

# Synthesis of 2-Imidazolidinylidenepropanedinitrile Derivatives as Stimulators of Gastrointestinal Motility. 1

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Ranitidine (1), the histamine H<sub>2</sub>-receptor antagonist, has been previously reported to increase gastric emptying and gastric motility by inhibition of acetylcholinesterase (AChE) and enhancement of acetylcholine (ACh) release. In order to obtain potent gastroprokinetic agents, a new series of ranitidine derivatives (5-32) possessing a nitrogen atom instead of a sulfur atom (B) was synthesized and their AChE inhibitory activity and potentiating action on electrically evoked contractions of guinea pig ileum were evaluated. Modification of substituents R<sup>1</sup> and R<sup>2</sup> markedly influenced the activities. In particular, compound 19, {1-[2-[[[5-(piperidinomethyl)-2-furanyl]methyl]amino]ethyl]-2-imidazolidinylidene}propanedinitrile fumarate, showed 20 and 100 times more potent AChE inhibitory activity and potentiating action on the ileal contraction, respectively, than ranitidine. Furthermore, compound 19 (KW-5092) enhanced gastrointestinal motility in anesthetized rabbits along with a negligible histamine H<sub>2</sub>-receptor blocking activity.

## Introduction

Alterations in the motility of the alimentary canal are associated with many symptoms of gastrointestinal disease. Examples of the digestive diseases that are manifested by a disturbance in motor activity are dysphagia, gastric stasis, vomiting, abdominal pain, paralytic ileus, and constipation.

A number of gastrointestinal motility enhancing agents, such as metoclopramide (3), neostigmine (4), and bethanechol, have been developed to improve those symptoms of gastrointestinal disease (Chart I).<sup>1,2</sup> Metoclopramide is a compound stimulating the upper gastrointestinal motility presumably by increase in acetylcholine (ACh) release from the cholinergic nerves of the gut. The gastrointestinal motility stimulating action of neostigmine and bethanechol is ascribed to augmentation of parasympathetic activity by acetylcholinesterase (AChE) inhibition and direct muscarinic ACh receptor agonism, respectively.

Recently, it has been reported that ranitidine (1), a histamine H<sub>2</sub>-receptor antagonist, enhances gastric emptying and gastric motility in animals.<sup>3-5</sup> Its detailed mechanism of gastroprokinetic action remains unclear. However, it is suggested that AChE inhibition<sup>6-9</sup> and enhancement of ACh release from the cholinergic nerves<sup>10-12</sup> are responsible for the gastroprokinetic activity of ranitidine. Furthermore, ranitidine is also reported to show gastroprokinetic activity in man with marked gastric hypomotility, whereas neostigmine induced only a marked increase in antroduodenal motor activity both with propagated and not-propagated clustered contractions.<sup>13</sup> In addition, a histamine H<sub>2</sub>-receptor antagonist 2 has been also reported to possess a gastric emptying activity although there is no explanation concerning its mechanism of action.<sup>14</sup> These reports prompted us to synthesize ranitidine analogs in a search for potent and selective gastroprokinetic agents.

In order to potentiate histamine H<sub>2</sub>-receptor blocking activity of ranitidine, the structural modification of a 2-nitro-1,1-ethenediamine moiety (A) was made.<sup>15</sup> Also, the compounds possessing an oxygen atom or a methylene group instead of a sulfur atom (B) in ranitidine were

studied.<sup>16</sup> These analogs showed a potent inhibitory activity of gastric acid secretion.

From these results, we designed novel ranitidine derivatives with general formula (I) in Chart I where a sulfur atom (B) is replaced by a nitrogen atom.

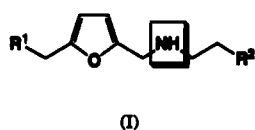
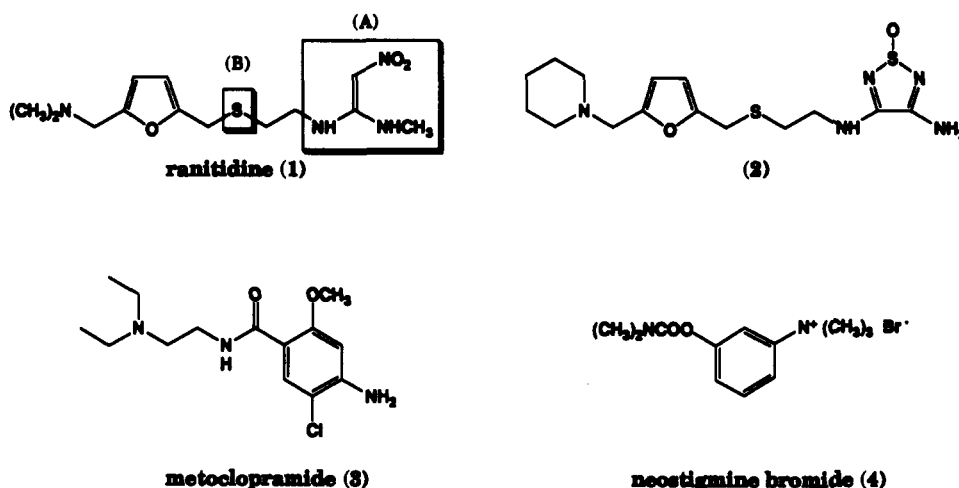
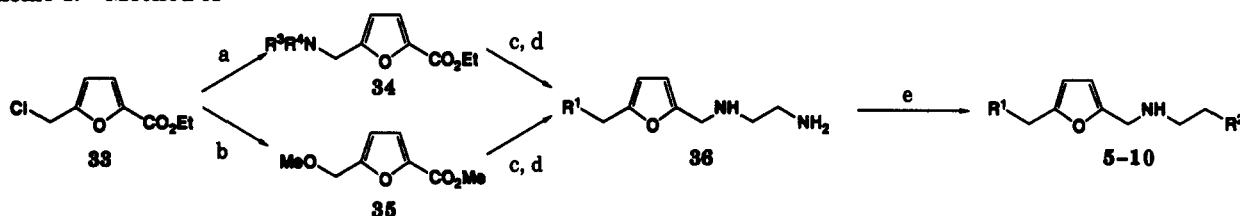
In the present paper, we describe the synthesis of ranitidine derivatives 5-32, and their enhancing activities of gastrointestinal motility. In our experiments, ranitidine (1), metoclopramide (3) and neostigmine (4) were used as reference compounds.

## Chemistry

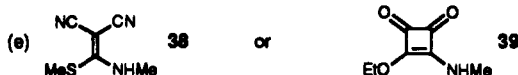
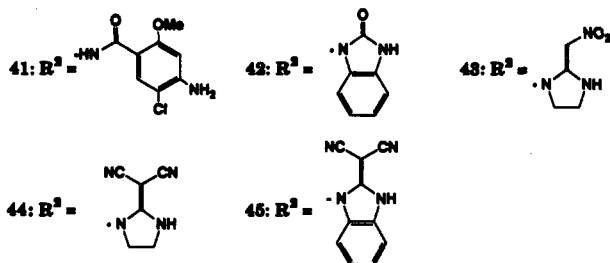
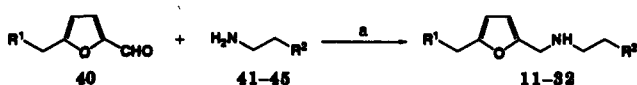
Compounds 5-10 were synthesized by the method A shown in Scheme I. Nucleophilic substitution of ethyl 5-(chloromethyl)-2-furoate (33)<sup>17</sup> with various *sec*-amines 37 or sodium methoxide gave compound 34 or 35. These esters were treated with excess ethylenediamine at 80 °C, and then reduction with LiAlH<sub>4</sub> in tetrahydrofuran (THF) at reflux temperature furnished diamine 36. The resulting amine 36 was reacted with compound 38 or 39 to afford the desired compounds 5-10.

Compounds 11-32 were obtained by the method B of Scheme II. A reductive alkylation of amino derivatives 41-45<sup>18,19</sup> which were prepared as depicted in Schemes III and IV, with various 5-substituted furfural 40 gave the target derivatives 11-32. The amines 43 and 44 were synthesized as follows. Reaction of 46 and 47 with *N*-(2-aminoethyl)ethanolamine, followed by treatment with *p*-toluenesulfonyl chloride in pyridine, yielded 48 and 49, respectively. Compounds 48 and 49 were reacted with NaN<sub>3</sub> to afford the azides, which were reduced with PPh<sub>3</sub>-H<sub>2</sub>O in ethyl acetate to the amine 43 and 44 (Scheme III). For the synthesis of benzimidazolidinylidenepropanedinitrile derivative 45, 1-bromo-2-nitrobenzene (50) was used for starting material (Scheme IV). The compound 50 was treated with ethanolamine, and the resulting alcohol was reduced by subsequent hydrogenation in the presence of palladium-charcoal catalyst to give diamine 51. Reaction of 51 with compound 47, followed by treatment with *p*-toluenesulfonyl chloride, gave tosylate 52. The desired amine 45 was obtained in the same manner as that

Chart I

Scheme I.<sup>a</sup> Method A

<sup>a</sup> Reagents and conditions: (a)  $R^3R^4NH$  **37**, toluene; (b) MeONa, MeOH; (c)  $H_2N(CH_2)_2NH_2$ , 80 °C; (d)  $LiAlH_4$ , THF, reflux;

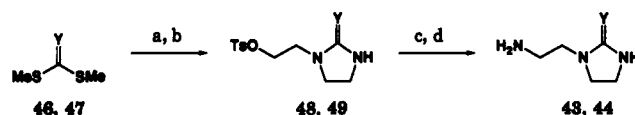
Scheme II.<sup>a</sup> Method B

<sup>a</sup> Reagents and conditions: (a)  $Et_3N$ , EtOH, and then  $NaBH_4$ .

for the compound **43** in Scheme III. The compounds synthesized are listed in Table I.

## Pharmacological Results and Discussion

The compounds synthesized were first evaluated for AChE inhibitory activity and in vitro gastrointestinal motility enhancing activity, and compounds that showed a potent activity were subjected to further evaluation.

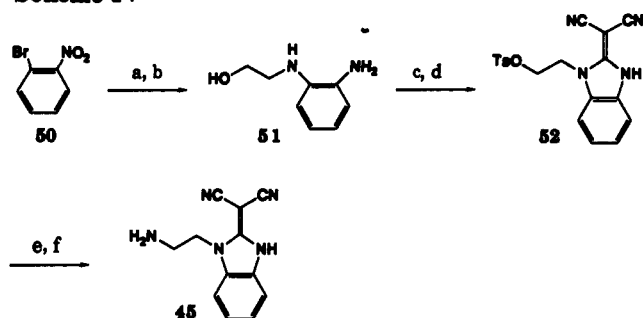
Scheme III.<sup>a</sup>

**46, 48, 43**:  $Y = CHNO_2$   
**47, 49, 44**:  $Y = C(CN)_2$

<sup>a</sup> Reagents and conditions: (a)  $HO(CH_2)_2NH(CH_2)_2NH_2$ ; (b) TsCl, pyridine; (c)  $NaN_3$ , DMF; (d)  $PPh_3$ ,  $H_2O$ , AcOEt, 70 °C.

The AChE inhibitory activity was measured by the photometric method of Ellman et al.<sup>20</sup> using acetylthiocholine as substrates. The inhibitory activity was indicated as  $IC_{50}$  value. The in vitro gastrointestinal motility enhancing activity was determined by potentiating action on electrically evoked contractions of the isolated guinea pig ileum.<sup>7,8</sup> The results were represented by  $EC_{30}$  which was the concentration of the tested compounds producing a 30% potentiation of the contractions induced by electrical stimulation. These results are summarized in Table I.

In our biological assays, ranitidine showed AChE inhibitory activity with an  $IC_{50}$  of 650 nM and potentiating activity on electrically stimulated contractions with an  $EC_{30}$  of 1.8  $\mu M$ . Metoclopramide was 4 times more potent

Scheme IV<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) HO(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub>; (b) 10% Pd/C, H<sub>2</sub>, EtOH; (c) TsCl, pyridine; (d) 47; (e) NaN<sub>3</sub>, DMF; (f) PPh<sub>3</sub>, H<sub>2</sub>O, AcOEt, 70 °C.

in potentiating activity than ranitidine. Neostigmine was the most active among tested compounds in AChE inhibition and potentiated electrically stimulated contractions at low concentrations (1–30 nM) with slowly developed elevation of base line tonus. Because the elevation of tonus obstructed the potentiation, the maximum contraction of neostigmine was not achieved to 30%.

In order to examine the effect of R<sup>2</sup> in a general formula (I), a variety of substituents were introduced in place of the 2-nitro-1,1-ethenediamine moiety (A). A 2,2-dicyano-1,1-ethenediamine moiety in compounds 5–9 and a cyclobutene-3,4-dione moiety in compound 10 are known as substituents of some histamine H<sub>2</sub>-receptor antagonists. Compound 5 was found to be almost equipotent to ranitidine both in inhibiting AChE and potentiating electrically stimulated contractions. The 2,2-dicyano-1,1-ethenediamine derivative 8 was more active than the cyclobutene-3,4-dione derivative 10 in both activities. Metoclopramide analog 11 and domperidone analog 12 showed more potent AChE inhibitory activity than compound 10. However, these analogs showed no potentiating effect on the twitch response even at 10<sup>-4</sup> M. Connection of the two nitrogen atoms in the 1,1-ethenediamine moiety by an ethylene group afforded compounds 13 and 14. Although compound 13 showed complete loss of both activities, compound 14 showed more potent activities in both assays than ranitidine and its parent compound 5 and was equipotent to metoclopramide in potentiating effect on the twitch response. Two nitrile groups of an imidazolidinylidenepropanedinitrile moiety in compound 14 may withdraw electrons more strongly than one nitro group in compound 13. An imidazolidinylidenepropanedinitrile moiety is also considered to be more rigid than the 2,2-dicyano-1,1-ethenediamine moiety in compound 5. Furthermore, imidazolidinylidenepropanedinitrile derivatives 14, 18, and 19 were more potent than the corresponding 2,2-dicyano-1,1-ethenediamine derivatives 5, 7, and 8, respectively, in both assays. However, introduction of benzimidazolidinylidenepropanedinitrile (giving compound 15), which seems to possess further rigidity in comparison with imidazolidinylidenepropanedinitrile, caused a complete loss of activity in potentiating electrically stimulated contractions, in spite of the potent AChE inhibitory activity (IC<sub>50</sub> = 73 ± 6.7 nM). From these results, not only electron-withdrawing ability and rigidity of the substituent R<sup>2</sup> but also other parameters, such as lipophilicity and bulkiness, may markedly influence both activities. Although there seemed to be no clear relationship between the AChE inhibitory activity and potentiation of electrically evoked contractions in the case of compounds 10–12 and 15, compounds 5 and 14 were

potent in both activities. Therefore, we next examined the influence of a substituent R<sup>1</sup> in compounds 5 and 14.

While replacement of the dimethylamino group of 5 by the bulky diisopropylamino group (giving 6) considerably reduced AChE inhibitory activity and potentiation of electrically stimulated contractions, compounds 7 and 8 possessing a 1-pyrrolidinyl and piperidino group, respectively, retained comparable activities to those of compound 5. However, introduction of a methoxy group as R<sup>1</sup> (giving 9) led to an almost complete loss of both activities. Furthermore, compared with the acyclic amino derivatives (compounds 14, 16, and 17), cyclic amino derivatives (compounds 18, 19, and 20) showed more potent activities. As for the size of heterocyclic ring of R<sup>1</sup>, the increasing order of both activities was the 7 (20) ≤ 5 (18) < 6 (19) membered ring. However, introduction of a methyl, hydroxyl, or methoxy group onto the piperidine ring in 19 markedly reduced both activities (21–28). Particularly, compound 24 possessing a bulky 2,6-dimethylpiperidino group showed a complete loss of potentiating effect on electrically induced contractions. Compound 29, having a 1,2,3,6-tetrahydropyridine instead of piperidine, was also less potent than 19 in both activities. Furthermore, substitution of other heterocyclic rings [morpholine (30), thiamorpholine (31), or *N*-methylpiperazine (32)] for piperidino group significantly reduced both activities. In case of modification of substituent R<sup>1</sup>, potentiating activity of electrically stimulated contractions correlated to AChE inhibitory activity.

On the whole, compound 19, {1-[2-[[[5-(piperidino-methyl)-2-furanyl]methyl]amino]ethyl]-2-imidazolidinylidene}propanedinitrile fumarate, was found to be the most active in potentiating activity of electrically elicited contractions among tested compounds. Therefore, gastrointestinal motor stimulating action of compound 19 was further evaluated in anesthetized rabbits. After anesthetization with urethane, the abdominal cavity was opened by midline incision, and two rubber balloons were inserted into the gastric antrum and descending colon to measure the gastrointestinal motility. Each balloon, filled with distilled water and coupled to a pressure transducer, detected the pressure change in the lumen of the gastrointestinal tract and this change was recorded on a ink-writing polygraph. The systemic blood pressure was also measured simultaneously through the polyethylene cannula inserted in the carotid artery. As shown in Figure 1, intravenous administration of compound 19 rapidly stimulated the motor activity of both gastric antrum and descending colon in a dose-dependent manner (1–10 mg/kg) and this excitatory response continued for 30–40 min. In addition, compound 19 did not produce any marked changes in the systemic blood pressure.

On the other hand, compound 19 was tested in a histamine H<sub>2</sub>-receptor binding assay by the method of Gajtkowski et al. using [<sup>3</sup>H]tiotidine.<sup>21</sup> Compound 19 showed lower affinity for the receptor than ranitidine (percent inhibition of [<sup>3</sup>H]tiotidine binding at 10<sup>-6</sup> and 10<sup>-4</sup> M: ranitidine, 75 and 99%; compound 19, 18 and 49%, respectively).

In conclusion, a novel ranitidine derivative compound 19 possessing a nitrogen atom and an imidazolidinylidenepropanedinitrile moiety showed potent AChE inhibitory activity and potentiating activity of electrically evoked contractions. Also, compound 19 enhanced motility of both gastric antrum and colon in anesthetized

rabbits without significant change of blood pressure. Furthermore, compound 19 showed less histamine H<sub>2</sub>-receptor blocking activity in contrast with ranitidine. Therefore, compound 19 should be a selective gastrointestinal motility enhancing agent. Further pharmacological evaluation of compound 19 (KW-5092) is now in progress.

### Experimental Section

**Chemistry.** All melting points were determined on a Yanako micromelting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IR-400 spectrometer and electron-impact mass spectra (EIMS) were recorded on a JEOL JMS D-300 or a JMS DA-500 spectrometer. <sup>1</sup>H-NMR spectra were taken at 90 MHz with a Hitachi R-90H spectrometer and at 270 MHz with a JEOL JNM GX-270 spectrometer. Chemical shifts are expressed as  $\delta$  (ppm) values with tetramethylsilane as an internal standard. Organic extracts were dried over anhydrous MgSO<sub>4</sub>. The solvent was evaporated under reduced pressure. Merck Kieselgel 60 was used for column chromatography.

**Method A-1.**  $\{[2-[[[5-[(\text{Dimethylamino})\text{methyl}]-2\text{-furyl]methyl]amino]ethyl]amino\}methylene\}$ propanedinitrile (5). **Step 1.** Dimethylamine (37; R<sup>3</sup>, R<sup>4</sup> = Me; 80 g, 1.77 mol) was passed through a stirred solution of 33<sup>17</sup> (111.46 g, 591 mmol) in toluene (1000 mL) at room temperature. The solution was stirred for 70 h. Dimethylammonium chloride was filtered off, and the filtrate was concentrated to dryness. The residue was distilled under reduced pressure to give 110.6 g (93%) of ethyl 5-[(dimethylamino)methyl]-2-furoate (34) (R<sup>3</sup>, R<sup>4</sup> = Me) as a light yellow oil: bp 98–101 °C/0.1 mmHg; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.10 (1 H, d,  $J$  = 3.3 Hz), 6.31 (1 H, d,  $J$  = 3.3 Hz), 4.33 (2 H, q), 3.53 (2 H, s), 2.29 (6 H, s), 1.36 (3 H, t).

**Step 2.** A mixture of 34 (R<sup>3</sup>, R<sup>4</sup> = Me; 49.0 g, 248 mmol) and anhydrous ethylenediamine (150 g, 2.5 mol) was heated at 80 °C for 2 h. The excess ethylenediamine was distilled off under reduced pressure to give 54.8 g (98%) of 5-[(dimethylamino)methyl]-*N*-(2-aminoethyl)-2-furancarboxamide as a light yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  6.99 (1 H, d,  $J$  = 3.3 Hz), 6.25 (1 H, d,  $J$  = 3.3 Hz), 6.90 (1 H, bs), 3.49 (2 H, s), 3.48 (2 H, t,  $J$  = 6.5 Hz), 2.86 (2 H, t,  $J$  = 6.5 Hz), 2.25 (6 H, s), 2.01 (2 H, bs). This was used for next reaction without further purification.

**Step 3.** In dry THF (250 mL) was suspended lithium aluminum hydride (1.67 g, 44 mmol) and a solution of 5-[(dimethylamino)methyl]-*N*-(2-aminoethyl)-2-furancarboxamide (5.0 g, 22 mmol) in dry THF (50 mL) was added dropwise under N<sub>2</sub> atmosphere at room temperature. After completion of addition, the mixture was heated under reflux for 12 h. The reaction mixture was cooled with ice, and then water (3.4 mL), 20% aqueous sodium hydroxide solution (1.7 mL), and water (8.5 mL) were gradually added in that order. The mixture was stirred at 5 °C for 0.5 h. The insoluble matter was filtered off and the filtrate was concentrated under reduced pressure. The residue was distilled under reduced pressure to yield 4.1 g (87%) of 5-[(dimethylamino)methyl]-*N*-(2-aminoethyl)-2-furfurylamine (36) (R<sup>1</sup> = Me<sub>2</sub>N): bp 114–116 °C/0.7 mmHg; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  6.31 (2 H, s), 3.71 (2 H, s), 3.64 (2 H, s), 2.69 (4 H, m), 2.25 (6 H, s), 1.89 (3 H, bs).

**Step 4.** A mixture of 36 (R<sup>1</sup> = Me<sub>2</sub>N; 1.29 g, 6.6 mmol) and [(methylthio)(methylamino)methylene]propanedinitrile (38; 1.0 g, 6.6 mmol) was heated at 80 °C under reduced pressure for 2 h. The mixture was chromatographed on silica gel with CHCl<sub>3</sub>-CH<sub>3</sub>OH-Et<sub>3</sub>N (100:10:1) to give 1.09 g (56%) of 5 as an oil: EIMS  $m/z$  302 (M<sup>+</sup>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.81 (1 H, bs), 6.10 (2 H, s), 5.80 (1 H, bt), 3.80 (2 H, s), 3.35 (2 H, s), 3.25 (2 H, q), 3.04 (3 H, d,  $J$  = 5.1 Hz), 2.84 (2 H, m), 2.24 (6 H, s), 1.79 (1 H, bs); IR (nujol) 2200, 2160 (both CN) cm<sup>-1</sup>.

Similarly, compounds 6–8 were obtained.

**Method A-2.**  $\{[2-[[[5-[(\text{Methoxymethyl}]-2\text{-furyl]methyl]amino]ethyl]amino\}methylene\}$ propanedinitrile (9). Compound 33 (5.0 g, 26.5 mmol) was dissolved in dry methanol (20 mL) and a 28% solution of sodium methoxide in methanol (20 mL) was added to the solution. After being stirred for 17 h, the reaction mixture was neutralized with 1 N HCl. The solvent was evaporated to dryness. The resulting residue was dissolved in CHCl<sub>3</sub> and washed with brine. The

organic layer was dried and concentrated to give 3.73 g (83%) of methyl 5-(methoxymethyl)-2-furoate (35) as a light yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.13 (1 H, d,  $J$  = 3.4 Hz), 6.45 (1 H, d,  $J$  = 3.4 Hz), 4.43 (2 H, s), 3.84 (3 H, s), 3.36 (3 H, s). Compound 9 was synthesized from compound 35 as described in step 2–4 of method A-1. This was isolated as the fumarate in the usual manner: 135–136 °C (0.5-fumarate from acetone); EIMS  $m/z$  289 (M<sup>+</sup>); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub> + CD<sub>3</sub>OD)  $\delta$  6.58 (0.5 × 2 H, s, fumarate), 6.36 (1 H, d,  $J$  = 3.1 Hz), 6.27 (1 H, d,  $J$  = 3.1 Hz), 4.31 (2 H, s), 3.79 (2 H, s), 3.29 (2 H, t,  $J$  = 5.5 Hz), 3.23 (3 H, s), 2.86 (3 H, s), 2.75 (2 H, t,  $J$  = 5.5 Hz); IR (KBr) 2200, 2160 (both CN) cm<sup>-1</sup>.

**Method A-3.** 1-(Methylamino)-2-[[2-[[[5-(piperidino)methyl]-2-furyl]methyl]amino]ethyl]amino)cyclobutene-3,4-dione (10). A mixture of 5-(piperidinomethyl)-*N*-(2-aminoethyl)-2-furfurylamine (36) (R<sup>1</sup> = piperidino; 2.8 g, 11.9 mmol) and 1-(methylamino)-2-ethoxycyclobutene-3,4-dione (39; 1.8 g, 11.9 mmol) was heated at 80 °C for 1 h. The reaction mixture was chromatographed on silica gel with CHCl<sub>3</sub>-CH<sub>3</sub>OH-Et<sub>3</sub>N (100:10:1) to give 1.23 g (30%) of 10. This crude solid was recrystallized from acetone to give pure 10: mp 145–147 °C; EIMS  $m/z$  351 (M<sup>+</sup>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.46 (2 H, bs), 6.07 (2 H, s), 3.76 (2 H, s), 3.68 (2 H, m), 3.44 (2 H, s), 3.29 (3 H, d,  $J$  = 5.3 Hz), 2.84 (2 H, m), 2.36 (4 H, m), 2.30 (1 H, bs), 1.50 (6 H, m); IR (KBr) 2900–2950 (C=O) cm<sup>-1</sup>.

**Method B-1.** *N*-2-[[[5-[(Dimethylamino)methyl]-2-furyl]methyl]amino]ethyl]-2-methoxy-4-amino-5-chlorobenzamide (11). A mixture of 5-[(dimethylamino)methyl]furfural (40; R<sup>1</sup> = Me<sub>2</sub>N; 1.0 g, 6.5 mmol), 4-amino-*N*-(2-aminoethyl)-5-chloro-2-methoxybenzamide<sup>18</sup> (41; 1.6 g, 6.6 mmol), triethylamine (2.7 mL, 19.4 mmol), and EtOH (20 mL) was stirred at room temperature for 15 h. To the reaction mixture was portionwise added sodium borohydride (250 mg, 6.6 mmol) under ice-cooling. After being stirred for 0.5 h in an ice-bath, the reaction mixture was concentrated to dryness. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed successively with water and dried. The solvent was evaporated and the residue was chromatographed on silica gel with AcOEt-CH<sub>3</sub>OH-Et<sub>3</sub>N (60:4:1) to obtain 1.2 g (48.2%) of 11 as a yellow solid: mp 91–93 °C; EIMS  $m/z$  383 (M<sup>+</sup> + 3), 381 (M<sup>+</sup> + 1); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.09 (1 H, s), 8.05 (1 H, m), 6.28 (1 H, s), 6.11 (2 H, s), 4.40 (2 H, bs), 3.87 (3 H, s), 3.80 (2 H, s), 3.52 (2 H, dd,  $J$  = 5.9, 11.5 Hz), 3.43 (2 H, s), 2.83 (2 H, t,  $J$  = 5.9 Hz), 2.25 (6 H, s), 2.19 (1 H, bs); IR (KBr) 1630 (C=O) cm<sup>-1</sup>.

Similarly, compound 12 was synthesized from 5-(piperidinomethyl)furfural (40; R<sup>1</sup> = piperidino) and 1-(2-aminoethyl)-2,3-dihydro-2-oxo-1*H*-benzimidazole (42).<sup>19</sup>

**Method B-2.** 1-[2-[[[5-[(Dimethylamino)methyl]-2-furyl]methyl]amino]ethyl]-2-imidazolidinylidene]propanedinitrile (14). **Step 1.** A mixture of 1,1-dicyano-2,2-bis(methylthio)ethylene (47; 5.1 g, 30 mmol) and *N*-(2-aminoethyl)ethanolamine (3.1 g, 30 mmol) was allowed to stand at room temperature under reduced pressure for 1 h. The resulting pale yellow solid was dissolved in anhydrous pyridine (50 mL) and *p*-toluenesulfonyl chloride (9.63 g, 50.6 mmol) was added to the solution. The mixture was stirred at room temperature for 3 h and concentrated to dryness. To the residue was added water, and the resulting precipitates were collected and washed with water and then with EtOH to give 8.76 g (94%) of 1-[2-[(*p*-tolylsulfonyl)oxy]ethyl]-2-imidazolidinylidene]propanedinitrile (49): mp 174–176 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  7.93 (1 H, bs), 7.88 (2 H, d,  $J$  = 9.2 Hz), 7.45 (2 H, d,  $J$  = 9.2 Hz), 4.23 (2 H, t,  $J$  = 6.5 Hz), 3.2–3.9 (6 H, m), 2.44 (3 H, s). Anal. (C<sub>15</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>S) C, H, N.












**Step 2.** A mixture of 49 (7.0 g, 21.1 mmol), sodium azide (6.9 g, 105.4 mmol), and DMF (100 mL) was stirred at 60 °C for 2 h. The reaction mixture was concentrated to dryness. The residue was partitioned between ethyl acetate and water, and the organic layer was dried and evaporated to give crude compound. This was recrystallized from *i*-PrOH to give 4.0 g (93.5%) of pure 1-[2-(azidoethyl)-2-imidazolidinylidene]propanedinitrile: mp 108–109 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  6.28 (1 H, bs), 3.3–4.1 (8 H, m). Anal. (C<sub>8</sub>H<sub>9</sub>N<sub>7</sub>) C, H, N.

**Step 3.** To a stirred solution of the azide derivative (10.0 g, 49.2 mmol) in ethyl acetate (250 mL) and water (9 mL) was added triphenylphosphine (21.9 g, 83.5 mmol) at room temperature.

Table I. Physiological and Pharmacological Data for Ranitidine Derivatives 5-32

no.	R <sup>1</sup>	R <sup>2</sup>	mp, °C	recryst solvent <sup>a</sup>	formula <sup>b</sup>	meth- od <sup>c</sup>	AChE IC <sub>50</sub> (nM) <sup>d</sup>	ES EC <sub>30</sub> (μM) <sup>e</sup>
5	(CH <sub>3</sub> ) <sub>2</sub> N		oil	-	C <sub>15</sub> H <sub>23</sub> N <sub>6</sub> O	A	630 ± 34	2.1
6	[(CH <sub>3</sub> ) <sub>2</sub> CH] <sub>2</sub> N		79-80	EA-PE	C <sub>19</sub> H <sub>30</sub> N <sub>6</sub> O	A	2100 ± 190	8.5
7	1-pyrrolidinyl		103-104	EA-PE	C <sub>17</sub> H <sub>24</sub> N <sub>6</sub> O	A	280 ± 24	2.0
8	piperidino		amorphous	-	C <sub>18</sub> H <sub>26</sub> N <sub>6</sub> O·2HCl·H <sub>2</sub> O	A	830 ± 35	4.1
9	CH <sub>3</sub> O		135-136	AC	C <sub>14</sub> H <sub>19</sub> N <sub>5</sub> O <sub>2</sub> ·0.5C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> <sup>f</sup>	A	>20000	NE <sup>h</sup>
10	piperidino		145-147	AC	C <sub>18</sub> H <sub>26</sub> N <sub>4</sub> O <sub>3</sub> ·0.4H <sub>2</sub> O	A	9300 ± 840	7.2
11	(CH <sub>3</sub> ) <sub>2</sub> N		91-93	EA-PE	C <sub>18</sub> H <sub>25</sub> ClN <sub>4</sub> O <sub>3</sub> ·0.5H <sub>2</sub> O	B	3100 ± 100	NE
12	piperidino		83-85	AC	C <sub>20</sub> H <sub>36</sub> N <sub>4</sub> O <sub>2</sub> ·2C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> ·0.4H <sub>2</sub> O	B	1200 ± 30	NE
13	(CH <sub>3</sub> ) <sub>2</sub> N		150-151	AC	C <sub>14</sub> H <sub>23</sub> N <sub>5</sub> O <sub>3</sub> ·2C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> ·0.2H <sub>2</sub> O	B	>2000	NE
14	(CH <sub>3</sub> ) <sub>2</sub> N		159-160	ET	C <sub>16</sub> H <sub>22</sub> N <sub>6</sub> O·C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	B	390 ± 23	0.37
15	piperidino		oil	-	C <sub>23</sub> H <sub>26</sub> N <sub>6</sub> O	B	73 ± 6.7	NE
16	CH <sub>3</sub> (C <sub>2</sub> H <sub>5</sub> )N		107-111	IP	C <sub>17</sub> H <sub>24</sub> N <sub>6</sub> O·C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> ·0.4H <sub>2</sub> O	B	430 ± 17	0.54
17	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N		115-118	IP	C <sub>18</sub> H <sub>26</sub> N <sub>6</sub> O·2HCl·H <sub>2</sub> O	B	600 ± 32	1.0
18	1-pyrrolidinyl		122-126	ET	C <sub>18</sub> H <sub>24</sub> N <sub>6</sub> O·C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> ·H <sub>2</sub> O	B	80 ± 3.2	0.31
19	piperidino		149-151	ET	C <sub>19</sub> H <sub>26</sub> N <sub>6</sub> O·C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	B	30 ± 0.33	0.016
20	1-perhydroazepinyl		amorphous	-	C <sub>20</sub> H <sub>26</sub> N <sub>6</sub> O·2HCl·C <sub>2</sub> H <sub>6</sub> O <sup>g</sup>	B	120 ± 6.7	0.32
21	4-CH <sub>3</sub> -piperidino		145-147	IP	C <sub>20</sub> H <sub>26</sub> N <sub>6</sub> O·C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	B	290 ± 15	0.26

Table I. (Continued)

no.	R <sup>1</sup>	R <sup>2</sup>	mp, °C	recryst solvent <sup>a</sup>	formula <sup>b</sup>	meth- od <sup>c</sup>	AChE IC <sub>50</sub> (nM) <sup>d</sup>	ES EC <sub>30</sub> (μM) <sup>e</sup>
22	3-CH <sub>3</sub> -piperidino		126–129	IP	C <sub>20</sub> H <sub>28</sub> N <sub>6</sub> O·1.5C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> · 0.4H <sub>2</sub> O	B	370 ± 21	0.41
23	2-CH <sub>3</sub> -piperidino		132–135 dec	IP	C <sub>20</sub> H <sub>28</sub> N <sub>6</sub> O·1.5C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> · 0.5H <sub>2</sub> O	B	540 ± 69	0.91
24	2,6-(CH <sub>3</sub> ) <sub>2</sub> -piperidino		96–97	EA–PE	C <sub>21</sub> H <sub>30</sub> N <sub>6</sub> O·0.6H <sub>2</sub> O	B	4500 ± 170	NE
25	4-HO-piperidino		122.5–123.5	EA–PE	C <sub>19</sub> H <sub>26</sub> N <sub>6</sub> O <sub>2</sub>	B	390 ± 12	0.43
26	3-HO-piperidino		amorphous	–	C <sub>19</sub> H <sub>26</sub> N <sub>6</sub> O <sub>2</sub> ·C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> · 0.5H <sub>2</sub> O	B	370 ± 12	0.46
27	4-CH <sub>3</sub> O-piperidino		amorphous	–	C <sub>20</sub> H <sub>28</sub> N <sub>6</sub> O <sub>2</sub> ·2HCl·H <sub>2</sub> O	B	NT <sup>i</sup>	11.0
28	3-CH <sub>3</sub> O-piperidino		amorphous	–	C <sub>20</sub> H <sub>28</sub> N <sub>6</sub> O <sub>2</sub> ·2HCl· 0.8C <sub>2</sub> H <sub>6</sub> O <sup>e</sup>	B	3300 ± 270	1.4
29	1,2,3,6-tetrahydropyridyl		amorphous	–	C <sub>19</sub> H <sub>24</sub> N <sub>6</sub> O·2HCl·H <sub>2</sub> O	B	95 ± 19	0.081
30	1-morpholino		154.5–155.5	AC	C <sub>18</sub> H <sub>24</sub> N <sub>6</sub> O <sub>2</sub> ·0.5C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> · 0.2H <sub>2</sub> O	B	11000 ± 400	13.0
31	thiamorpholino		152–153	AC	C <sub>18</sub> H <sub>24</sub> N <sub>6</sub> OS·C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> · 0.2H <sub>2</sub> O	B	1500 ± 60	2.9
32	4-CH <sub>3</sub> -1-piperazinyI		126–128	ET	C <sub>19</sub> H <sub>27</sub> N <sub>7</sub> O·2.5C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	B	4500 ± 0	1.7
	1 (ranitidine)						650 ± 38	1.8
	3 (metoclopramide)						>20000	0.43
	4 (neostigmine)						22 ± 1.5	j

<sup>a</sup> AC = acetone, EA = AcOEt, PE = i-Pr<sub>2</sub>O, ET = EtOH, IP = i-PrOH. <sup>b</sup> All compounds were analyzed for C, H, and N; analytical results were within ±0.4% of the theoretical values. <sup>c</sup> See the Experimental Section. <sup>d</sup> The IC<sub>50</sub> values are means ± SE of three separate experiments done with four different concentrations. <sup>e</sup> Electrical stimulation: The mean concentration of three experiments producing a 30% potentiation of the electrically stimulated contractions of the isolated guinea pig ileum. <sup>f</sup> Fumaric acid. <sup>g</sup> Ethanol. <sup>h</sup> No effect; Remarkable effect was not observed at 10<sup>-4</sup>M. <sup>i</sup> Not tested. <sup>j</sup> Although neostigmine (4) potentiated the electrical stimulation at low concentration (1–30 nM), the maximum contraction was not achieved to 30% (See text).

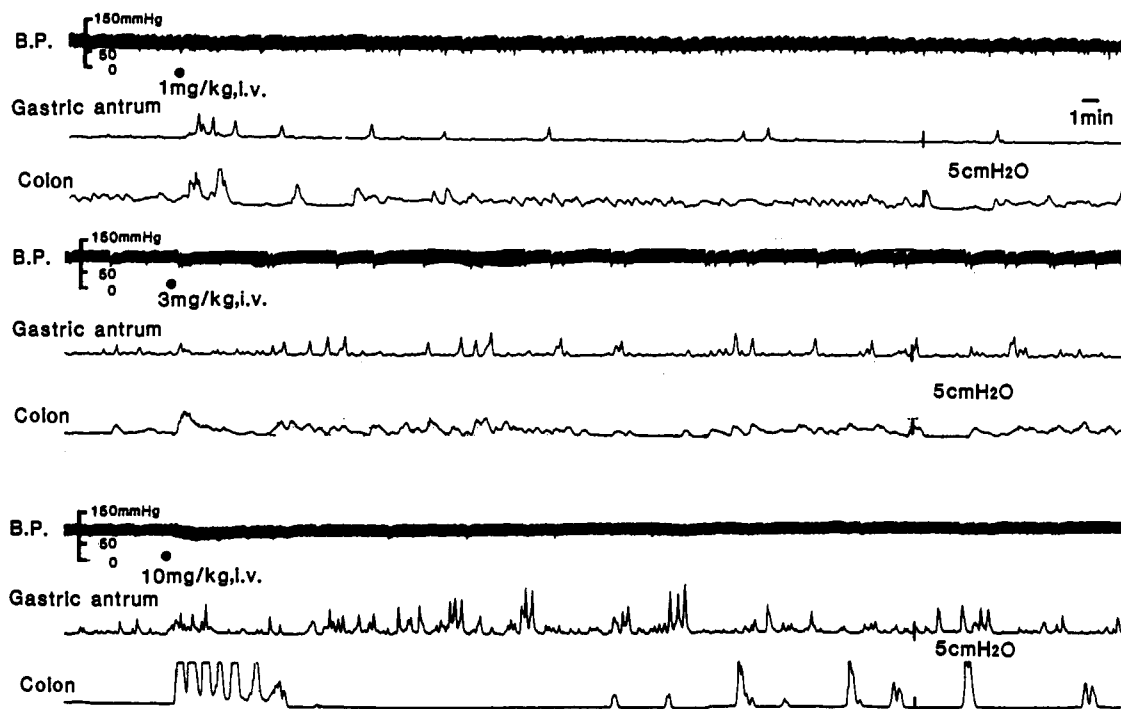
The solution was stirred at 60 °C for 3 h. The reaction mixture was concentrated and azeotroped with toluene three times. The resulting residue was dissolved in EtOH (100 mL), and fumaric acid (3.4 g, 29.3 mmol) was added to the solution. The resulting precipitates were collected by filtration, washed with EtOH to give 10.8 g (93.1%) of [1-(2-aminoethyl)-2-imidazolidinylidene]-propanedinitrile (44) as 0.5-fumarate: mp 201–203 °C; <sup>1</sup>H NMR (D<sub>2</sub>O) δ 6.40 (0.5 × 2 H, s, fumarate), 3.20–3.95 (6 H, m), 2.93 (2 H, t, J = 6.7 Hz). Anal. (C<sub>8</sub>H<sub>11</sub>N<sub>5</sub>·0.5C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N.

Compound 14 was obtained from the amine 44 and 5-[(dimethylamino)methyl]furfural (40: R<sup>1</sup> = Me<sub>2</sub>N) as described in method B-1. This was converted to the fumarate in the usual manner: mp 159–160 °C (fumarate from ethanol); EIMS *m/z* 316 (M<sup>+</sup>); <sup>1</sup>H NMR (D<sub>2</sub>O; fumarate) δ 6.77 (1 H, d, J = 2.9 Hz), 6.73 (1 H, d, J = 2.9 Hz), 6.51 (2 H, s), 4.41 (2 H, s), 4.38 (2 H, s), 3.89 (2 H, t, J = 6.9 Hz), 3.38 (2 H, t, J = 6.9 Hz), 3.82 (2 H, t, J = 9.0 Hz), 3.63 (2 H, t, J = 9.0 Hz), 2.89 (6 H, s); IR (KBr) 2200, 2160 (both CN) cm<sup>-1</sup>.

Compounds 13 and 16–32 were synthesized as described above.

**Method B-3.** {1-[2-[[[5-(Piperidinomethyl)-2-furanyl]-methyl]amino]ethyl]-2-benzimidazolidinylidene}propanedinitrile (15). **Step 1.** A mixture of 1-bromo-2-nitrobenzene (50; 10.0 g, 49.5 mmol) and ethanolamine (15 g, 245.6 mmol) was heated at 100 °C for 8 h. The excess ethanolamine was distilled off under reduced pressure. The residue was chromatographed on silica gel with AcOEt-*n*-hexane (1:2) to afford 6.11 g (68%) of 2-[*N*-(2-nitrophenyl)amino]ethanol as a red solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.18 (1 H, bs), 8.16 (1 H, m), 7.43 (1 H, m), 6.88 (1 H, d, J = 8.7 Hz), 6.45 (1 H, m), 3.93 (2 H, m), 3.53 (2 H, m), 2.08 (1 H, bs). Anal. (C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub>) C, H, N.

**Step 2.** To the stirred solution of 2-[*N*-(2-nitrophenyl)amino]-ethanol (5.8 g, 31.8 mmol) in ethanol (120 mL) was portionwise added 10% palladium on carbon (0.6 g). The resulting suspension was stirred under hydrogen atmosphere at room temperature for 0.5 h. The reaction mixture was filtered and the filtrate was concentrated to give 4.7 g (97%) of 2-[*N*-(2-aminophenyl)amino]-



**Figure 1.** Effects of compound 19 on gastrointestinal motor activity in anesthetized rabbits.

ethanol (51) as a dark brown oil. This amino alcohol was used for next reaction without further purification.

**Step 3.** A mixture of 51 (5.18 g, 34.5 mmol) and 47 (5.87 g, 34.5 mmol) was heated at 80 °C under reduced pressure for 15 min. To the reaction mixture was added  $\text{CHCl}_3$  (100 mL), and precipitates were collected by filtration and washed with  $\text{CHCl}_3$  to give 6.0 g (77%) of [1-(2-hydroxyethyl)-2-benzimidazolidinylidene]propanedinitrile as a brown solid:  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  6.8–7.8 (5 H, m), 4.53 (2 H, t,  $J = 5.7$  Hz), 3.81 (2 H, t,  $J = 5.7$  Hz). Anal. ( $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}$ ) C, H, N.

**Step 4.** The alcohol (3.0 g, 13.3 mmol) was dissolved in anhydrous pyridine (60 mL), and *p*-toluenesulfonyl chloride (3.0 g, 15.7 mmol) was added to the solution. The mixture was stirred at room temperature for 8 h and concentrated to dryness. To the residue was added water, and the resulting precipitates were collected and washed with water to give 3.86 g (76%) of {1-[2-(*p*-tolylsulfonyloxy)ethyl]-2-benzimidazolidinylidene}propanedinitrile (52):  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  7.1–7.5 (8 H, m), 4.49 (4 H, m), 2.38 (3 H, s). Anal. ( $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_3\text{S}$ ) C, H, N. The title compound 15 was obtained from compound 52 as described in steps 2 and 3 of method B-2: EIMS  $m/z$  402 ( $\text{M}^+$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.0–7.9 (5 H, m), 6.28 (2 H, s), 4.39 (2 H, t,  $J = 6.7$  Hz), 3.79 (2 H, s), 3.46 (2 H, s), 3.11 (2 H, t,  $J = 6.7$  Hz), 2.38 (4 H, m), 1.49 (6 H, m); IR (nujol) 2200, 2160 (both CN)  $\text{cm}^{-1}$ .

**Pharmacological Methods. Inhibition of Acetylcholinesterase.** AChE inhibitory activity was measured at 25 °C and pH 8.0 by the photometric method of Ellman et al.<sup>20</sup> using acetylthiocholine (ATCh) as substrates. In the standard procedure, to 50- $\mu\text{L}$  aliquots of rat brain AChE (equal to 2.5 mg wet tissue) in 0.1 M potassium phosphate buffer (pH 8.0, 2.65 mL) was added 0.1 mL of 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB) in buffer (final concentration; 0.3 mM). A volume of 0.1 mL of inhibitor in buffer or buffer alone was then added to the enzyme. The samples were preincubated at 25 °C for 5 min prior to the addition of 0.1 mL of ATCh to start the hydrolysis. The variations in optical absorbance at 412 nm were measured at 60-s intervals for 5 min by means of a Hitachi U-3210 spectrophotometer.

**Gastrointestinal Motility Enhancing Activity in Vitro: Effect on Electrically Evoked Contractions.**<sup>7,8</sup> The ileum was isolated from male Hartley guinea pigs, weighing 250–400 g. Ileal strips, 20–30 mm long, were suspended vertically in an organ bath containing warmed Tyrode's solution ( $37 \pm 1$  °C), gassed with a mixture of 95%  $\text{O}_2$  and 5%  $\text{CO}_2$ . The muscle strips were initially loaded at 1 g tension and their mechanical activities were measured by isotonic transducer (Nihon Kohden). To excite

the neuronal components in the intestinal wall, the preparations were stimulated electrically by single rectangular pulses (1-msec duration, 0.1-Hz frequency, supramaximal voltage) through a pair of platinum electrodes. The electrical stimulation caused the reproducible twitch response which was abolished by tetrodotoxin and atropine, indicating the cholinergic nature of the contraction. After a stabilization of the twitch response (30 min), the test compounds were dissolved or suspended in physiological saline and were added cumulatively in the organ bath, and effects on the electrically induced contraction were examined. The activity of the test compounds were represented as  $\text{EC}_{30}$  value that was the concentration of the compounds producing 30% potentiation of electrically induced contraction.

**Gastrointestinal Motility Enhancing Activity in Vivo: Effect of Compound 19 on Gastrointestinal Motility in Anesthetized Rabbits.** Male rabbits (Japan White strain), weighing 2.3–3.3 kg, were anesthetized with urethane (1.3 g/kg, ip). After anesthetization, the trachea was cannulated to preserve the respiration. Polyethylene cannulas were inserted into the left carotid artery for measurement of the systemic blood pressure through a pressure transducer and into the right ear vein for systemic application of drugs. The abdominal cavity was opened by midline incision, and the gastric antrum and the descending colon were exposed. To measure the gastrointestinal motility, intraluminal pressure changes were detected by rubber balloons inserted in the gastric antrum and the descending colon. Each balloon was filled with distilled water (Water pressure applied to the balloon was usually set at 10 cm  $\text{H}_2\text{O}$ ) and connected to a pressure transducer equipped with the ink-writing polygraph. After the operation procedures were completed, the animals were allowed to equilibrate for 60 min at which time steady contractile activity and blood pressure were established. And then, each dose of compound 19 (1, 3, and 10 mg/kg) was dissolved in physiological saline and administered intravenously into an ear vein at 60-min intervals and effects on the gastrointestinal motility and blood pressure were examined.

**Histamine  $\text{H}_2$ -Receptor Binding Assay.** The test compounds at the concentration of  $10^{-5}$  and  $10^{-4}$  M were tested in binding assays using guinea pig cerebral cortex for competition with 2 nM [ $^3\text{H}$ ]tiotidine.<sup>21</sup> Nonspecific binding was determined by the addition of 5 mM histamine. Samples were incubated at 25 °C for 30 min. Assay was terminated by rapid filtration through Whatman GF/C glass-filters under reduced pressure. The filters were washed three times with 5 mL of 50 mM sodium-potassium phosphate buffer (pH 7.4) and transferred to scin-

tillation vials with Scintisol EX-H. The radioactivities in the filters were counted using a Packard 2200CA scintillation counter.

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## References

- (1) Gidda, J. S.; Monkovic, I. Gastrointestinal Motility Enhancing Agents. *Annu. Rep. Med. Chem.* 1985, 20, 117-125.
- (2) King, F. D.; Sanger, G. J. Gastrointestinal Motility Enhancing Agents. *Annu. Rep. Med. Chem.* 1988, 23, 201-210.
- (3) Bertaccini, G.; Scarpignato, C. Histamine H<sub>2</sub>-Antagonists Modify Gastric Emptying in the Rat. *Br. J. Pharmacol.* 1982, 77, 443-448.
- (4) Bertaccini, G.; Poli, E.; Adami, M.; Coruzzi, G. Effect of Some New H<sub>2</sub>-Antagonists on Gastrointestinal Motility. *Agents Actions* 1983, 13, 157-162.
- (5) Fioramonti, J.; Soldani, G.; Honde, G.; Bueno, L. Effects of Ranitidine and Oxmetidine on Gastrointestinal Motility in Conscious Dog. *Agents Actions* 1984, 15, 260-263.
- (6) Hansen, W. E.; Bertl, S. Inhibition of Cholinesterases by Ranitidine. *The Lancet* 1983, 29, 235.
- (7) Galli, A.; Mantovani, P.; Pepeu, G. Effect of Ranitidine on Ileal Myenteric Plexus Preparation and on Acetyl- and Butyrylcholinesterase. *Biochem. Pharmacol.* 1984, 33, 1845-1850.
- (8) Kouzenis, G.; Koutsoviti-Paradopolou, M.; Elezoglou, V. The Inhibition of Acetylcholinesterase by Ranitidine: A Study on the Guinea Pig Ileum. *J. Pharmacobio.-Dyn.* 1986, 9, 941-945.
- (9) Mehta, S. M.; Bhalara, D. D.; Goyal, R. K. Effects of Ranitidine on the Enzyme Cholinesterase and the Rat Anococcygeus Muscle. *Agents Actions* 1987, 21, 38-40.
- (10) Bertaccini, G.; Coruzzi, G. Cholinergic-like Effects of the New Histamine H<sub>2</sub>-Antagonist Ranitidine. *Agents Actions* 1982, 12, 168-171.
- (11) Yoshida, N.; Karasawa, T.; Kadokawa, T. Effect of Metoclopramide and Ranitidine on Acetylcholine Release from Isolated Rat Stomach. *Arch. Int. Pharmacodyn.* 1988, 295, 245-256.
- (12) Poli, E.; Coruzzi, G.; Bertaccini, G. Ranitidine but not Famotidine Releases Acetylcholine from the Guinea Pig Myenteric Plexus. *Agents Actions* 1990, 30, 191-194.
- (13) Bortolotti, M.; Cucchiara, S.; Brunelli, F.; Sarti, P.; Samimi, M.; Mazza, M.; Del Campo, L.; Barbara, L. Effect of Prostigmine and Ranitidine on Interdigestive Antroduodenal (A-D) Motility in Chronic Idiopathic Gastroparesis (CIG). *Gastroenterology* 1992, 102 (Part 2), A428.
- (14) Gidda, J. S.; Monkovic, I. Thiadiazole Oxides for Treating Gastrointestinal Motility Disorders. U.S. US 4 829 073, 1988; *Chem. Abstr.* 1989, 111, 225322a, 67.
- (15) For a recent review of histamine H<sub>2</sub>-receptor antagonists, see: Bauer, R. F.; Collins, P. W.; Jones, P. H. Agents for the Treatment of Peptic Ulcer Disease. *Annu. Rep. Med. Chem.* 1987, 22, 191-200.
- (16) Price, B. J.; Clitherow, J. W.; Bradshaw, J. Pharmaceutical Alkylfuran Derivatives. Ger. Offen. 2 734 070, 1976; *Chem. Abstr.* 1978, 88, 190580b, 741.
- (17) Moldenhauer, O.; Gunter, T.; Wilhelm, I.; Richard, P.; Helene, D.; Dominik, M.; Heinrich, M.; Schulte, R. Furan Chemistry I. *Ann.* 1953, 580, 169-190.
- (18) Morimoto, A.; Takasugi, H. N-(Aminoethyl)-2-methoxybenzamides. Ger. Offen. 2 355 365, 1972; *Chem. Abstr.* 1974, 81, 63354m, 444.
- (19) Koeppel, H.; Mentrup, A.; Renth, E. O.; Schromm, K.; Hoefke, W.; Muacevic, G. Substituted Cyclic Amines. Can. CA 1 125 751, 1976; *Chem. Abstr.* 1982, 97, 182415x, 829.
- (20) Eilman, G. L.; Courtney, K. D.; Andres, V., Jr.; Featherstone, R. M. A New and Rapid Colorimetric Determination of Acetylcholinesterase Activity. *Biochem. Pharmacol.* 1961, 7, 88-95.
- (21) Gajtkowski, G. A.; Norris, D. B.; Rising, T. J.; Wood, T. P. Specific Binding of <sup>3</sup>H-Tiotidine to Histamine H<sub>2</sub> Receptors in Guinea Pig Cerebral Cortex. *Nature* 1983, 304, 65-67.