electronic and steric characteristics of the substituents on the benzoxazole ring. Smaller and electron-donating substituents tend to increase the intrinsic activity, but bulkier and/or electron-withdrawing substituents lower it. Further SAR study of the substituent effect is under way to confirm this hypothesis. The distinction between the NH and $NCH_3$ series as regards their intrinsic activity appears to be

**Table 2.** In Vitro Activity and Metabolic Stability of 5-$HT_3$ Receptor Partial Agonists

| | contraction activity | | | |
|---|---|---|---|---|
| compd | $pD_2$ ± SEM | ia ± SEM | 5-$HT_3$ receptor binding ($K_i$, nM) | metabolic act.[a] (nmol/min/mg protein) |
| **6a** | 5.01 ± 0.13 | 0.62 ± 0.12 | 40 | n.t.[b] |
| **6b** | 5.74 ± 0.10 | 0.59 ± 0.08 | 20 | n.t. |
| **6c** | 6.32 ± 0.13 | 0.62 ± 0.12 | 6.0 | n.t. |
| **6d** | 7.07 ± 0.07 | 0.13 ± 0.03 | 3.4 | 0.80 ± 0.02 |
| **6e** | 6.70 ± 0.13 | 0.24 ± 0.07 | 5.5 | 1.30 ± 0.05 |
| **6f** | 7.56 ± 0.11 | 0.14 ± 0.01 | 4.7 | 0.55 ± 0.02 |
| **4** | 7.76 ± 0.14 | 0.12 ± 0.02 | 1.1 | 1.18 ± 0.05 |
| **6g** | 7.48 ± 0.11 | 0.12 ± 0.03 | 2.52 | 0.57 ± 0.03 |
| alosetron | - | -[c] | 1.13 | - |

[a] Metabolic activity was measured by using rat S9; mean ± SD, $n$ = 3. [b] n.t.; not tested. [c] Alosetron did not induce a contractile response.

**Scheme 1**[a]




[a] (A) Pd/C, EtOH; (B) Pt on sulfide carbon, EtOH; (C) $CS_2$, KOH, EtOH, reflux; (D) amine, toluene, reflux; (E) amine, chloroform

**Table 3.** Binding Affinities for **6g** to Other 5-HT Receptors

| receptor | radioligand | % inhibition ($10^{-5}$ M)[a] |
|---|---|---|
| 5-$HT_{1A}$ | [$^3$H]-8-OH-DPAT | 17.5 |
| 5-$HT_{1B}$ | [$^{125}$I]-iodocyanopindolol | 93 ($K_i$ = 786 nM) |
| 5-$HT_{2A}$ | [$^3$H]-ketanserin | 7.6 |
| 5-$HT_4$ | [$^3$H]-GR113808 | 73 ($K_i$ = 3120 nM) |
| 5-$HT_{5A}$ | [$^{125}$I]-LSD | 7.8 |
| 5-$HT_6$ | [$^{125}$I]-LSD | 8.3 |
| 5-$HT_7$ | [$^{125}$I]-LSD | 18.9 |

[a] % Inhibition are the means of two experiments.

**Table 4.** Inhibition of 5-HT-Induced Diarrhea and Effect on Colonic Propulsion

| | inhibition of 5-HT-induced diarrhea,[a] $ID_{50}$ (mg/kg po) | effects on colonic propulsion (s)[b] | | | |
|---|---|---|---|---|---|
| compd | (95% CL) | control | 10 mg/kg | 20 mg/kg | 30 mg/kg |
| **6g** | 0.86 (0.00−14.6) | 258 ± 20 | 332 ± 47 | 370 ± 38 | 394 ± 67 |
| alosetron | 1.16 (0.48−3.68) | 258 ± 20 | 424 ± 69 | 479 ± 73** | 549 ± 69 |

[a] Twelve animals were used at each dose. CL: confidence limits. **$p < 0.01$ vs vehicle control. [b] Each result represents the mean ± SE of eight animals. The test compound was treated po.

based on a fundamental difference of their natures, i.e., the intrinsic activity of the $NCH_3$ series is dominated by the electronic effect rather than the steric effect of the substituents, whereas that of the NH series is more susceptible to the steric character of the substituents. Therefore, the weakly electron-donating $CH_3$ groups in **6c** allow retention of intrinsic activity equal to that of the unsubstituted analogue **6a**, while the electron-withdrawing chlorine atom in **6e** lowers the intrinsic activity. In the cases of **6d** and **6f**, either substituent (5,7-dimethyl of **6d** and 5-chloro-7-methyl of **6f**) equally increases the steric bulk of the molecule, and consequently both lower the intrinsic activity.[23] Compound **6g**, a homopiperazine-containing NH compound derived from compound **4**, was also synthesized and evaluated. This compound showed similar or superior activity at the 5-$HT_3$ receptor to the other compounds and had the same intrinsic activity as **6f** and **4**.

The metabolic stability of **6d**−**g** in the presence of rat liver microsomes was also evaluated,[24] and the results are summarized in Table 2. Compounds possessing a NH-containing heterocycle showed superior stability to those in the $NCH_3$-containing heterocycle series. Compound **4** had the strongest affinity for the 5-$HT_3$ receptor in both the contraction test and binding assay, but its metabolic stability was inferior to that of **6g**. We chose compound **6g** for further investigation since it possessed not only a suitable profile at the 5-$HT_3$ receptor, but also had high metabolic stability. Binding study of **6g** to other 5-HT receptors revealed that this compound is selective for the 5-$HT_3$ receptor (Table 3).[25] We examined the effects of **6g** on 5-HT-induced diarrhea in mice to evaluate the in vivo antidiarrhetic efficacy, [16,26] and the effects on colonic propulsion in normal mice to estimate the propensity to cause constipation, using alosetron as a reference compound.[16,27] Compounds were administered orally (Table 4). Compound **6g** showed comparable antidiarrhetic activity to alosetron in the 5-HT-induced diarrhea model in mice. The $ID_{50}$ values were 0.86 mg/kg for **6g**, and 1.16 mg/kg for alosetron. In the normal mouse model, **6g** did not affect colonic propulsion, with no statistically significant difference from the control even at 30 mg/kg, though alosetron markedly delayed colonic propulsion at 20 mg/kg and higher ($p < 0.01$ compared to vehicle control). The results indicate that the therapeutic index (ratio of the efficacious dose to the maximum tolerable dose) of **6g** is greater than in the case of alosetron and strongly support our concept that 5-$HT_3$ partial agonists may be useful to treat diarrhea-predominant IBS without the side effect of constipation.

## Conclusion

As part of our search for novel therapeutic agents to treat IBS, we synthesized 2-(1-piperazinyl)benzoxazole and 2-(1-homopiperazinyl)benzoxazole derivatives and investigated their activities as 5-$HT_3$ receptor partial agonists. Compound **6g** exhibited favorable profiles both in vitro and in vivo. This compound possessed not only high affinity and appropriate intrinsic activity for the 5-$HT_3$ receptor, together with high metabolic stability in an in vitro study, but also exhibited antidiarrhetic activity without preventing normal bowel function in vivo. These results suggest that compounds of this type are promising candidates for the treatment of irritable bowel syndrome, having satisfactory antidiarrhetic activity without causing constipation.

## Experimental Section

**Chemistry.** All melting points are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8100 spectrometers. NMR spectra were obtained on JEOL GX-400 FT- NMR spectrometers. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, and br = broad. MS were measured with Hitachi M-80B and JEOL JMS-700 instruments. Serotonin (**1**) was a commercial product, and alosetron (**2**) was synthesized according to the procedure reported previously. The synthesis and characterization of compound **6a**, **6b**, **6c**, **6e** were represented in our previous report.[16]

**5,7-Dimethyl-2-(1-piperazinyl)benzoxazole (6d). Procedures A, C, and D.** 2,4-Dimethyl-6-nitrophenol[28] (6 g, 35.9 mmol) was dissolved in ethanol (50 mL), and 10% palladium−carbon (600 mg) was added to the solution. The reaction mixture was stirred under a hydrogen atmosphere for 24 h, and the palladium−carbon was removed by filtration. The solution was concentrated in vacuo, then the crude 2-amino-4,6-dimethylphenol was refluxed for 8 h with potassium hydroxide (4.7 g, 84 mmol) and carbon disulfide (33 mL) in ethanol (100 mL). The reaction mixture was concentrated in vacuo, and 5 N aqueous hydrochloric acid (18 mL) and ethyl acetate (100 mL) were added to the residue. The organic layer was washed with water (100 mL), dried over $MgSO_4$, and concentrated in vacuo. 2-Mercapto-5,7-dimethylbenzoxazole (**9d**) was obtained as a pale-brownish solid (6.0 g) and used in the next step without further purification. **9d** (2.43 g, 13.6 mmol) and piperazine (2.3 g, 27.1 mmol) were dissolved in dry toluene (15 mL), and the mixture was refluxed for 16 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel with dichloromethane−methanol (10:1) to give **6d** (9.66 mmol) as a yellow solid. mp. 68−70 °C (ether−hexane). NMR ($CDCl_3$) $\delta$: 1.81 (1H, brs), 2.35 (3H, s), 2.37 (3H, s), 2.99 (4H, m), 3.68 (4H, m), 6.65 (1H, s), 6.97 (1H, s). MS (TSP) *m/z* 232 (M + 1). Anal. ($C_{13}H_{17}N_3O$) C, H, N.

**5-Chloro-7-methyl-2-(1-piperazinyl)benzoxazole (6f). Procedures B, C, and D.** This procedure illustrates the general method for preparation of compound **6f**−**g**. 4-Chloro-2-methyl-6-nitrophenol[29] (2.0 g, 10.7 mmol) was dissolved in ethyl acetate (60 mL), and 5% platinum on sulfide carbon (60 mg: Aldrich Chemical Co.) was added to the solution. The reaction mixture was stirred under a hydrogen atmosphere

for 24 h, and the platinum on sulfide carbon was removed by filtration. The solution was concentrated in vacuo, then the crude 2-amino-4-chloro-6-methylphenol (**8f**, 1.68 g, 10.7 mmol) was treated as described for the preparation of **9d**. 5-Chloro-2-mercapto-7-methylbenzoxazole (**9f**) was obtained as pale-brownish needles (893 mg) and used in the next step without further purification. **9f** (200 mg, 1.00 mmol) and piperazine (172 mg, 2.00 mmol) were dissolved in dry toluene (5 mL), and the mixture was refluxed for 16 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel with dichloromethane−methanol (10:1) to give **6f** (224 mg, 0.85 mmol) as yellow plates. NMR ($CDCl_3$) $\delta$: 1.67 (1H, brs), 2.99 (4H, t, $J$ = 7 Hz), 3.67 (4H, t, $J$ = 5 Hz), 6.81 (1H, s), 7.14 (1H, s). MS (TSP) *m/z* 252 (M + 1). Anal. ($C_{12}H_{14}ClN_3O$) C, H, N.

**5-Chloro-7-methyl-2-(1-homopiperazinyl)benzoxazole (6g).** Obtained as a brownish solid, 67% yield from 4-chloro-2-methyl-6-nitrophenol. mp. 68−70 °C ($CH_3CN$). NMR ($CDCl_3$) $\delta$: 1.96 (2H, quin, $J$ = 6 Hz), 2.37 (3H, s) 2.93 (2H, t, $J$ = 6 Hz), 3.07 (2H, m), 3.07 ∼ 3.83 (4H. m), 7.02 (1H, d, $J$ = 1.7 Hz), 6.78 (1H, d, $J$ = 2 Hz), 7.13 (1H, d, $J$ = 2 Hz). MS (TSP) *m/z* 266 (M + 1). Anal. ($C_{13}H_{16}ClN_3O$) C, H, N.

**5-HT$_3$ Receptor Binding Assay.** The assay was performed according to the method of Kilpatrick et al.[22] Brain cortices were isolated from male Wistar rats (250−300 g), and a membrane fraction was prepared by standard techniques. The membrane fraction (0.04 mg) was incubated with 0.2 nM [$^3$H]-GR656630 for 60 min at 22 °C. Membranes were collected by filtration and washed three times. The radioactivity on the filters was counted to determine [$^3$H]GR656630 specifically bound. Nonspecific binding was estimated in the presence of 1 mM ICS205-930. For obtaining $K_i$ values, assays were carried out six times at each dose and displacement curves were fitted by nonlinear regression. $IC_{50}$ values were obtained directly. $K_i$ values were calculated from $IC_{50}$ values by using the equation of Cheng and Prusoff.[30]

**Contraction Test.**[20] Male Hartley guinea pigs weighing 500−600 g were killed by bleeding from the neck, and the ileum was excised. Pieces (about 20 mm) of ileal longitudinal muscles were placed in a 5 mL organ bath containing Krebs solution aerated with 95% $O_2$ and 5% $CO_2$ at 37 °C. The composition of the solution was as follows (mM): NaCl 118, KCl 4.7, $KH_2PO_4$ 1.19, $MgSO_4$ 1.2, $CaCl_2$ 2.54, $NaHCO_3$ 25, and glucose 11. The solution also contained ritanserin ($10^{-7}$ M) to inhibit the 5-HT$_2$ receptor. The preparations were allowed to equilibrate for at least 30 min under 0.5 g of tension. After equilibration, the preparations were repeatedly exposed to $3 \times 10^{-7}$ M 5-HT to desensitize the 5-HT$_4$ receptor. Compounds were added to the bath, and contractions were recorded isometrically. The potencies of agonists were expressed as $pD_2$ values, i.e., the negative logarithm of the molar concentration which produced 50% of the maximum contraction obtained from individual concentration−response curves. The ia of a partial agonist was expressed as the ratio between the maximum response to a test compound and that to 5-HT ($10^{-5}$ M).

**Rat S9 Metabolic Activity.[24] Preparation of Microsomes**. Rats were anesthetized with diethyl ether, and livers were removed, perfused with ice-cold saline, and weighed. Then a 20% (w/v) homogenate was prepared using 100 mM potassium phosphate buffer containing 1.15% potassium chloride (pH 7.4). The homogenate was centrifuged at 600*g* for 10 min. The supernatant was centrifuged at 12500*g* for 20 min, and the supernatant was recentrifuged at 105000*g* for 60 min. The microsomal pellet was suspended in the same buffer and centrifuged again at 105000*g* for 60 min. The washed pellet was resuspended in 100 mM potassium phosphate buffer (pH 7.4). Microsomal protein concentration was measured by the method of Lowry et al. (1951). The microsomes were stored at −80 °C until use.

**In Vitro Metabolism by Rat Liver Microsomes**. All incubations [rat liver microsomes, substrate, glucose-6-phosphate, $\beta$-$NADP^+$, G-6-P dehydrogenase, $MgCl_2$ $6H_2O$, phosphate buffer (pH 7.4), and EDTA $Na_2$] were performed on a gently shaking platform maintained at 37 °C. Incubations were started by the addition of substrate and were stopped after 0, 15, 30, and 60 min by addition of DMF. Precipitated proteins were removed by centrifugation and supernatants were injected into the HPLC system to determine the remaining amount of each compound. HPLC analysis was performed with an Inertsil C4 ($\phi$4.6 × 250 mm) column (GL Science Inc, Tokyo, Japan), which was attached to an Inertsil C4 ($\phi$4.0 × 10 mm) guard column cartridge. The column was developed with a linear gradient from acetonitrile/50 mM sodium acetate (pH = 6.5) 35:65 to 45:55 from 0 to 20 min, and then with a linear gradient to 80:20 from 20 to 35 min, at a flow rate of 1 mL/min. The column temperature was kept at 40 °C, and the eluate was monitored at 250 nm.

**Inhibition of 5-HT-Induced Diarrhea In Mice.**[26] Male mice were starved for 18 h before the experiment. Test compounds were orally administered 30 min before the injection of 5-HT (10 mg/kg, sc) or saline as a control. The severity of diarrhea was scored for 35-min observation period, as follows; 0: no diarrhea, 1: mild diarrhea (soft or watery feces) and 2: severe diarrhea (water-like feces). 5-HT (10 mg/kg, sc) caused diarrhea in 100% of the mice within 35min. The dose of a test compound required to reduce incidence of the diarrhea to 50% of the treated animals ($ID_{50}$) was determined by the probit analysis, and the confidence limits for $p$ = 0.95 (95% CL) were calculated.

**Measurement of Transition Time in Distal Colon in Mice.**[27] Male mice were starved for 4 h before the experiments. Thirty minutes following the po administration of test compounds, a glass bead (3 mm in diameter) was inserted into the distal colon 3 cm above the anus. The time required to evacuate the bead was measured. The group data were compared by analysis of variance followed by Steel's multiple range test.

**Supporting Information Available:** Purity data for **6a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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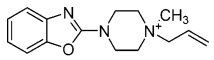

compound **I**
pD2 = 5.57± 0.19
ia = 0.74 ± 0.08

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