Pergamon

Bioorganic & Medicinal Chemistry, Vol. 2, No. 10, pp. 1107-1117, 1994

0968-0896/94 $7.00 + .00

0968-0896(94)00138-3

Synthesis of 2-Imidazolidinylidene Propanedinitrile Derivatives as Stimulators of Gastrointestinal Motility—II

Setsuya Sasho, Hiroyuki Obase,* Hiroyuki Harakawa, Shunji Ichikawa, Takio Kitazawa,† Nobuyuki Kishibayashi, Toshihide Yokoyama, Hiromi Nonaka, Rika Yoshizaki, Akio Ishii and Katsuichi Shuto

Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co., Ltd, 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka-ken, 411 Japan

Abstract—In a previous paper, we reported that a novel ranitidine derivative **2** (fumarate: KW-5092), which had a 2-imidazolidinylidene propanedinitrile moiety (A), showed potent gastrointestinal motility enhancing activity. In order to obtain more potent gastrointestinal motility enhancing agents than compound **2** and to examine the effects of various substituents both at a nitrogen atom (B) in the 2-imidazolidinylidene propanedinitrile moiety and a basic nitrogen atom (C), compounds **5–29** were synthesized and evaluated for acetylcholinesterase (AChE) inhibitory activity and potentiating action on electrically stimulated contractions of guinea pig ileum. Introduction of alkyl, benzyl, aryl or acyl groups to the nitrogen (B) or (C), remarkably influenced both activities. Among these, compounds **14** and **15** showed more potent AChE inhibitory activity (IC_{50} = 6.7, 6.8 nM, respectively) than compound **2** and were active in potentiating action on the ileal contraction (EC_{30} = 9.5, 11 nM, respectively) together with a negligible histamine H_2-receptor blocking property. Furthermore, these compounds were found to be more effective in the enhancement of gastrointestinal motility in anesthetized rabbits than compound **2**.

Introduction

It has become apparent that an abnormal motility pattern of the upper and lower digestive system may accompany a number of diseases characterized by alterations in the myogenic and neurogenic control of the gastrointestinal smooth muscle. Well known and frequently occurring disorders of the upper alimentary canal, such as gastritis, gastric indigestion and gastroparesis may be caused by deficiency in muscle tone or peristalsis as well as by a lack of coordinated digestive motor activity. The commonest colonic disorders are diarrhea and constipation.[1] Several gastrointestinal motility enhancing agents, such as metoclopramide [acetylcholine (ACh) release enhancer and D_2-receptor antagonist], domperidone (D_2-receptor antagonist) and neostigmine [acetylcholinesterase (AChE) inhibitor] have been developed to ameliorate these symptoms of gastrointestinal disease.[1–3]

Recently, ranitidine (**1**, Chart 1), a histamine H_2-receptor antagonist, has been reported to enhance gastric emptying and gastric motility both in animals[4–6] and in man[7] by inhibition of AChE[8–11] and enhancement of ACh release from the cholinergic nerves.[12–14] In a previous paper, we reported that novel ranitidine derivatives, possessing a 2-imidazolidinylidene propanedinitrile moiety (A), showed a potent AChE inhibitory activity and a potentiating action on electrically evoked contractions of the isolated guinea pig ileum.[15] Particularly, compound **2** (fumarate: KW-5092) increased gastrointestinal motility in anesthetized rabbits together with a negligible histamine H_2-receptor blocking property.

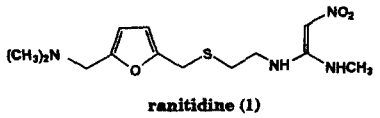
On the other hand, Sowell *et al.* reported that bis(ranitidine) analogues, in which 2-nitro-1,1-ethenediamine moieties had been exchanged for phenyl groups, exhibited remarkable increases in AChE inhibitory activity (e.g. compounds **3** and **4** in Chart 1).[16] Besides this, we have found that introduction of phenyl groups on the nitrogen at the 3-position of the 2-imidazolidinylidene propanedinitrile moiety (A) [i.e. a nitrogen (B)] enhanced both the AChE inhibitory activity and the gastrointestinal motility stimulatory activity *in vitro*.[17] Therefore, we focused on introduction of various substituents R^2 to the nitrogen (B) as illustrated in the general formula (I) in Chart 1. In addition, compounds possessing substituents R^1 on a basic nitrogen atom (C) were also prepared and evaluated.

The present paper describes the synthesis of novel nitrogen (B)- and (C)-substituted derivatives **5–29** and their gastrointestinal motility enhancing activities. In our experiments, ranitidine (**1**), compound **2**, metoclopramide and neostigmine were used as reference compounds.

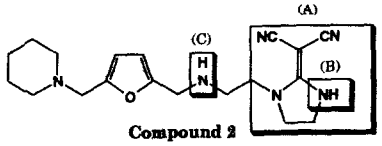
Synthesis

The general synthetic methods for the preparation of compound (**1**) follow the routes outlined in Schemes I–III.

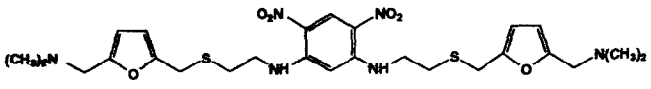
†Present address: Department of Veterinary Pharmacology, Rakuno Gakuen University, 582-1 Midori-cho, Bunkyo-dai, Ebetsu-shi, 069 Japan



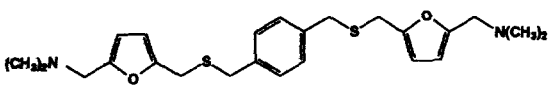
ranitidine (1)



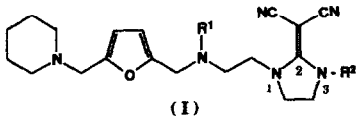
Compound 2



Compound 3

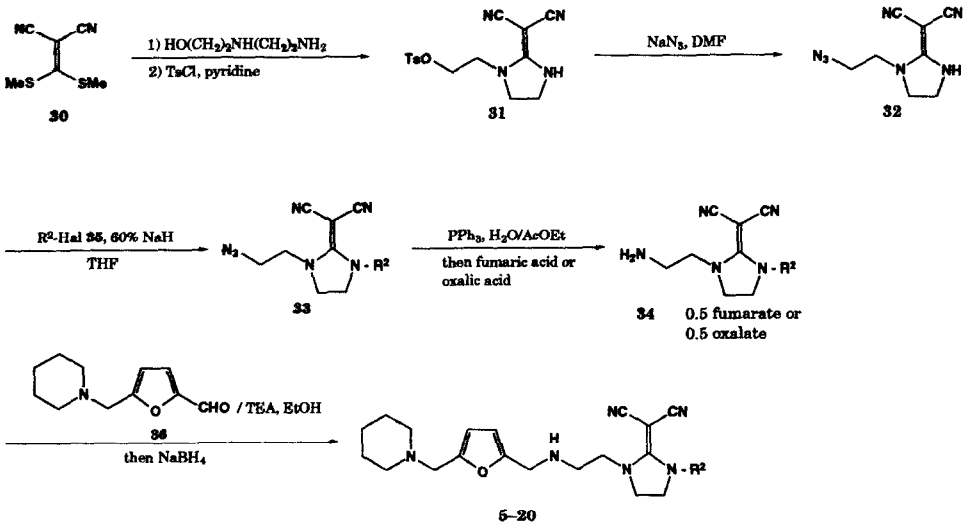


Compound 4

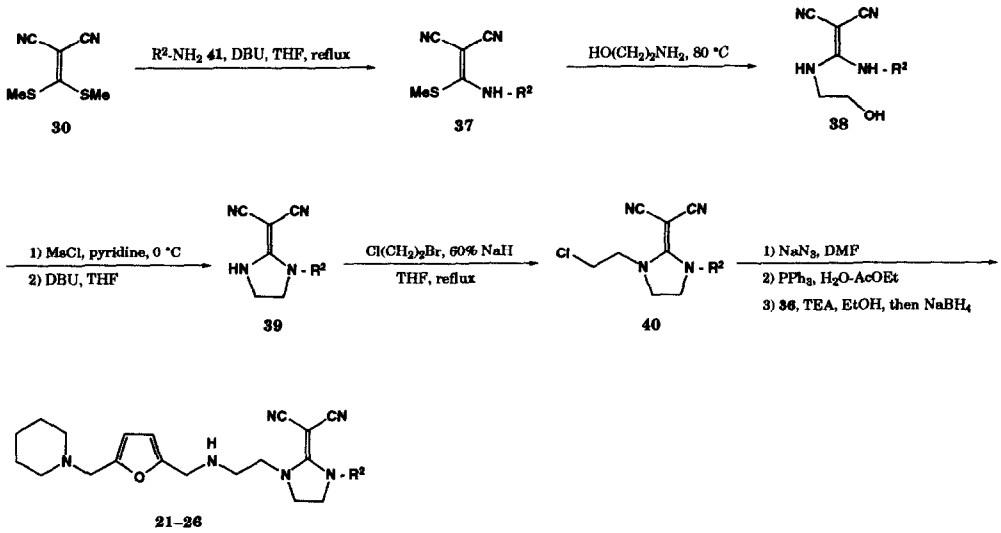


(I)

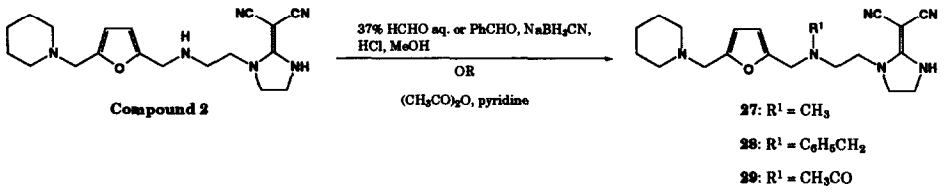
Chart 1.



Scheme I.



Scheme II.



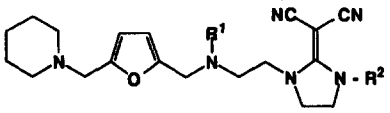
Scheme III.

Reaction of **30** with *N*-(2-aminoethyl)ethanolamine, followed by treatment with *p*-toluenesulfonyl chloride in pyridine, yielded **31**. The *p*-toluenesulfonate **31** was reacted with NaN_3 to afford the azide **32**.[15] Treatment of the azide **32** with NaH in DMF or THF under ice-cooling, followed by alkylation or benzylation with appropriate alkyl or benzyl halides **35** afforded *N*-3 substituted 2-imidazolidinylidene propanedinitrile derivatives **33** in excellent yields. Then, reduction of the azide group of **33** (a resulting amine **34** was isolated as a salt of fumaric acid or oxalic acid) and successive reductive alkylation of **34** with 5-piperidinomethylfurfural **36** afforded the desired compounds **5–20** (Scheme I, method A). Reaction of acetic anhydride or benzoyl chloride with the compound **32** under the same conditions as described above gave the azide derivative **33** (R^2 = $COCH_3$, COPh) in good yield. However, on reduction of the azides, the acyl group migrated to the primary amino group and thus compounds of general formula (**1**) with an *N*-3 acyl group could not be prepared.

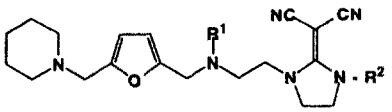
N-3 Arylated derivatives **21–26** were obtained from compound **39**, which was prepared by an intramolecular cyclization of an amino alcohol **38** in a good yield (Scheme II, method B).[17]

Introduction of methyl (**27**) and benzyl (**28**) functions as R^1 to a basic nitrogen (C) of compound **2** was achieved by use of a reductive amination method. Reaction of compound **2** with acetic anhydride in pyridine gave compound **29** as a sole product (Scheme III, method C). The compounds synthesized are listed in Table 1.

Table 1. Physiological and pharmacological data for 2-imidazolidinylidene propanedinitrile derivatives **5–29**



no.	R^1	R^2	mp, °C	recryst solvent[a]	formula[b]	method[c]	AChE IC_{50} (nM)[d]	ES. EC_{30} (nM)[e]
5	H	CH_3	amorphous	—	$C_{20}H_{28}N_6O \cdot 2HCl \cdot H_2O$	A	71 ± 3.8	420
6	H	C_2H_5	149–150	ET	$C_{21}H_{30}N_6O \cdot 2C_2H_2O_4{}^f \cdot 0.4H_2O$	A	13 ± 0.6	6.7
7	H	n-C_3H_7	88–91.5	ET	$C_{22}H_{32}N_6O \cdot 1.5C_2H_2O_4{}^f \cdot 0.5H_2O$	A	22 ± 2.8	—[h]
8	H	$(CH_3)_2CH$	129.5–131.5	ET	$C_{22}H_{32}N_6O \cdot 1.5C_2H_2O_4{}^f \cdot 0.5H_2O$	A	14 ± 0.3	11
9	H	$(CH_3)_2CHCH_2$	129–130	ET	$C_{23}H_{34}N_6O \cdot 1.5C_2H_2O_4{}^f \cdot H_2O$	A	15 ± 0.9	12
10	H	$CH{\equiv}CCH_2$	amorphous	—	$C_{22}H_{30}N_6O \cdot 1.5C_2H_2O_4{}^f \cdot H_2O$	A	80 ± 4.3	510
11	H	$CH_3CH_2O(CH_2)_2$	109–111	ET	$C_{23}H_{34}N_6O_2 \cdot 1.5C_2H_2O_4{}^f \cdot H_2O$	A	16 ± 0.6	—[h]
12	H	$(CH_3)_2C{=}CHCH_2$	159.5–161	ET	$C_{24}H_{36}N_6O \cdot 2C_2H_2O_4{}^f$	A	11 ± 0.2	10
13	H	c-$C_6H_{11}CH_2$	159–160.5	ET	$C_{26}H_{38}N_6O \cdot 1.5C_2H_2O_4{}^f$	A	11 ± 0.3	—[h]
14	H	$C_6H_5CH_2$	125–128	ET	$C_{26}H_{32}N_6O \cdot 2HCl$	A	6.7 ± 0.1	9.5
15	H	4-$FC_6H_4CH_2$	133–135	ET	$C_{26}H_{31}FN_6O \cdot 2HCl$	A	6.8 ± 1.2	11
16	H	3,4-$(CH_3O)_2$-$C_6H_3CH_2$	149–150	ET	$C_{28}H_{36}N_6O_3 \cdot 1.5C_2H_2O_4{}^f \cdot 0.5H_2O$	A	4.9 ± 0.03	5.9
17	H	3,4-$Cl_2C_6H_3CH_2$	135.5–137	ET	$C_{26}H_{30}Cl_2N_6O \cdot 1.5C_2H_2O_4{}^f \cdot 0.5H_2O$	A	55 ± 18	270



no.	R^1	R^2	mp, °C	recryst solvent[a]	formula[b]	method[c]	AChE IC_{50} (nM)[d]	ES. EC_{30} (nM)[e]
18	H	$C_6H_5CH{=}CHCH_2$	147.5–148	ET	$C_{28}H_{34}N_6O{\cdot}C_2H_2O_4{}^f{\cdot}H_2O$	A	6.7 ± 0.73	—[h]
19	H	3-$C_5H_4NCH_2$[i]	154.5–155	ET	$C_{25}H_{31}N_7O{\cdot}2C_2H_2O_4{}^f$	A	16 ± 1.7	—[h]
20	H	$(C_6H_5)_2CH$	115.5–116.5	ET	$C_{32}H_{36}N_6O{\cdot}2C_2H_2O_4{}^f{\cdot}0.5H_2O$	A	470 ± 100	N.E.[j]
21[k]	H	C_6H_5	104–106	IP	$C_{25}H_{30}N_6O{\cdot}1.5C_2H_2O_4{}^f$	B	14 ± 0.7	10
22[k]	H	4-$(CH_3)C_6H_4$	151–152.5	IP	$C_{26}H_{32}N_6O{\cdot}2C_2H_2O_4{}^f{\cdot}0.5H_2O$	B	22 ± 1.2	52
23[k]	H	3-$(CH_3)C_6H_4$	132–134	IP	$C_{26}H_{32}N_6O{\cdot}1.5C_2H_2O_4{}^f$	B	13 ± 0.7	19
24[k]	H	4-$(CH_3O)C_6H_4$	128–129	IP	$C_{26}H_{32}N_6O_2{\cdot}1.5C_2H_2O_4{}^f{\cdot}0.5H_2O$	B	19 ± 1.5	12
25[k]	H	3-$(CH_3O)C_6H_4$	127.5–129	IP	$C_{26}H_{32}N_6O_2{\cdot}1.5C_2H_2O_4{}^f$	B	14 ± 1.3	14
26[k]	H	2-$(CH_3O)C_6H_4$	132–136	IP	$C_{26}H_{32}N_6O_2{\cdot}1.5C_2H_2O_4{}^f{\cdot}H_2O$	B	66 ± 1.5	490
27	CH_3	H	144.5–147	THF	$C_{20}H_{28}N_6O{\cdot}C_4H_4O_4{}^g$	C	1900 ± 48	190
28	$C_6H_5CH_2$	H	129–132	AC	$C_{26}H_{32}N_6O{\cdot}0.5C_2H_2O_4{}^f{\cdot}0.6H_2O$	C	>10000	N.E.[j]
29	CH_3CO	H	166–167	ET	$C_{21}H_{28}N_6O_2{\cdot}C_4H_4O_4{}^g$	C	>10000	N.E.[j]
1	(ranitidine)						650 ± 38	1800
2[l]	H	H			$C_{19}H_{26}N_6O{\cdot}C_4H_4O_4{}^g$		30 ± 0.33	16
metoclopramide							> 10000	430
neostigmine							22 ± 1.5	—[h]

[a]ET = EtOH, IP = i-PrOH, THF = tetrahydrofuran, AC = acetone.
[b]All compounds were analysed for C, H and N; See the Experimental Section.
[c]See the Experimental Section
[d]The IC_{50} values are means ± S.E. of three separate experiments done with four different concentrations.
[e]Electrical stimulation: The mean concentration of three experiments producing a 30 % potentiation of the electrically stimulated contractions of the isolated guinea pig ileum.
[f]Oxalic acid.
[g]Fumaric acid.
[h]Although these compounds potentiated the electrical stimulation, the maximum contraction was not achieved to 30 % (See text).
[i]3-pyridylmethyl.
[j]No effect: Remarkable effect was not observed at 10^{-4} M.
[k]The effect of each phenyl group in compounds **21**–**26** was previously discussed in reference 17.
[l]See reference 15.

Pharmacological Results and Discussion

The compounds prepared were first evaluated for AChE inhibitory activity and *in vitro* gastrointestinal motility enhancing activity. Moreover, compounds that were shown to be significant in both activities were subjected to further evaluation, namely, histamine H_2-receptor binding assays and gastrointestinal motility enhancing activity in anesthetized rabbits.

The AChE inhibitory activity was measured by the photometric method of Ellman *et al.*[18] using acetylthiocholine as a substrate. The inhibitory activity was expressed as the IC_{50} value. The *in vitro* gastrointestinal motility enhancing activity was determined by the potentiating action on electrically induced contractions of the isolated guinea pig ileum.[9,10,15] The results were represented by the EC_{30} value, i. e. the concentration of the tested compounds producing a 30 % potentiation of the

contractions induced by electrical stimulation. These results are summarized in Table 1.

In our biological assays, ranitidine showed AChE inhibitory activity with an IC_{50} of 650 nM and potentiating activity on electrically induced contractions with an EC_{30} of 1800 nM. Metoclopramide was inactive in AChE inhibition and 4 times more potent in potentiating activity than ranitidine. Compound **2** showed more potent than ranitidine in both inhibiting AChE and potentiating electrically elicited contractions. Neostigmine was active in AChE inhibition. Although it potentiated electrically stimulated ileal contractions at low concentration (1–30 nM), the baseline tonus of the contractions was remarkably elevated. As a result, the twitch response of neostigmine outwardly decreased and the maximum contraction to 30 % was not achieved. Bortolotti *et al.* reported[7] that neostigmine induced only an uncoordinated antroduodenal hypermotility in patients with marked gastric hypomotility. From these results, tested compounds that showed such a baseline tonus elevation were not evaluated any further, despite being potent in AChE inhibition.

Firstly, we examined the influence of alkyl, benzyl or aryl functions at the nitrogen atom (B) of 2-imidazolidinylidene propanedinitrile moiety. Almost all of the derivatives prepared were more potent in both activities than ranitidine or metoclopramide. With respect to alkyl functions, introduction of ethyl (**6**), *n*-propyl (**7**), iso-propyl (**8**), iso-butyl (**9**), 2-ethoxyethyl (**11**), 2-methyl-2-butenyl (**12**) and cyclohexylmethyl (**13**) as the substituent R^2 enhanced AChE inhibitory activity over the unsubstituted compound **2**. These compounds were also slightly more potent in potentiating electrically elicited ileal contractions than compound **2** except **7**, **11** and **13**, which seemingly showed a decrease in the potentiating action on the twitch response owing to elevation of the baseline tonus similar to neostigmine. Compounds **5** (R^2 = methyl) and **10** (R^2 = propargyl) were apparently less potent than **2** in both tests. Thus, although various alkyl groups increased potency by up to 3-fold, there was no clear relationship between potency and lipophilicity or size of the groups. Therefore, we next examined the effect of benzyl groups. Compound **14** (R^2 = benzyl) showed 4 times more potent AChE inhibitory activity (IC_{50} = 6.7 nM) than compound **2** and potentiated the ileal contraction (EC_{30} = 9.5 nM). Also, compounds **15** (R^2 = 4-fluorobenzyl) and **16** (R^2 = 3,4-dimethoxybenzyl) were equipotent to **14** in both assays. In contrast with compounds **15** and **16**, compound **17** possessing a 3,4-dichlorobenzyl group showed a significant decrease especially in potentiating action on the twitch response. Compound **20** possessing a bulky benzhydryl group showed a complete loss of activity in potentiating electrically elicited contractions. Compounds **18** and **19** exhibited an ostensible decrease in potentiating action for the twitch response due to elevation of the baseline tonus, in spite of their potent AChE inhibitory activity (IC_{50} = 6.7, 16 nM, respectively). The cause of this unfavorable baseline tonus elevation to these specific compounds is unknown. The effect of aryl groups at the nitrogen atom (B) was as follows. Introduction of a phenyl ring (giving **21**) enhanced both activities. Substitution of methyl or methoxy groups at *para* or *meta* positions on the phenyl ring had no significant effect on the activities, whereas compound **26** possessing an *ortho* methoxy group showed a remarkable decrease in both assays (AChE IC_{50} = 66 nM, ES. EC_{30} = 490 nM). This result suggests that substituents at the *ortho* position of the phenyl ring are not sterically tolerated.[17]

In contrast, introduction of a substituent R^1 at a nitrogen (C) considerably reduced both activities. Compound **27** (R^1 = methyl) was 60 times and 11 times less potent in AChE inhibition (IC_{50} = 1900 nM) and electrically stimulated ileal contractions (EC_{30} = 190 nM), respectively, than compound **2**. Introduction of benzyl group (**28**) and electron withdrawing acetyl group (**29**) resulted in a complete loss of both activities. A few possible explanations exist for a decrease in these activities of compounds **27–29**. Firstly, some conformational changes in these compounds may occur by introduction of the substituents R^1. Alternatively, a proton on a nitrogen atom (C) or the basicity of it may play an important role in mechanism of AChE inhibition and enhancement of ileum contraction. In order to test this hypothesis, we are now preparing 2-imidazolidinylidene propanedinitrile derivatives having a sulfur atom instead of a nitrogen atom (C). This work will be reported elsewhere.

Because of the potent AChE inhibitory activity and electrical stimulation potentiating activity, compounds **8**, **14**, **15** and **16** were further evaluated by the histamine H_2-receptor binding assay. The histamine H_2-receptor binding assay was carried out by the method of Gajtkowski *et al.*[19] using [^{3}H]tiotidine. As shown in Table 2, all of these compounds showed lower affinity for the H_2-receptor than ranitidine.

Table 2. Histamine H_2-receptor binding of 2-imidazolidinylidene propanedinitrile derivatives

no.	H_2-receptor binding[a] 10^{-5} M	10^{-4} M
8	-11	12
14	34	62
15	18	47
16	4	50
1 (ranitidine)	75	99
2	18	49

[a]Mean percent inhibition of two experiments of [^{3}H]tiotidine binding to the histamine H_2-receptor in guinea pig cortex.

Compounds **14** and **15** were selected and evaluated for their gastrointestinal motor stimulating action 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 an ink-writing polygraph. The systemic blood pressure was also measured simultaneously through a polyethylene cannula which was inserted into the carotid artery. Figure 1 shows that intravenous

administration of compounds **14** and **15** (1 mg/kg) rapidly stimulated the motor activity of both the gastric antrum and the descending colon without any marked changes in the systemic blood pressure and this excitatory response continued for over 30 min. In addition, these effects on gastrointestinal motility were greater than those of compound **2**.

In conclusion, *N*-3-substituted-2-imidazolidinylidene propanedinitrile derivatives showed potent AChE inhibitory activity and potentiating activity of electrically stimulated contractions. Among these, compounds **8** and **14–16** demonstrated low affinity for histamine H_2-receptors in comparison with ranitidine. Furthermore, compounds **14** and **15** enhanced the motility of both the

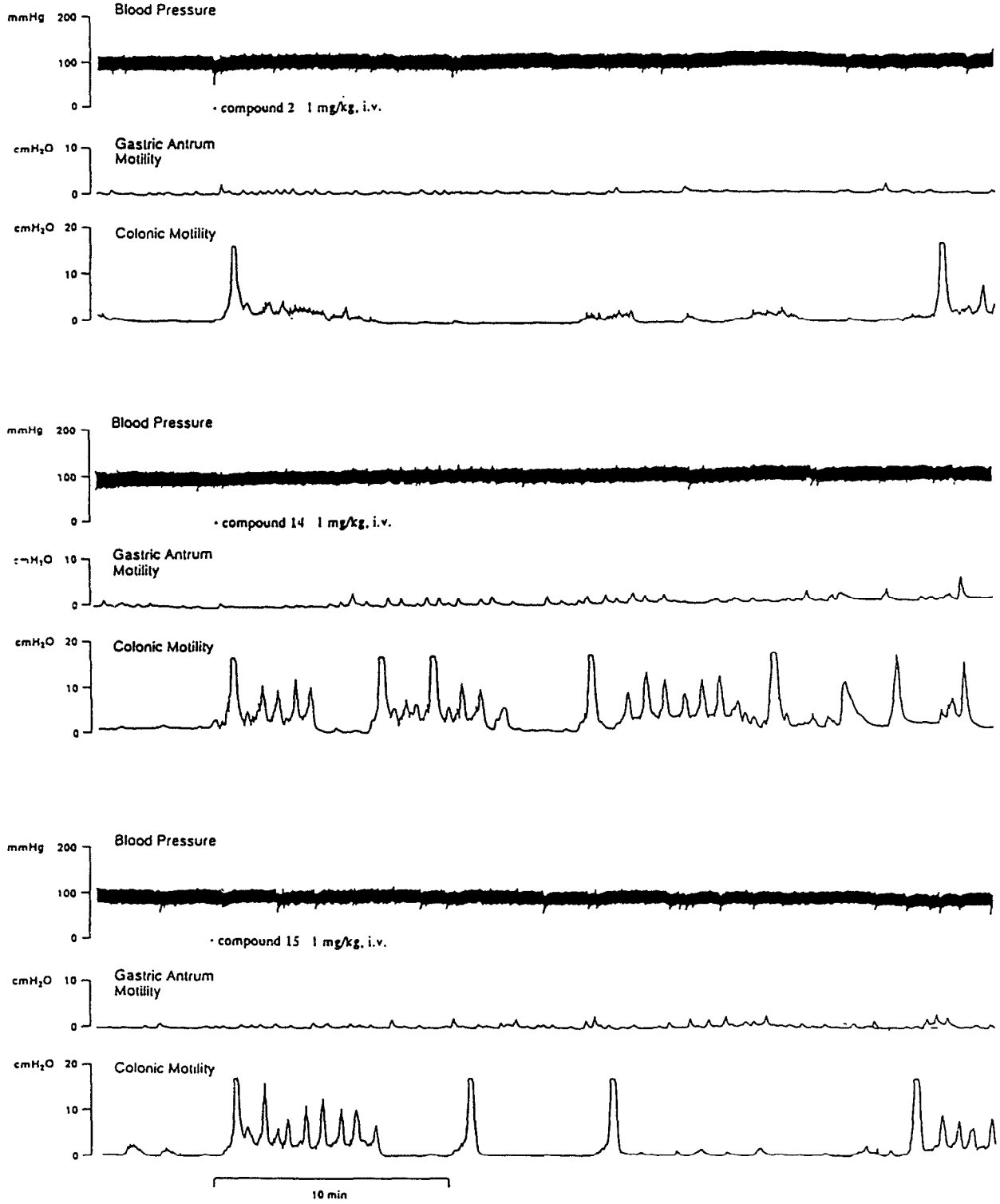


Figure 1. Effects of compounds **2**, **14**, and **15** on gastrointestinal motor activity in anesthetized rabbits.

gastric antrum and colon in anesthetized rabbits. Therefore, these compounds may be selective gastrointestinal motility enhancing agents. Further pharmacological evaluation of these analogs is now in progress.

Experimental

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. ^{1}H NMR spectra were measured 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 δ (ppm) values with tetramethylsilane as the internal standard (NMR abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). Organic extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. Merck Kieselgel 60 was used for column chromatography.

Method A. {1-[2-[[[5-(Piperidinomethyl)-2-furanyl]-methyl] amino] ethyl] -3- methyl -2- imidazolidinylidene}-propanedinitrile (5). Step 1. A mixture of 1,1-dicyano-2,2-bis(methylthio)ethylene (**30**; 5.1 g, 30 mmol) and *N*-(2-aminomethyl)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 then *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 (**31**): mp 174–176 °C; ^{1}H NMR (DMSO-d_6) δ 7.93 (1H, bs), 7.88 (2H, d, J = 9.2 Hz), 7.45 (2H, d, J = 9.2 Hz), 4.23 (2H, t, J = 6.5 Hz), 3.2–3.9 (6H, m), 2.44 (3H, s); calcd for $C_{15}H_{16}N_4O_3S$: C, 54.20 %, H, 4.85 %, N, 16.86 %; found C, 54.55 %, H, 4.69 %, N, 17.20 %.

Step 2. A mixture of **31** (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 a crude compound. This was recrystallized from *i*-PrOH to give 4.0 g (93 %) of pure [1-(2-azidoethyl)-2-imidazolidinylidene]propanedinitrile (**32**): mp 108–109 °C; ^{1}H NMR ($CDCl_3$) δ 6.28 (1H, br s), 3.3–4.1 (8H, m); calcd for $C_8H_9N_7$: C, 47.28 %, H, 4.46 %, N, 48.25 %; found C, 47.29 %, H, 4.23 %, N, 48.51 %.

Step 3. To a stirred solution of **32** (2.0 g, 9.8 mmol) in DMF (20 mL) was added portionwise 60 % NaH (0.52 g, 13.0 mmol) while cooling under ice. After the resulting mixture was stirred at 4 °C for 30 min, MeI (0.9 mL, 14.5 mmol) was added. The mixture was further stirred at room temperature for 30 min. The reaction mixture was concentrated to dryness, and the resulting residue was partitioned between ethyl acetate and brine. The organic layer was concentrated to yield a crude oil of [1-(2-azidoethyl) -3- methyl -2- imidazolidinylidene] propanedinitrile (**33**; R^2 = methyl), which was chromatographed on silica gel with $CHCl_3$:MeOH (100:1) to give 1.99 g (93 %) of pure **33** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.69 (8H, m), 3.20 (3H, s).

Step 4. Compound **33** (R^2 = Me; 1.7 g, 7.8 mmol) was dissolved in ethyl acetate (50 mL), then water (1.4 mL) and triphenylphosphine (2.46 g, 9.4 mmol) were added to the solution. The resulting mixture was stirred at 50 °C for 1.5 h. The solvent was evaporated and the resulting oil was azeotroped twice with toluene. The residue was dissolved in EtOH (40 mL), and fumaric acid (0.55 g, 4.7 mmol) was added to the solution. The resulting precipitates were collected by filtration, washed with EtOH to afford 1.39 g (71 %) of [1-(2-aminoethyl)-3-methyl-2-imidazolidinylidene]propanedinitrile as 0.5 fumarate (**34**; R^2 = methyl): mp 163.5–165 °C; ^{1}H NMR (D_2O) δ 6.44 (0.5 × 2H, s), 3.30–3.90 (6H, m), 3.07 (3H, s), 2.97 (2H, t, J = 6.7 Hz); calcd for $C_9H_{13}N_5 \cdot 0.5\ C_4H_4O_4$: C, 53.00 %, H, 6.07 %, N, 28.10 %; found C, 53.28 %, H, 6.38 %, N, 28.43 %.

Step 5. A mixture of 5-piperidinomethylfurfural **36** (1.0 g, 5.2 mmol), **34** (R^2 = methyl; 1.3 g, 5.2 mmol), triethylamine (1.3 g, 12.8 mmol) and EtOH (15 mL) was stirred at room temperature for 18 h. To the reaction mixture was added portionwise sodium borohydride (0.24 g, 6.3 mmol) while cooling under ice. After being stirred for 1 h in an ice-bath, the reaction mixture was concentrated to dryness. The residue was partitioned between CH_2Cl_2 and water, and the organic layer was dried. The solvent was evaporated to yield 1.33 g (70 %) of crude **5** as an oil, which was converted to the hydrochloride salt in ethanol in the usual manner: EIMS m/z 368 (M^+); ^{1}H NMR ($CDCl_3$; free base form) δ 6.06 (2H, s), 3.75 (2H, s), 3.63 (6H, m), 3.45 (2H, s), 3.16 (3H, s), 2.89 (2H, t, J = 6.2 Hz), 2.38 (4H, m), 1.81 (1H, br s), 1.50 (6H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{20}H_{28}N_6O \cdot 2HCl \cdot H_2O$: C, 52.29 %, H, 7.02 %, N, 18.29 %; found C, 52.01 %, H, 7.17 %, N, 18.61 %.

Similarly, compounds **6–20** were obtained.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]-ethyl]-3-ethyl-2-imidazolidinylidene}propanedinitrile (6). EIMS m/z 382 (M^+); ^{1}H NMR ($CDCl_3$; free base form) δ 6.11 (2H, s), 3.77 (2H, s), 3.63 (8H, m), 3.47 (2H, s), 2.91 (2H, t, J = 6.4 Hz), 2.40 (4H, m), 1.99 (1H, br s), 1.59 (4H, m), 1.42 (2H, m), 1.27 (3H, t, J = 6.9 Hz); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{21}H_{30}N_6O \cdot 2C_2H_2O_4 \cdot 0.4H_2O$: C, 52.70 %, H, 6.16 %, N, 14.75 %; found C, 52.52 %, H, 6.11 %, N, 14.99 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]-ethyl]-3-(1-propyl)-2-imidazolidinylidene}propanedinitrile (7). EIMS m/z 396 (M^+); ^{1}H NMR ($CDCl_3$; free base form) δ 6.10 (2H, s), 3.78 (2H, s), 3.63 (6H, m), 3.47 (2H,

m), 3.46 (2H, s), 2.91 (2H, t, J = 6.1 Hz), 2.40 (4H, m), 1.97 (1H, br s), 1.53 (8H, m), 0.96 (3H, t, J = 6.8 Hz); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{22}H_{32}N_6O{\cdot}1.5C_2H_2O_4{\cdot}0.5H_2O$: C, 55.54 %, H, 6.71 %, N, 15.55 %; found C, 55.35 %, H, 6.81 %, N, 15.59 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]-ethyl]-3-(2-propyl)-2-imidazolidinylidene}propanedinitrile (8). EIMS m/z 396 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 6.11 (2H, s), 4.61 (1H, m), 3.77 (2H, s), 3.61 (6H, m), 3.48 (2H, s), 2.91 (2H, t, J = 6.2 Hz), 2.42 (4H, m), 2.15 (1H, br s), 1.51 (6H, m), 1.24 (6H, d, J = 5.6 Hz); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{22}H_{32}N_6O{\cdot}1.5C_2H_2O_4{\cdot}0.5H_2O$: C, 55.54 %, H, 6.71 %, N, 15.55 %; Found C, 55.83 %, H, 6.70 %, N, 15.59 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]-ethyl]-3- (2-methyl-1-propyl)-2-imidazolidinylidene} propanedinitrile (9). EIMS m/z 410 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 6.10 (2H, s), 3.77 (2H, s), 3.63 (6H, m), 3.47 (2H, s), 3.35 (2H, d, J = 7.5 Hz), 2.91 (2H, t, J = 6.6 Hz), 2.41 (4H, m), 2.10 (1H, br s), 2.04 (1H, m), 1.50 (6H, m), 0.98 (6H, d, J = 6.6 Hz); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{23}H_{34}N_6O{\cdot}1.5C_2H_2O_4{\cdot}H_2O$: C, 55.41 %, H, 6.97 %, N, 14.91 %; found C, 55.55 %, H, 7.12 %, N, 14.94 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]-ethyl]-3-propargyl-2-imidazolidinylidene}propanedinitrile (10). EIMS m/z 392 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 6.11 (2H, s), 4.37 (2H, d, J = 2.4 Hz), 3.71 (9H, m), 3.47 (2H, s), 2.95 (2H, t, J = 6.2 Hz), 2.45 (4H, m), 2.27 (1H, br s), 1.55 (6H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{22}H_{28}N_6O{\cdot}1.5C_2H_2O_4{\cdot}H_2O$: C, 55.04 %, H, 6.10 %, N, 15.40 %; found C, 55.11 %, H, 6.02 %, N, 15.51 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]-ethyl] -3- (2- ethoxy-1-ethyl) -2-imidazolidinylidene} propanedinitrile (11). EIMS m/z 426 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 6.11 (2H, s), 3.77 (2H, s), 3.4–3.7 (14H, m), 2.91 (2H, t, J = 6.2 Hz), 2.41 (4H, m), 2.09 (1H, br s), 1.51 (6H, m), 1.19 (3H, t, J = 7.0 Hz); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{23}H_{34}N_6O_2{\cdot}1.5C_2H_2O_4{\cdot}H_2O$: C, 53.88 %, H, 6.78 %, N, 14.50 %; found C, 53.78 %, H, 6.68 %, N, 14.69 %.

{1- [2- [[[5- (Piperidinomethyl) 2-furanyl] methyl]amino]-ethyl]-3- [4- (2-methyl-2-butenyl)]-2-imidazolidinylidene}-propanedinitrile (12). EIMS m/z 422 (M^+); ^1H NMR (DMSO-d_6; 2 oxalate) δ 6.56 (2H, s), 5.24 (1H, m), 4.10 (4H, m), 3.67 (6H, m), 3.10 (4H, m), 2.89 (4H, m), 1.79 (3H, s), 1.73 (3H, s), 1.62 (6H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{26}H_{38}N_6O{\cdot}1.5C_2H_2O_4$: C, 55.80 %, H, 6.36 %, N, 13.95 %; found C, 55.68 %, H, 6.54 %, N, 13.91 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl]methyl]amino]-ethyl] -3- cyclohexylmethyl -2- imidazolidinylidene} propanedinitrile (13). EIMS m/z 392 (M^+); ^1H NMR (DMSO-d_6; 1.5 oxalate) δ 6.11 (2H, s), 3.77 (2H, s), 3.62 (6H, m), 3.48 (2H, s), 3.34 (2H, d, J = 7.3 Hz), 2.91 (2H, t, J = 6.2 Hz), 2.42 (4H, m), 1.0–2.0 (17H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{26}H_{38}N_6O{\cdot}1.5C_2H_2O_4$: C, 59.47 %, H, 7.06 %, N, 14.35 %; found C, 59.75 %, H, 7.31 %, N, 14.61 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]-ethyl] -3- benzyl -2- imidazolidinylidene} propanedinitrile (14). EIMS m/z 444 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 7.10 (5H, m), 6.11 (2H, s), 4.73 (2H, s), 3.75 (2H, s), 3.72 (6H, m), 3.47 (2H, s), 2.89 (2H, t, J = 6.2 Hz), 2.40 (4H, m), 1.53 (6H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{26}H_{32}N_6O{\cdot}2HCl$: C, 60.34 %, H, 6.62 %, N, 16.24 %; found C, 60.24 %, H, 6.69 %, N, 15.92 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]-ethyl]-3-(4-fluorobenzyl) -2-imidazolidinylidene} propanedinitrile (15). EIMS m/z 462 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 7.11 (4H, m), 6.11 (2H, s), 4.73 (2H, s), 3.78 (2H, s), 3.75 (6H, m), 3.47 (2H, s), 2.94 (2H, t, J = 6.2 Hz), 2.39 (4H, m), 1.55 (6H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{26}H_{31}FN_6O{\cdot}2HCl$: C, 58.32 %, H, 6.21 %, N, 15.69 %; found C, 58.06 %, H, 6.09 %, N, 15.78 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]-ethyl] -3- [(3,4- dimethoxybenzyl)]-2-imidazolidinylidene}-propanedinitrile (16). EIMS m/z 504 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 6.85 (3H, m), 6.10 (2H, s), 4.68 (2H, s), 3.88 (6H, s), 3.77 (2H, s), 3.61 (6H, m), 3.46 (2H, s), 2.94 (2H, t, J = 6.2 Hz), 2.41 (4H, m), 1.61 (6H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{28}H_{36}N_6O_3{\cdot}1.5C_2H_2O_4{\cdot}0.5H_2O$: C, 57.40 %, H, 6.22 %, N, 12.96 %; found C, 57.56 %, H, 6.00 %, N, 12.94 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]-ethyl]-3-(3,4-dichlorobenzyl)-2-imidazolidinylidene} propanedinitrile (17). EIMS m/z 513 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 7.32 (3H, m), 6.11 (2H, s), 4.72 (2H, s), 3.78 (2H, s), 3.61 (6H, m), 3.45 (2H, s), 2.95 (2H, t, J = 6.2 Hz), 2.37 (4H, m), 1.48 (6H, m); IR (KBr) 2200, 2155 (both CN) cm^{-1}; calcd for $C_{26}H_{30}Cl_2N_6O{\cdot}1.5C_2H_2O_4{\cdot}0.5H_2O$: C, 52.97 %, H, 5.21 %, N, 12.78 %; found C, 53.11 %, H, 5.31 %, N, 12.82 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]-ethyl]-3-[3-(1-phenyl-1-propenyl)]-2-imidazolidinylidene}-propanedinitrile (18). EIMS m/z 470 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 7.33 (5H, m), 6.34 (2H, m), 6.10 (2H, s), 4.32 (2H, d, J = 6.1 Hz), 3.76 (2H, s), 3.62 (6H, m), 3.47 (2H, s), 2.94 (2H, t, J = 6.2 Hz), 2.45 (4H, m), 1.63 (6H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{28}H_{34}N_6O{\cdot}C_2H_2O_4{\cdot}H_2O$: C, 62.27 %, H, 6.62 %, N, 14.52 %; found C, 62.12 %, H, 6.51 %, N, 14.24 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]-ethyl]-3-(3-pyridylmethyl)-2-imidazolidinylidene}propane-dinitrile (19). EIMS m/z 445 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 8.59 (2H, m), 7.71 (1H, m), 7.34 (1H, m),

6.14 (2H, s), 4.80 (2H, s), 3.78 (2H, s), 3.62 (6H, m), 3.52 (2H, s), 2.91 (2H, t, J = 6.2 Hz), 2.44 (4H, m), 1.53 (6H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{25}H_{31}N_7O \cdot 2C_2H_2O_4$: C, 55.67 %, H, 5.64 %, N, 15.67 %; found C, 55.75 %, H, 5.88 %, N, 15.67 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]- ethyl] -3- benzhydryl -2- imidazolidinylidene} propanedinitrile (20). EIMS m/z 520 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 7.29 (10H, m), 6.10 (2H, s), 3.77 (2H, s), 3.60 (7H, m), 3.44 (2H, s), 2.95 (2H, t, J = 6.2 Hz), 2.26 (4H, m), 1.44 (6H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{32}H_{36}N_6O \cdot 2C_2H_2O_4 \cdot 0.5H_2O$: C, 60.92 %, H, 5.82 %, N, 11.84 %; found C, 60.72 %, H, 6.05 %, N, 12.11 %.

Method B. {1-[2-[[[5-(Piperidinomethyl)-2-furanyl]- methyl]amino]ethyl]-3-phenyl-2-imidazolidinylidene}propanedinitrile (21). Step 1. A mixture of **30** (5.2 g, 30.6 mmol), aniline (3.0 g, 32.3 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 7.0 g, 46.1 mmol), and THF (60 mL) was heated under reflux for 3 h. The reaction mixture was poured into ice-water, and the resulting solution was extracted twice with CH_2Cl_2. The extracts were washed successively with diluted HCl, saturated aqueous $NaHCO_3$ solution and brine in that order. The organic layer was dried, and concentrated to give a crude product of [(methylthio)(phenylamino)-methylene]propanedinitrile (**37**: R^2 = phenyl), which was recrystallized from EtOH to yield 3.85 g (59 %) of pure **37** as orange needles: mp 172.5–174 °C; ^1H NMR (DMSO-d_6) δ 10.46 (1H, bs), 7.25 (5H, m), 2.48 (3H, s); calcd for $C_{11}H_9N_3S$: C, 61.37 %, H, 5.82 %, N, 11.84 %; found C, 61.50 %, H, 5.71 %, N, 11.59 %.

Step 2. A mixture of **37** (4.0 g, 18.6 mmol) and ethanolamine (1.13 g, 18.5 mmol) was allowed to stand at 80 °C under reduced pressure for 1.5 h. The reaction mixture was chromatographed on silica gel with $CHCl_3$:MeOH (20:1) to give 1.58 g (37%) of [[(2-hydroxy) ethylamino](phenylamino)methylene] propanedinitrile (**38**: R^2 = phenyl) as a pale yellow oil: ^1H NMR (DMSO-d_6) δ 9.32 (1H, bs), 7.71 (1H, bs), 7.18 (5H, m), 5.07 (1H, bs), 3.52 (2H, m), 3.31 (2H, m).

Step 3. To a stirred solution of **38** (R^2 = phenyl; 1.5 g, 6.58 mmol) in anhydrous pyridine (15 mL) was added dropwise methanesulfonyl chloride (1.0 mL, 12.9 mmol) under ice-cooling. After the reaction mixture was stirred for 1 h, the solvent was evaporated. The resulting residue was dissolved in THF (10 mL) and the solution was cooled in an ice-bath. DBU (1.1 g, 7.24 mmol) was added dropwise to the cooled solution. The mixture was stirred at 4 °C for 30 min, and then, the solvent was evaporated to dryness. The resulting residue was dissolved in CH_2Cl_2 and washed with diluted HCl, saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried, and concentrated to yield crude crystals of (1-phenyl-2-imidazolidinylidene) propanedinitrile (**39**; R^2 = phenyl). This was recrystallized from ethyl acetate–i-Pr_2O to give 1.19 g (86 %) of **39** as a pale yellow powder: mp 205–206 °C; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 7.68 (1H, bs), 7.34 (5H, m), 4.02 (2H, m), 3.71 (2H, m); calcd for $C_{12}H_{10}N_4$: C, 68.55 %, H, 4.79 %, N, 26.65 %; found C, 68.48 %, H, 4.81 %, N, 26.57 %.

Step 4. To a stirred solution of **39** (R^2 = phenyl: 1.1 g, 5.24 mmol) in THF (50 mL) was added portionwise 60 % NaH (0.27 g, 6.75 mmol) while cooling under ice. After the reaction mixture was stirred at 4 °C for 30 min, 1-bromo-2-chloroethane (4.4 mL, 52.8 mmol) was added. The mixture was further stirred at refluxing temperature for 20 h. To the resulting mixture was added ice-water (5 mL), and the solvent was evaporated. The resulting residue was partitioned between CH_2Cl_2 and brine. The organic layer was dried, and concentrated to afford a crude solid, which was chromatographed on silica gel with $CHCl_3$:MeOH (50:1) to give 1.12 g (78 %) of [1-(2-chloroethyl)-3-phenyl-2-imidazolidinylidene] propanedinitrile (**40**; R^2 = phenyl) as a white powder: mp 168.5–170 °C; ^1H NMR ($CDCl_3$) δ 7.32 (5H, m), 3.94 (8H, m); calcd for $C_{14}H_{13}ClN_4$: C, 61.65 %, H, 4.80 %, N, 20.54 %; found C, 61.99 %, H, 4.56 %, N, 20.63 %.

Compound **21** was obtained from **40** (R^2 = phenyl) as described in steps 2, 4 and 5 of method A. This was isolated as the oxalate in the usual manner: EIMS m/z 430 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 7.29 (5H, m), 6.11 (2H, s), 3.86 (4H, m), 3.79 (2H, s), 3.73 (2H, t, J = 6.2 Hz), 3.48 (2H, s), 2.98 (2H, t, J = 6.2 Hz), 2.43 (4H, m), 1.54 (6H, m); IR (KBr) 2200, 2155 (both CN) cm^{-1}; calcd for $C_{25}H_{30}N_6O \cdot 1.5C_2H_2O_4$: C, 59.46 %, H, 5.88 %, N, 14.86 %; found C, 59.25 %, H, 6.01 %, N, 14.75 %.

Similarly, compounds **22–26** were synthesized.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]- ethyl]-3-(4-methylphenyl)-2-imidazolidinylidene}propane-dinitrile (22). EIMS m/z 444 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 7.18 (4H, m), 6.12 (2H, s), 3.84 (4H, m), 3.80 (2H, s), 3.73 (2H, t, J = 6.0 Hz), 3.47 (2H, s), 2.98 (2H, t, J = 6.0 Hz), 2.39 (4H, m), 2.36 (3H, s), 1.88 (1H, br s), 1.50 (6H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{26}H_{32}N_6O \cdot 1.5C_2H_2O_4 \cdot 0.5H_2O$: C, 56.86 %, H, 5.89 %, N, 13.26 %; found C, 56.59 %, H, 5.94 %, N, 13.16 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl]methyl]amino]- ethyl]-3-(3-methylphenyl)-2-imidazolidinylidene}propane-dinitrile (23). EIMS m/z 444 (M^+); ^1H NMR (D_2O; 1.5 oxalate) δ 7.29 (4H, m), 6.75 (2H, s), 4.42 (2H, s), 4.35 (2H, s), 4.03 (4H, m), 3.87 (2H, m), 3.47 (4H, m), 2.97 (2H, m), 2.36 (3H, s), 1.85 (6H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{26}H_{32}N_6O \cdot 1.5C_2H_2O_4$: C, 60.09 %, H, 6.69 %, N, 14.50 %; found C, 59.94 %, H, 6.37 %, N, 14.29 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]- ethyl]-3- (4-methoxyphenyl) -2- imidazolidinylidene} propanedinitrile (24). EIMS m/z 460 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 7.15 (2H, d, J = 8.9 Hz), 6.86 (2H, d, J = 8.9 Hz), 6.08 (2H, s), 3.77 (3H, s), 3.76 (4H, m), 3.75 (2H, s), 3.71 (2H, t, J = 5.9 Hz), 3.45 (2H, s), 2.96 (2H, t, J =

5.9 Hz), 2.36 (4H, m), 1.50 (6H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{26}H_{32}N_6O_2 \cdot 1.5C_2H_2O_4 \cdot 0.5H_2O$: C, 57.61 %, H, 6.00 %, N, 13.90 %; found C, 57.76 %, H, 6.14 %, N, 14.03 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl]methyl]amino]-ethyl] -3- (3- methoxyphenyl)-2-imidazolidinylidene} propanedinitrile (25). EIMS m/z 460 (M^+); ^1H NMR (D_2O; 1.5 oxalate) δ 7.43 (1H, t, J = 7.9 Hz), 7.01 (3H, m), 6.75 (2H, s), 4.42 (2H, s), 4.35 (2H, s), 4.03 (4H, m), 3.88 (2H, m), 3.85 (3H, s), 3.48 (2H, m), 3.46 (2H, t, J = 6.8 Hz), 2.97 (2H, m), 1.86 (6H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{26}H_{32}N_6O_2 \cdot 1.5C_2H_2O_4$: C, 58.48 %, H, 5.92 %, N, 14.11 %; found C, 58.23 %, H, 6.24 %, N, 14.15 %.

{1- [2- [[[5- (Piperidinomethyl)-2-furanyl] methyl]amino]-ethyl] -3- (2- methoxyphenyl)-2-imidazolidinylidene} propanedinitrile (26). EIMS m/z 460 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 7.24 (2H, m), 6.96 (2H, m), 6.08 (2H, s), 3.87 (3H, s), 3.81 (2H, s), 3.75 (6H, m), 3.44 (2H, s), 2.97 (2H, t, J = 6.0 Hz), 2.39 (4H, m), 1.52 (6H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{26}H_{32}N_6O_2 \cdot 1.5C_2H_2O_4 \cdot H_2O$: C, 56.76 %, H, 6.08 %, N, 13.70 %; found C, 57.00 %, H, 6.03 %, N, 13.51 %.

Method C-1. {1-[2-[N-Methyl-N-[[5-(piperidinomethyl)-2-furanyl] methyl] amino]ethyl]-2-imidazolidinylidene}propanedinitrile (27). To a solution of compound **2** (free base; 0.98 g, 2.76 mmol) in MeOH (50 mL) was added $NaBH_3CN$ (95 %: 0.28 g, 4.23 mmol) and a trace of bromocresol green. An HCl–EtOH solution (8.7 M) was added until the color turned yellow, and 37 % aqueous formaldehyde (0.3 mL, 4.0 mmol) was added with stirring. During reaction, the HCl–EtOH solution was occasionally added dropwise to maintain the yellow color. After the mixture was stirred at room temperature for 2 h, the solvent was evaporated and the residual yellow oil was dissolved in H_2O. The aqueous solution was brought to pH 12.5 with 10 N NaOH, saturated with NaCl, and extracted twice with CH_2Cl_2. The combined extracts were washed with brine, dried and concentrated to afford 0.96 g of crude **27** as an oil, which was converted to the fumaric acid salt in THF in the usual manner (50 %): EIMS m/z 368 (M^+); ^1H NMR (D_2O; fumarate) δ 6.81 (1H, d, J = 3.5 Hz), 6.78 (1H, d, J = 3.5 Hz), 6.53 (2H, s), 4.43 (2H, s), 4.36 (2H, s), 3.94 (2H, t, J = 6.9 and 7.9 Hz), 3.79 (2H, m), 3.62 (2H, m), 3.47 (2H, m), 3.41 (2H, t, J = 6.9 and 7.9 Hz), 2.97 (2H, m), 2.89 (3H, s), 1.3–2.0 (6H, m); IR (KBr) 2200, 2155 (both CN) cm^{-1}; calcd for $C_{20}H_{28}N_6O \cdot C_4H_4O_4$: C, 59.49 %, H, 6.66 %, N, 17.34 %; found C, 59.09 %, H, 6.79 %, N, 17.04 %.

Compound **28** was similarly obtained from compound **2** and benzaldehyde.

{1- [2- [N- Benzyl -N- [[5- (piperidinomethyl) -2- furanyl]-methyl]amino]ethyl]-2-imidazolidinylidene}propanedinitrile (28). EIMS m/z 444 (M^+); ^1H NMR (DMSO-d_6; 0.5 oxalate) δ 7.84 (1H, br s), 7.31 (5H, m), 6.44 (1H, s), 6.33 (1H, s), 3.96 (2H, s), 3.66 (2H, s), 3.62 (2H, s), 3.60 (4H, m), 3.41 (2H, t, J = 8.9 Hz), 2.80 (4H, m), 2.68 (2H, t, J = 5.6 Hz), 1.64 (4H, m), 1.45 (2H, m); IR (KBr) 2200, 2160 (both CN) cm^{-1}; calcd for $C_{26}H_{32}N_6O \cdot 0.5C_2H_2O_4 \cdot 0.6H_2O$: C, 64.81 %, H, 6.89 %, N, 16.79 %; found C, 64.50 %, H, 6.80 %, N, 16.55 %.

Method C-2. {1-[2-[N-Acetyl-N-[[5-(piperidinomethyl)-2-furanyl] methyl] amino]ethyl]-2-imidazolidinylidene}propanedinitrile (29). To a stirred solution of compound **2** (fumarate: 0.8 g, 1.7 mmol) in anhydrous pyridine (12 mL) was added dropwise acetic anhydride (0.24 mL, 2.54 mmol). After the reaction mixture was stirred for 15 min, MeOH (5 mL) was added to the solution. The solvent was evaporated and the oily residue was dissolved in H_2O. The aqueous solution was brought to pH = 13 with 10 N NaOH, saturated with NaCl, and extracted twice with CH_2Cl_2. The organic layer was washed with brine, dried, and concentrated to yield 0.66 g of crude **29** as an oil, which was isolated as the fumarate in the usual manner (74 %): EIMS m/z 396 (M^+); ^1H NMR ($CDCl_3$; free base form) δ 6.22 (1H, d, J = 3.2 Hz), 6.09 (1H, d, J = 3.2 Hz), 5.83 (1H, bs), 4.51 (2H, s), 3.5–4.0 (8H, m), 3.46 (2H, s), 2.40 (4H, m), 2.23 (3H, s), 1.48 (6H, m); IR (KBr) 2200, 2155 (both CN), 1690 (C=O) cm^{-1}; calcd for $C_{21}H_{28}N_6O_2 \cdot C_4H_4O_4$: C, 58.58 %, H, 6.29 %, N, 16.40 %; found C, 58.78 %, H, 6.34 %, N, 16.53 %.

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.*[18] using acetylthiocholine (ATCh) as a substrate. In the standard procedure, to 50 μL 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 a buffer (final concentration 0.3 mM). A volume of 0.1 mL of inhibitor in buffer or buffer alone were 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.* 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 ± 1 °C) and a gaseous mixture of 95 % O_2 and 5 % CO_2 was passed through the solution. 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 to the organ bath, and the effects on the electrically induced contraction were examined. The activity of the test compounds were represented as EC_{30} values, i.e. the concentration of the compounds producing 30 % potentiation of electrically induced contraction.

Gastrointestinal motility enhancing activity in vivo: *effect of compounds 2, 14 and 15 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 the systemic administration 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 H_2O) and connected to a pressure transducer equipped with an ink-writing polygraph. After the operation procedures were complete, the animals were allowed to equilibrate for 60 min at which time steady contractile activity and blood pressure were established. Following this, a dose of 1 mg/kg of each compound (**2**, **14** and **15**) was dissolved in physiological saline and administered intravenously into an ear vein at 60 min intervals and the effects on the gastrointestinal motility and blood pressure were examined and monitored, respectively.

Histamine 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}H]tiotidine.[19] Nonspecific binding was determined by the addition of 5 mM histamine. Samples were incubated at 25 °C for 30 min. The 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 scintillation vials with Scintisol EX-H. The radioactivities in the filters were counted using a Packard 2200CA scintillation counter.

Acknowledgments

We are grateful to Mr H. Ueno, Ms I. Hattori and Ms M. Yoshida for analytical and spectral data, and especially to Dr T. Kumazawa and Dr K. Suzuki for their continuous support and pertinent discussion.

References

1. Scarpignato, C. In *Drugs in Gastroenterology*, Chapter 1, Braga, P. C.; Gusland, M.; Tittobello, A., Eds; Ravan; New York, 1991.

2. Gidda, J. S.; Monkovic, I. *Ann. Rep. Med. Chem.* **1985**, *20*, 117.

3. King, F. D.; Sanger, G. J. *Ann. Rep. Med. Chem.* **1988**, *23*, 201.

4. Bertaccini, G.; Scarpignato, C. *Br. J. Pharmacol.* **1982**, *77*, 443.

5. Bertaccini, G.; Poli, E.; Adami, M.; Coruzzi, G. *Agents and Actions* **1983**, *13*, 157.

6. Fioramonti, J.; Soldani, G.; Honde, G.; Bueno, L. *Agents and Actions* **1984**, *15*, 260.

7. Bortolotti, M.; Cucchiara, S.; Brunelli, F.; Sarti, P.; Samimi, M.; Mazza, M.; Del Campo, L.; Barbara, L. *Gastroenterology* **1992**, *102*, Part 2, A428.

8. Hansen, W. E.; Bertl, S. *Lancet* **1983**, *29*, 235.

9. Galli, A.; Mantovani, P.; Pepeu, G. *Biochem. Pharmacol.* **1984**, *33*, 1845.

10. Kounenis, G.; Koutsoviti-Paradopolou, M.; Elezoglou, V. *J. Pharmacobio. Dyn.* **1986**, *9*, 941.

11. Mehta, S. M.; Bhalara, D. D.; Goyal, R. K. *Agents and Actions* **1987**, *21*, 38.

12. Bertaccini, G.; Coruzzi, G. *Agents and Actions* **1982**, *12*, 168.

13. Yoshida, N.; Karasawa, T.; Kadokawa, T. *Arch. Int. Pharmacodyn.* **1988**, *295*, 245.

14. Poli, E.; Coruzzi, G.; Bertaccini, G. *Agents and Actions* **1990**, *30*, 191.

15. Sasho, S.; Obase, H.; Ichikawa, S.; Kitazawa, T.; Nonaka, H.; Yoshizaki, R.; Ishii, A.; Shuto, K. *J. Med. Chem.* **1993**, *36*, 572.

16. Sowell, Sr J. W.; Tang, Y.; Valli, M. J.; Chapman, Jr J. M.; Usher, L. A.; Vaughan, C. M.; Kosh, J. W. *J. Med. Chem.* **1992**, *35*, 1102.

17. Sasho, S.; Obase, H.; Ichikawa, S.; Yoshizaki, R.; Ishii, A.; Shuto, K. *BioMed. Chem. Lett.* **1994**, *4*, 615.

18. Ellman, G. L.; Courtney, K. D.; Andres, Jr V.; Featherstone, R. M. *Biochem. Pharmacol.* **1961**, *7*, 88.

19. Gajtkowski, G. A.; Norris, D. B.; Rising, T. J.; Wood, T. P. *Nature* **1983**, *304*, 65.

(*Received in Japan* 7 *September* 1994; *accepted* 13 *September* 1994)